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Transcript of
FIFRA Scientific Advisory Panel
Open Meeting
Holiday Inn - Ballston
4610 North Fairfax Drive
Arlington, Virginia
August 17-18, 2000

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ATTENDANCE LIST

1
2 Panel Members
3 MARY ANNA THRALL Veterinary Clinical Pathologist,
4 ----- Professor at Colorado State
5 University
6 CHARLES CAPEN Professor and Chairman of the
7 Department of Veterinary
8 ----- Biosciences at Ohio State
9 University
10 DAVID BRUSICK Vice President, Covance
11 Laboratories
12 JAMES CHEN National Center for
13 Toxicological Research
14 DAVID GAYLOR Sciences International
15 JEFF EVERITT Senior Scientist at the Chemical
16 ----- Industry Institute of Toxicology
17 GARY BOORMAN National Toxicology Program,
18 National Institute of
19 Environmental Health Sciences
20 HERBERT NEEDLEMAN Professor of Psychiatry and
21 Pediatrics at the University of
22 Pittsburgh

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ATTENDANCE LIST (cont'd)Panel Members:

STEPHEN ROBERTS Professor and Director, Center
for Environmental and Human
Toxicology at the University of
Florida

ERNEST MCCONNELL President of Toxpath,
Incorporated

GARY WILLIAMS Professor of Pathology at New
York Medical College

Also Present:

MARCIA E. MULKEY Director, Office of Pesticide
Programs, Office of Prevention,
Pesticides and Toxic Substances,
EPA

JOSEPH DEGEORGE Associate Director for
Pharmacology and Toxicology in
the Office of Review Management,
Center for Drug Evaluation
Research

WILLIAM BURNAM Office of Pesticide Programs,
EPA

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ATTENDANCE LIST (cont'd)Also Present:

1
2
3 STEVEN K. GALSON Director, Office of Science
4 Coordination and Policy, Office
5 of Prevention, Pesticides and
6 Toxic Substances, EPA
7 MARION COPLEY Office of Pesticide Programs,
8 EPA
9 JESS ROWLAND Office of Pesticide Programs,
10 EPA
11 BRIAN DEMENTI Office of Pesticide Programs,
12 EPA
13 PENNY FINNERCRISP Senior Science Advisor to the
14 Director of the Office of
15 Pesticide Programs
16 PAUL LEWIS Designated Federal Official
17
18
19
20
21
22

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1 DR. CHEN: My name is James Chen. I am at the
2 National Center for Toxicological Research in FDA. My
3 area of expertise is biostatistics.

4 DR. GAYLOR: Dave Gaylor, recently formerly with
5 the National Center for Toxicological Research of the
6 FDA. Recently I have joined Sciences International. My
7 areas of expertise are statistics and risk assessment.

8 DR. MCCONNELL: My name is Gene McConnell,
9 President of Toxpath, Incorporated. I am a veterinary
10 pathologist and toxicologist. My areas of expertise are
11 in the design, conduct and interpretation of animal
12 bioassays.

13 MR. DEGEORGE: Joseph DeGeorge, Associate
14 Director for Pharmacology and Toxicology in the Office of
15 Review Management, Center for Drug Evaluation Research.
16 I chair our Carcinogenic Assessment Committee, and I am
17 not a member of the SAP.

18 DR. THRALL: Okay. Well, let's just skip around
19 to Dr. Williams now.

20 FEMALE SPEAKER: Excuse me. Who are you
21 skipping?

22 DR. THRALL: We're skipping EPA.

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1 FEMALE SPEAKER: Why?

2 DR. THRALL: They'll be introducing themselves
3 in just a moment.

4 DR. WILLIAMS: Gary Williams. I am an M.D.
5 Pathologist. I'm a Professor of Pathology at New York
6 Medical College. And my expertise is in the area of
7 chemical carcinogenesis and safety assessment.

8 DR. EVERITT: I'm Jeff Everitt. I'm a
9 Veterinary Pathologist. I'm a Senior Scientist at the
10 Chemical Industry Institute of Toxicology in Research
11 Triangle Park. And my area of expertise is comparative
12 medicine and experimental pathology.

13 DR. BOORMAN: I'm Gary Boorman. I'm with the
14 National Toxicology Program at the National Institute of
15 Environmental Health Sciences. I'm a Veterinary
16 Pathologist and I've been working in the area of rodent
17 pathology and rodent cancer studies for the past 25
18 years.

19 DR. NEEDLEMAN: I'm Herbert Needleman. I'm a
20 Professor of Psychiatry and Pediatrics at the University
21 of Pittsburgh. And I work in the studies of lead at low
22 doses in children's development.

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1 DR. ROBERTS: I'm Steve Roberts. I'm a
2 Toxicologist, Professor and Director of the Center for
3 Environmental and Human Toxicology at the University of
4 Florida.

5 DR. THRALL: Thank you. I would now like to
6 introduce Mr. Paul Lewis, who is our designated federal
7 official this morning. And he will be going over some
8 administrative procedures with us.

9 MR. LEWIS: Thank you, Dr. Thrall. I want to
10 first thank the Panel members for agreeing to serve at
11 today's meeting, for spending the time to prepare for the
12 materials to be presented today, and for the subsequent
13 report writing process that will be occurring after this
14 meeting.

15 As Dr. Thrall mentioned, I'm the designated
16 federal official for this meeting. We have a challenging
17 scientific issue being presented today. We have a full
18 agenda for the next two days. The agenda is a floating
19 agenda. Thus, we may not keep to the exact times as
20 noted due to Panel discussions, public comments and Panel
21 deliberations. We want to ensure adequate time for
22 presentations and the public comments to be presented,

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1 and following that the Panel deliberations.

2 We have a number of public commenters that
3 registered beforehand, and we'll also open the floor up
4 again for any additional public commenters who want to
5 have time. I request that the commenters summarize their
6 remarks in order to give all public commenters an
7 opportunity to present their comments and issues to the
8 FIFRA SAP.

9 Also I want to mention for all presenters, Panel
10 members and public commenters to please identify yourself
11 and speak into the microphones since today's meeting is
12 recorded. And for the Panel members, we have distributed
13 a copy of the slides that will be presented today for you
14 to take notes, and they will also be available to the
15 public in the public docket.

16 My role as a designated federal official to the
17 FIFRA SAP serves as a liaison between the Panel and the
18 agency. With that being the case, I am responsible for
19 ensuring that provisions of the Federal Advisory
20 Committee Act are met. With that, this is an open
21 meeting. There is a public docket. All materials are
22 available in the docket. And I'll mention that in a few

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1 moments.

2 In addition, to ensure the participants on the
3 Panel are aware of federal conflict of interest laws.
4 Each participant has filed a standard government ethics
5 report, and I, along with our Deputy Ethics Officer, have
6 reviewed the form to ensure compliance with appropriate
7 ethics regulations.

8 As I mentioned, all the background materials,
9 the questions posed to the Panel, public comments that we
10 have received and other documents relating to this SAP
11 are available on the docket. In addition, many of the
12 materials such as the agenda and the background documents
13 are also available on our web site. And the web site and
14 the docket phone number is listed on the agenda, which is
15 located outside this room.

16 At the conclusion of the meeting, the Scientific
17 Advisory Panel will prepare a report as a response to the
18 questions and as a summary of the remarks made at today
19 and tomorrow's meeting. Basically the report serves as
20 meeting minutes, and we anticipate the final report in
21 approximately 45 to 60 days.

22 Again, I want to thank the Panel for agreeing to

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1 serve today. I'm looking forward to both a challenging
2 and an interesting scientific deliberation.

3 Dr. Thrall?

4 ----- DR. THRALL: Thank you, Mr. Lewis. We'll now
5 have some welcoming remarks from Dr. Steve Galson --
6 Steven Galson -- who is the Director of the Office of
7 Science Coordination and Policy, Office of Prevention,
8 Pesticides and Toxic Substances.

9 Dr. Galson?

10 DR. GALSON: Thanks very much. I wanted to
11 welcome all of the members of the Panel, EPA staff and
12 members of the public. We're very grateful for the time
13 commitment that you've made in this hot summer time where
14 I know you have a lot of competing interests for your
15 time.

16 ----- Malathion is an important weapon in our public
17 health pesticide arsenal. It is critically important
18 that we get this safety assessment right. And so we're
19 really very grateful to the panelists for their
20 commitment to public health and public service in
21 agreeing to lend us your expertise and your time for this
22 meeting and for the work to put together the report when

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1 we're done.

2 I think I'll leave it at that and pass the
3 microphone on to Marcia Mulkey, the Director of the
4 Office of Pesticide Programs.

5 MS. MULKEY: Thank you, and welcome to all of
6 you, everybody who has showed up today. The permanent
7 members of this Panel, with whom I get a chance to share
8 these few moments with increasing frequency, know how
9 strongly we in the Pesticide Program feel about the value
10 that we receive from the work of the FIFRA Scientific
11 Advisory Panel.

12 The value you add to our work truly is
13 incalculable. And those of you sitting on this Panel,
14 I'll be saying a few words in a moment about how
15 particularly important this Panel is to us. But this
16 kind of open, accountable peer review is vital to the
17 quality of our science. It is vital to our credibility.
18 And it is vital to our ability to perform our
19 responsibilities as public servants. And we are
20 committed to sound science, and we see the role you play
21 for us and with us as an absolutely essential element of
22 our ability to fulfill that commitment.

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1 The Panel today has been convened to help us
2 work through the issues related to the carcinogenic
3 potential of the compound malathion. Malathion, as
4 Steven mentioned, is a compound that shall we say has
5 some experience in the limelight? It has historically
6 played a role in some very high profile situations, such
7 as the control of the Mediterranean fruit fly and the
8 control of mosquitoes, especially at times when mosquito
9 control has unusually keen public health concerns. And
10 it has played a very important role -- a very important
11 economic role in the boll weevil eradication program.

12 So this is a compound which matters, and perhaps
13 even more than usual. It is important that we assure the
14 soundest possible scientific approach to our thinking
15 about this compound, and in the case of today's work to
16 our thinking about its carcinogenic potential.

17 It will be completely apparent, we hope and we
18 expect, from the presentations today that there is not
19 full consensus about exactly how to think about the
20 carcinogenic potential of this compound. We have within
21 our own staff some differences of view about how to think
22 about these issues. I think it will be apparent that the

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1 perspective of the agency does not align perfectly with
2 the perspective of the registrant about how to think
3 about these data. And so your value added will be
4 significant for that reason as well.

5 It may also become apparent over the next couple
6 of days that there are strongly held and passionately
7 articulated views about this compound, and perhaps
8 particularly about its carcinogenic potential, among
9 other members of the public beyond the registrant. We
10 regard all of this as entirely healthy, as entirely
11 appropriate and as entirely necessary to sound science,
12 so that alternate points of view can be as fully aired as
13 we can do and as fully understood. And that from that,
14 we have confidence we'll emerge with the best job we can
15 do in understanding the carcinogenic potential of this
16 compound.

17 So we look forward to the benefit of your work.
18 We look forward to an orderly and professional and
19 exciting period of time working together over the next
20 two days. And I thank you again for your service with us
21 and for sharing with us the daily joys of public service.

22 DR. THRALL: Thank you, Ms. Mulkey. We'll

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1 now --

2 DR. MCCONNELL: Dr. Thrall? Dr. Thrall, could I
3 ask a quick question?

4 DR. THRALL: Yes, Dr. McConnell.

5 DR. MCCONNELL: I know it's not pertinent to our
6 discussions and so forth today, but just as a matter of
7 interest -- my own personal interest -- what are the
8 alternatives to malathion in a Med fly or mosquito
9 situation? Have they been thought through? I mean, this
10 isn't, I know, part of our discussion. But just for my
11 own interest?

12 MS. MULKEY: We have actually in the last year
13 in particular been trying to provide a lot of information
14 to the public about the range of compounds that are
15 registered and available for use, for example, in
16 mosquito control because of the West Nile virus
17 situation.

18 There is a relatively newly registered compound
19 that has been made available for Med fly control that is
20 an exciting new change in that area. The active
21 ingredient is called spinosad. We do have the
22 information about all the compounds on the mosquito

1 control, and rather than my attempting to remember and
2 name the compounds, why don't I suggest that we make that
3 available by tomorrow morning? Because I think there
4 might be other people here, too, who are interested in
5 understanding that.

6 There are alternatives to malathion in many of
7 the uses, but there are some unique properties and some
8 special values associated with malathion in these uses.
9 And as you said, this is not really the thrust of the
10 purpose of the forum. But those are factors that we do
11 consider.

12 But we can definitely provide you with the
13 information about mosquitocides. We've made that
14 generally available to the public, because there happens
15 to be a lot of keen public interest, especially in the
16 last couple of years in mosquitocides.

17 DR. MCCONNELL: Thank you.

18 DR. Thrall: Dr. Finnercrisp, would you like to
19 make any comments?

20 DR. FINNERCRISP: No. I just wanted to
21 introduce myself. I am Dr. Penny Finnercrisp, and I am
22 the Senior Science Advisor to the Director of the Office

1 of Pesticide Programs.

2 MR. THRALL: Thank you. All right. At this
3 time I'll introduce Mr. William Burnam, who is from the
4 EPA. And perhaps you can introduce your group and give
5 some introductory remarks.

6 MR. BURNAM: Yeah. I'll go ahead and turn this
7 over to Dr. Copley, who will do the introductions.

8 DR. THRALL: Okay. Dr. Copley?

9 DR. COPLEY: I am Marion Copley, a Toxicologist
10 in the Health Effects Division of OPP and a member of
11 the --

12 DR. THRALL: Could you pull the microphone to
13 you a little bit, because I think we're going to have
14 some problems here.

15 DR. COPLEY: I'm Marion Copley, a Toxicologist
16 in the Health Effects Division of OPP and a member of the
17 Carcinogen Assessment Review Committee. The title of my
18 presentation is A Consultation on the Health Effects
19 Division's Proposed Classification of the Human
20 Carcinogenic Potential of Malathion.

21 The cancer classification of the organophosphate
22 malathion is a very complicated issue. Therefore, the

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1 purpose of this presentation is to obtain the SAP's
2 advice regarding the proposed HED cancer classification.
3 Although we are well aware that there are many other
4 issues regarding the toxicity of malathion, this session
5 will be limited to issues that relate to the cancer
6 classification.

7 The members of the HED OPP Panel are William
8 Burnam, Jess Rowland and Brian Dementi. The following is
9 a list of abbreviations I will be using throughout this
10 presentation. HED is the Health Effects Division of the
11 Office of Pesticide Programs in EPA. NCI is the National
12 Cancer Institute. NTP is the National Toxicology
13 Program. CPRC is HED's Cancer Peer Review Committee.
14 This committee was replaced by the Cancer Assessment
15 Review Committee several years ago.

16 C A R C -- or CARC -- is HED's Cancer Assessment
17 Review Committee. CARC II refers to CARC's reevaluation
18 and subsequent malathion cancer document that was issued
19 in April of this year. This document superseded the
20 first CARC malathion cancer document of February of this
21 year. PWG is the Pathology Working Group, and WOE is
22 weight of evidence.

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1 My presentation is divided into several
2 sections: a very brief history chronology of the
3 agency's carcinogenicity classification of malathion with
4 regards to the old NCI studies, and a discussion of the
5 adequacy of each of the three new cancer studies used in
6 the recent cancer evaluation, along with a discussion of
7 the tumor findings of the CARC that were considered to be
8 either related to, or possibly related to, malathion
9 treatment.

10 There will be a discussion of the weight of
11 evidence and the resultant cancer classification for
12 malathion proposed by the HED CARC II in April this year.
13 There will also be a discussion of some other tumors that
14 were evaluated in detail during the CARC and CARC II
15 deliberations. Dr. Dementi will then present an
16 alternative interpretation of the data as it relates to
17 the carcinogenic potential of malathion.

18 In addition, FDA has just completed an
19 evaluation of the carcinogenic potential of malathion.
20 And I am pleased to introduce several members from the
21 Cancer for Drug Evaluation and Research in FDA that are
22 in our audience who are involved in this evaluation.

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1 Drs. Joe DeGeorge, who has already been introduced
2 earlier, Abby Jacobs and Linda Reed.

3 Next will be a brief history chronology of the
4 agency's cancer classification. In the 1970's NCI
5 conducted five bioassays: two in the rat and one in the
6 mouse with malathion, and a rat and mouse study with
7 malaaxon, which is the oxygen analog and cholinesterase
8 inhibiting metabolite of malathion.

9 The pathology of the rat studies was
10 subsequently reevaluated by the NTP with the results
11 published in 1985 in Environmental Research. And that
12 was in the Panel's package, Reference 20. In 1990 HED
13 CPRC met to evaluate the carcinogenic potential based on
14 these studies. The following is a very brief overview of
15 the NCI, NTP and 1990 CPRC conclusions about these
16 studies and the carcinogenicity of malathion.

17 The NCI report of the malathion mouse study
18 concluded that there was no clear evidence of
19 carcinogenicity in this study. The CPRC concluded that
20 there were numerous deficiencies in design, evaluation
21 and reporting with respect to contemporary guidelines,
22 and that this student was inadequate to make a clear

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1 conclusion about the carcinogenicity of malathion.

2 The NCI report of the malathion Fischer 344 rat
3 study concluded that malathion was not carcinogenic in
4 male or female rats, but the females may not have
5 received a maximum tolerated dose.

6 NTP concluded that there was no evidence of
7 carcinogenicity in male or female rat -- Fisher rats.
8 And the CPRC concluded that this study was also
9 inadequate to make a definitive determination of
10 carcinogenicity of malathion.

11 The NCI report of the malathion Osborne-Mendel
12 rat study concluded that there was no clear evidence of
13 carcinogenicity. NTP also concluded that there was no
14 evidence of carcinogenicity. And the CPRC concluded that
15 there were numerous deficiencies in design, evaluation
16 and reporting with respect to contemporary guidelines and
17 that this study was inadequate to make a clear conclusion
18 about the carcinogenicity of malathion.

19 The NCI report of the malaoxon mouse study
20 concluded that under the conditions of this study
21 malaoxon was not carcinogenic in mice. The CPRC agreed
22 with the NCI, that in this study malaoxon did not induce

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1 a treatment related increase in tumors in mice. This was
2 the only study of the five that the CPRC considered
3 acceptable.

4 The NCI report of the malaoxon Fischer rat study
5 concluded that under conditions of this study, malaoxon
6 was not carcinogenic in Fischer rats. NTP concluded that
7 there was equivocal evidence of carcinogenicity based on
8 increased incidence of thyroid C-cell neoplasms in both
9 males and females.

10 The CPRC agreed with the NTP that there was
11 equivocal evidence of carcinogenicity based on the
12 increased incidence of these tumors in both males and
13 females. It also noted numerous deficiencies again in
14 design, evaluation and reporting with respect to
15 contemporary guidelines, and concluded that this study
16 was inadequate to make a definitive determination of the
17 carcinogenicity in Fischer rats.

18 The NTP cancer classification, as presented in
19 the abstract of the 1985 article, was that the NTP
20 pathology reexamination confirmed the original NCI
21 interpretive conclusions that malathion was not
22 carcinogenic. The NTP went on to say that for the

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1 malaoxon study there was equivocal evidence of
2 carcinogenicity for male and female rats.

3 Based on the criteria of the eight -- 1986 EPA
4 cancer guidelines, the CPSC in 1990 agreed to classify
5 malathion as a group D carcinogen. That is, malathion is
6 not classifiable as to human carcinogenicity based on the
7 inadequacy of the available studies to make definitive
8 determinations on the carcinogenicity of malathion or
9 malaoxon. However, the committee felt that there were
10 many issues regarding the adequacy of each study which
11 needed to be addressed before a firm conclusion regarding
12 the carcinogenic potential of malathion could be made.

13 In addition, while there may have been doubts
14 about the significance of each tumor type in each of the
15 individual studies, there was the suggestive appearance
16 of similar tumors, such as C-cell tumors in the thyroid
17 and of multiple tumors occurring in more than one study.

18 It also reaffirmed the requirements from the
19 1988 registration standard for new up-to-date
20 carcinogenicity studies testing malathion in the rat and
21 mouse and malaoxon in the rat.

22 This is the end of my part one. Kathy, do you

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1 have the current -- the new file?

2 KATHY: No.

3 MS. COPLEY: Okay. Okay. In this part I will
4 discuss the adequacy of the studies and the positive
5 tumor findings. This section will focus on the adequacy
6 -- okay. Since the 1990 CPRC evaluation, the three
7 required studies listed on the screen have been submitted
8 and evaluated by HED. The remainder of my presentation
9 will focus primarily on these studies.

10 Before I get to the details of these studies,
11 however, and the results of the most recent cancer
12 assessment, I would like to mention the previous cancer
13 classification by the CARC dated February 2, 2000. At
14 that time, they classified malathion as a likely human
15 carcinogen. However, a minority of the members were of
16 the opinion that malathion should be classified as a
17 suggestive human carcinogen, and that this classification
18 best describes the carcinogenic potential of malathion.

19 The following definitions and descriptions from
20 the July 1999 draft guidelines for the carcinogen risk
21 assessment were considered by the CARC II in April when
22 in interpreting the data for malathion. And this should

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1 be slide eight, Kathy.

2 Okay. These guidelines note the importance of
3 maximizing exposure conditions in the test material while
4 being careful to minimize using excessive high dose
5 levels that would confound the interpretation of study
6 results to humans. An adequate high dose -- oh, I'm
7 sorry. It is the previous -- an adequate high dose is
8 one that produces some toxic effects without either
9 unduly effecting mortality from non-cancer causes or
10 producing significant adverse effects on the mortality.
11 Excuse me. From non-cancer causes or producing
12 significant adverse effects on the mortality and health
13 of the test animals.

14 Body weight gain reductions of five to ten
15 percent over the life span of the animal are considered
16 to reflect an adequate dose. Excessive toxicity might be
17 indicated by signs or effects such as unduly affected
18 mortality and perturbation of physiological function,
19 reduction of body weight gain greater than 10 percent,
20 marked changes in organ weight morphology and
21 histopathology.

22 These guidelines also provide guidance regarding

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1 interpretation of tumor data in the presence of excessive
2 high doses as follows. Studies that show tumor effects
3 only at excessive doses may be compromised and may or may
4 not carry weight, depending upon the interpretation of
5 the context of other study results and other lines of
6 evidence.

7 Results of such studies, however, are generally
8 not considered suitable for dose response extrapolation
9 if it is determined that the modes of action underlying
10 the tumorigenic responses at high doses are not operative
11 at lower doses. Studies that show tumors at lower doses,
12 even though the high dose is excessive and may be
13 discounted, should be evaluated on their own merits.

14 If the study does not show an increase in tumor
15 incidence at a toxic high dose and appropriately spaced
16 lower doses are used without such toxicity or tumors, the
17 study is generally judged as negative for
18 carcinogenicity.

19 The following definitions for the five
20 descriptors for summarizing weight of the evidence have
21 been paraphrased from the 1999 draft of the cancer
22 guidelines.

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1 Carcinogenic to humans. This is used where
2 there is convincing epidemiologic evidence demonstrating
3 causality between human exposure and cancer.

4 Likely to be carcinogenic to humans. This is
5 used when available tumor effects and other key data are
6 adequate to demonstrate carcinogenic potential to humans.
7 Adequate data ranges from an association between human
8 exposure to the agent and cancer, or strong experimental
9 evidence of cancer in animals on one hand. On the other
10 hand, with no human data the weight of experimental
11 evidence shows animal carcinogenicity by a mode or modes
12 of action that are relevant or assumed to be relevant to
13 humans.

14 Suggestive evidence of carcinogenicity, but not
15 sufficient to assess human carcinogenic potential, is
16 used when the evidence from human or animal data is
17 suggestive of cancer, which raises a concern for
18 carcinogenic effects, but is judged not sufficient for a
19 conclusion as to the human carcinogenic potential.

20 Data are inadequate for an assessment of human
21 carcinogenic potential. This is used when available data
22 are judged inadequate to perform an assessment. This

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1 includes a case where there is a lack of pertinent or
2 useful data, or when existing evidence is conflicting,
3 such as some evidence is suggestive of carcinogenic
4 effects and other equally pertinent evidence does not
5 confirm this concern.

6 Not likely to be carcinogenic to humans is used
7 when the available data are considered robust for
8 deciding that there is no basis for human hazard concern.

9 The guidelines allow for different conclusions
10 for the same agent regarding different routes of exposure
11 and doses. For example, the agent is likely to be
12 carcinogenic by one route of exposure but not others, or
13 an agent is likely carcinogenic above a certain dose
14 range but not likely to be carcinogenic below that range.

15 And now I will discuss the study data.

16 Are we able to put the new program now, because
17 this is the time to do it?

18 FEMALE SPEAKER: Kathy, we need to put up the
19 new version.

20 DR. COPLEY: I'm sorry for the delay, but we had
21 found some errors in the previous version and the current
22 version has those -- we found some numerical errors in

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1 some of the tables in the previous version. They have
2 been corrected in this new version.

3 DR. THRALL: While we're waiting on this, do any
4 of the Panel members have any questions for clarification
5 up to this point? Okay.

6 MALE SPEAKER: Are the handouts the corrected
7 version of this?

8 DR. COPLEY: Yes.

9 MALE SPEAKER: Yeah. I have a question about
10 the test material. I mean, my reading is that what is
11 being tested throughout all of these, the NCI as well as
12 the new studies, is technical grade malathion, not
13 malathion. Can you enlighten me on that?

14 DR. COPLEY: It's the technical grade malathion,
15 not the formulations that are used for pesticide
16 applications.

17 MALE SPEAKER: You've got to speak louder.

18 DR. COPLEY: I'm sorry. It is the technical
19 grade of the material.

20 MALE SPEAKER: Right.

21 DR. COPLEY: That is correct.

22 MALE SPEAKER: So it's malathion plus

1 impurities, right?

2 DR. COPLEY: Correct.

3 DR. GAYLOR: Question.

4 DR. THRALL: Yes, Dr. Gaylor?

5 DR. GAYLOR: Is that on?

6 DR. THRALL: I think so.

7 DR. GAYLOR: When you said we have a corrected
8 copy, we have a handout dated August 11th and then we got
9 one this morning. Those two are not the same?

10 DR. COPLEY: Use the one this morning.

11 DR. GAYLOR: Just the one this morning is
12 correct. The August 11th is not correct?

13 DR. COPLEY: I think the August 11th is the
14 same. We sent it out early and then we just made extra
15 copies to bring today for people that might not have had
16 them...

17 DR. GAYLOR: Okay.

18 DR. COPLEY: Yeah. And some of the number
19 errors that I found, they had been changed and
20 handwritten on here. So this is corrected, but not
21 necessarily printed out that way.

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

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1 to --

2 DR. COPLEY: Talk louder?

3 DR. THRALL: Just pull it right up to you.

4 DR. GAYLOR: It's still not clear to me. The
5 August 11th --

6 DR. COPLEY: Okay. The numbers that you have on
7 that thing are all correct. One of them was handwritten
8 corrected, but they are all correct and they should match
9 the numbers that are on this version.

10 DR. GAYLOR: So the August 11th handout we got
11 is correct. Okay.

12 DR. COPLEY: It's the same as the one today.
13 Okay. That looks like the right slide.

14 MALE SPEAKER: Is this what you're looking for,
15 Marion?

16 DR. COPLEY: Slide 10.

17 MALE SPEAKER: Okay.

18 DR. COPLEY: Okay. Groups of mice were fed
19 diets containing malathion at zero, 100, 800, 8,000 or
20 16,000 parts per million for 18 months. The committee
21 concluded that the 800 parts per million dose level was
22 adequate to assess the carcinogenic potential of

1 malathion based on a biological decrease of 24 percent
2 for plasma, 44 percent for red blood cell cholinesterase
3 in males, and a statistical decrease of 36 percent per
4 plasma and 58 percent for red blood cell cholinesterase
5 in females.

6 However, the 8,000 and 16,000 parts per million
7 doses were considered excessive based on greater than 90
8 percent inhibition of plasma cholinesterase greater than
9 92 percent for red blood cell and from 20 to 40 percent
10 for brain cholinesterase inhibition in both sexes.

11 There was also a 10 to 20 percent decrease in
12 absolute body weight in both sexes when compared to
13 controls. This is actually an understatement of the body
14 weight change, since there was also an increase in liver
15 weight in the males. And that's at both mid and high
16 dose, and at 16,000 parts per million in the females.

17 In the following three slides, the percent of
18 tumors are based on censored data. This means that the
19 denominators include only those animals that were
20 considered to be at risk. Animals dead before the
21 occurrence of the first tumor are excluded. Interim
22 sacrificed animals are also excluded.

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1 As can be seen in the table, male mice had a
2 positive trend for liver adenomas and combined tumors.
3 The incidence of adenomas was significantly increased 25
4 percent at 8,000 and 96 percent at 16,000 parts per
5 million when compared to 7 percent in the controls.
6 Similarly, the combined tumors showed pair-wise
7 significance with a 27 percent incidence at 8,000 and 96
8 percent at 16,000 parts per million when compared to 7
9 percent in controls.

10 Although carcinomas were seen at 100, 800 and
11 8,000 parts per million compared to zero in controls,
12 none of the incidence showed statistical significance,
13 nor was there a dose related increase at any dose level.
14 These values were compared to historical control values.
15 It should be noted that historical control values are
16 based on uncensored data.

17 That is, the denominators represent the number
18 of animals with the tissue that were examined. Censored
19 percents are often larger since some animals are deleted
20 from the denominator. When compared with historical
21 control ranges of the testing facility, the incidence of
22 adenomas at 8,000 and 16,000 doses exceeded the

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1 historical control range of 14 to 22 percent.

2 The incidence of carcinomas was 4 percent at 800
3 and 8,000, which was within the historical range of zero
4 to 6.4 percent. There were no carcinomas seen at 16,000
5 parts per million. The incidence of carcinomas at 100
6 parts per million was 7 percent, which was slightly
7 outside the historical control range.

8 The question arose as to whether the tumors at
9 the low two doses were related to treatment. For
10 adenomas at the lower two doses, 15 percent at 100 and 13
11 percent at 800 parts per million. There was no
12 statistical significance by pair-wise comparison, no dose
13 related increase and the values were actually at the low
14 end of the historical control range, which again was 14
15 to 22 percent. The concurrent controls at 7 percent were
16 well below the historical control range.

17 This supported the CARC II's conclusion that
18 what could have been interpreted as a treatment related
19 increase in adenomas at the two low doses was actually
20 due to unusually low control incidence. The incidence of
21 carcinomas of 7 percent at 100 parts per million was
22 slightly outside the historical control range of zero to

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1 6.4 percent, and the incidence of carcinomas of 5 percent
2 at 800 parts per million and 4 percent at 8,000 parts per
3 million were within the historical control range.

4 ----- In the five historical control studies, the
5 incidence of liver carcinomas were zero in three of the
6 studies, one mouse in one study, which is about 2.2
7 percent, and three mice in another study, which was the
8 6.4 percent.

9 The committee also discussed the multiplicity
10 component of liver tumors in tumor bearing animals. This
11 refers to the presence of multiple adenomas and
12 carcinomas in the different lobes of the liver in the
13 same mouse. As can be seen in the table, the large
14 increase in multiple adenomas occurred in males only at
15 the high dose. The CARC considered the significance of
16 this finding to be unclear since it occurred only at an
17 excessively toxic dose.

18 MALE SPEAKER: Can I make -- is that rat on the
19 last line wrong? Shouldn't it be mouse?

20 DR. COPLEY: Yes. Sorry.

21 In female mice there was a positive trend for
22 liver adenomas and the combined tumors. The incidence of

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1 adenomas was significantly increased at 17 percent in the
2 8,000 parts per million group and 82 percent at 16,000
3 parts per million when compared to controls which were
4 zero.

5 Similarly, the combined tumors shown pair-wise
6 significance at 8,000 parts per million where the
7 incidence was 19 percent and at 16,000 parts per million
8 with an incidence of 84 percent when compared to 2
9 percent in the controls. No statistically significant
10 increases in carcinomas alone was seen at any dose.

11 The CARC concluded that while there was evidence
12 of carcinogenicity in both sexes in mice at 8,000 -- next
13 slide, please. At 8,000 and 16,000 dose groups, there
14 was no evidence of carcinogenicity in either male or
15 female mice at 800 or 16 -- sorry -- at 100 or 800 parts
16 per million.

17 Next slide, please, Kathy. Okay. Now I'm on
18 the following slide, slide 15. The next study I would
19 like to discuss is the malathion rat study. Groups of
20 rats were fed diets containing malathion at 0, 100, 500,
21 6,000 and 12,000 parts per million for two years. The
22 CARC concluded that in males the 500 parts per million

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1 dose was adequate to assess the carcinogenic potential of
2 malathion based on a non-statistic but biologically
3 significant increase in mortality, 47 percent as compared
4 to 33 percent in controls.

5 This was accompanied by a 29 percent decrease in
6 plasma cholinesterase. The 6,000 parts per million dose
7 was considered excessive in males due to a 74 percent
8 mortality and increased cholinesterase inhibition. At
9 12,000 parts per million the mortality was up to 100
10 percent.

11 In females the 6,000 parts per million dose was
12 considered adequate based on a 61 percent decrease in
13 plasma, 44 percent in RBC and 18 percent in brain
14 cholinesterase. This dose was one half of the next dose
15 where mortality was increased. The 12,000 parts per
16 million dose in females was considered excessive based on
17 a 64 percent mortality, as well as an 89 percent
18 inhibition in plasma, 52 percent for red blood cell and
19 67 percent for brain cholinesterase activity.

20 Due to the survival disparity, the Peto's
21 Prevalence Test was used for tumor analysis in both male
22 and female rats. In the original study report, the liver

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1 adenomas and combined liver tumors were significant in
2 female rats at 6,000 and 12,000 parts per million. There
3 were also significant increasing trends for adenomas and
4 combined tumors. There was no statistical increases in
5 liver carcinomas at any dose level in female rats. This
6 data was used by the CARC in the February 2000 report.

7 However, in March 2000 Kemy Nova, Inc. conducted
8 a reevaluation of female liver slides using a pathology
9 working group, or PWG. In 1995 HED issued PR Notice
10 94-5, which described procedural requirements in order
11 for HED to accept and use new and different tumor values
12 that were obtained from a PWG reevaluation of the tumor
13 data. This process is similar to that described in the
14 NTP technical reports.

15 As can be seen, the review must have the
16 following characteristics. For any target tissue which
17 is being reevaluation, all slides containing this tissue
18 in all groups must be re-read for a peer review
19 pathologist. This Notice does not specify a blind
20 reading of the slides.

21 The reports from the original study and peer
22 review pathologists, as well as the original slides, are

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1 then submitted to the PWG. The PWG is to review at a
2 minimum all slides where the diagnoses are significantly
3 different between the study and peer review pathologist.

4 (END OF TAPE 1, SIDE A)

5 MS. COPLEY: -- should consist of the peer
6 review pathologist and other pathologists, including the
7 original study pathologist.

8 This group is to examine the chosen slides
9 blind. This means that they have no knowledge of dose
10 groups or previously rendered diagnoses. When the PWG
11 consensus differs from the study pathologist, the
12 diagnosis is changed. The PR Notice goes on to say that
13 the resulting report should include the PWG findings, the
14 original diagnosis and the new diagnosis for each slide
15 read. A comment column noting any discrepancies, missing
16 slides, etc., should also be included.

17 CARC II evaluated Kemy Nova's PWG report which
18 described the procedures used as follows. The methods
19 included a pathology peer review of all female rat livers
20 by Dr. Brusey, followed by a blind PWG evaluation of all
21 liver slides that contain the following: any diagnosis
22 by either the study or peer review pathologist of

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1 cellular alteration, moderate or severe, hyperplasia,
2 adenoma and carcinoma. Also included were any gross
3 observations at necrose.

4 ----- The CARC II deliberations and discussion are
5 more fully detailed in the Reference 15 that you received
6 in your package and the correction to that Reference 15.
7 There were several concerns raised before and during the
8 CARC II meeting.

9 One issue was, would using the criteria provided
10 in the guides for toxicology pathology by Goodman, et al.
11 -- and that was the criteria used by the PWG to diagnose
12 liver lesions. Would using that criteria make it
13 difficult to compare the data to historical control data
14 that didn't use this criteria. Dr. Hardesty, the PWG
15 Chair, explained that NTP has used that criteria for many
16 years. Therefore, comparison with the NTP database would
17 be appropriate from this standpoint. It cannot be
18 determined what impact using these criteria would have on
19 the testing facility historical control data, however.

20 Concern was also expressed regarding the
21 incomplete evaluation of cellular alteration by the PWG.
22 The question was raised as to why the PWG did not

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1 evaluate these foci if they were less than moderate in
2 severity and the implications of this. In response to
3 this question, Dr. Hardesty said that the intent of the
4 PWG review was to identify neoplasms, and that moderate
5 and severe foci were the ones most likely to be
6 reclassified as neoplasms.

7 Following considerable discussion by the CARC
8 II, it was concluded that (a) cellular alteration is
9 frequently not a reliable indicator of progression to
10 neoplasia, (b) there was no basis for considering this to
11 be a preanal plastic lesion in this study, since there
12 was no increase of basophilia foci based on the original
13 study report.

14 The question was also raised as to whether the
15 PWG should discuss the possible role these foci might
16 play in the progression to neoplasia. However, since the
17 foci were not increased in the original report, the
18 majority of the committee was satisfied that foci were
19 not an issue of concern.

20 The observation was also made that there was no
21 explanation why several adenomas and carcinomas were
22 downgraded. However, the CARC II concluded that since

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1 both the study and peer reviewing pathologists were part
2 of the PWG and they had no problem with the new
3 diagnosis, this explanation was not necessary and it was
4 not required in the PR Notice.

5 The CARC II concluded that the PWG was conducted
6 in accordance with PR Notice -- with the PR Notice. They
7 also concluded that the revised female rat liver tumor
8 values from the reevaluation, as presented on the screen,
9 should be used. The only differences between these
10 values and the ones in the PWG report are: animals from
11 the interim sacrifice have been removed and the
12 denominators only include animals considered to be at
13 risk as described earlier.

14 There were no carcinomas observed by the PWG in
15 any group. For adenomas there was a positive trend and
16 pair-wise comparison only at 12,000 parts per million.
17 The incidence of liver adenomas at 12,000 parts per
18 million dose in this study were compared to the
19 historical control data from the studies conducted at the
20 testing facility. The 13 percent incidence of adenomas
21 exceeded the historical control range of zero to 5
22 percent in a mean of 1.6 percent. This incidence also

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1 exceeded the historical control incidence for adenomas in
2 the 1998 NTP report, which was about half a percent.

3 MALE SPEAKER: Okay. Can I ask a real quick
4 question? I'm sorry.

5 DR. THRALL: Where is it coming from?

6 MALE SPEAKER: Coming from here. Can I ask a
7 real quick question for clarification on the last slide,
8 because it also applies to the mouse tumor data.

9 DR. COPLEY: Yes.

10 MALE SPEAKER: There are asterisks for the zero
11 parts per million. Is that a comparison with --

12 DR. COPLEY: That's the trend.

13 MALE SPEAKER: That's the trend. Okay.

14 DR. COPLEY: Let me just say that statistical
15 significance for trend is located on the control group
16 and for pair-wise it's located at the particular group
17 where the significance is. One asterisk is .05, and two
18 is .01. And as I said before, all the rat statistics is
19 using the Peto's Prevalence Test, which accounts for
20 survival problems.

21 MALE SPEAKER: Thank you.

22 DR. COPLEY: The committee concluded that

1 although the incidence of liver tumors in female rats was
2 observed only at an excessively toxic dose, which is
3 12,000 parts per million, it provided evidence of
4 carcinogenicity, because the incidence was statistically
5 significant by pair-wise comparison, there was a
6 statistical trend and the incidence was outside the range
7 of both testing facility and NTP historical control
8 databases. It was also reiterated, though, that this was
9 an excessively toxic dose.

10 Nasal tumors in rats were also discussed. First
11 I will discuss the sectioning procedures that were used.
12 The original study report reported that two histologic
13 sections of nasal tissue were used. Histologic sections
14 two and four are labelled on the screen as original.

15 At the request of HED, Kemy Nova re-cut the
16 nasal tissue, obtaining a total of five sections as noted
17 on the screen. I just want to point out that the most
18 rostral section is number five and the most caudal
19 section is number four. This numbering was used because
20 the company's original numbering system allowed for only
21 four sections.

22 The locations of the cuts for these sections was

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1 for level Roman numeral I, the area between the upper
2 incisor tooth and the incisive papilla. For level Roman
3 numeral II, the area between the incisive papilla and the
4 first palatal ridge. For level Roman numeral III, the
5 area between the second palatal ridge and the first upper
6 molar tooth. For level Roman numeral IV, the area
7 between the first upper molar tooth and the nasal
8 pharynx. Level Roman numeral I was taken -- V, I'm sorry
9 -- was taken anterior to level Roman numeral I. These
10 tissues were embedded anterior surface down. Therefore,
11 the histologic samples for histologic sections one
12 through five were from the anterior surface of the
13 respective levels.

14 Now the NTP uses three sections with the first
15 at approximately where sections one and two -- where
16 section one is here. The section -- the second level
17 from NTP is usually between where level II and III are,
18 so that would be about here. And the third is where
19 level IV is. They do not section the area called section
20 five on this slide.

21 In fact, I wasn't able to find any laboratories
22 that routinely section this area. Therefore, I was

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1 unable to obtain any historical control data for the
2 nasal tumors in this section of the nose. I would also
3 like to point out that there would usually be palate
4 present in sections two through four. And this will be
5 of importance later in the discussion.

6 Now for the tumor data. In male rats there was
7 an adenoma of the respiratory epithelium at 12,000 parts
8 per million in section one, and an adenoma of the
9 olfactory epithelium in 6,000 parts per million in 6,000
10 parts per million in section four, compared to zero for
11 both in the concurrent controls.

12 Although the narrative and general summary
13 tables lump these adenomas together as nasal epithelial
14 tumors, the summary -- the peer review findings table and
15 the individual animal tables -- and this is all in the
16 study report -- specify that one tumor is a nasal mucosal
17 respiratory adenoma, and the other one is a nasal mucosal
18 olfactory adenoma.

19 The CARC II observed that the only respiratory
20 epithelial adenoma occurred in a group where there was
21 excessive toxicity. The incidence of one, however,
22 exceeded the historical control incidence of zero at a

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1 240 for the testing facility.

2 The NTP 1990 report, combining dietary and
3 inhalation studies, reported respiratory tract tumors in
4 the respiratory epithelium of six out of 4,000 male rats.
5 However, four of these were actually squamous cell tumors
6 rather than adenomas of the respiratory epithelium.
7 Therefore, the relevant historical control incidence for
8 respiratory epithelial adenomas was only two out of 4,000
9 males.

10 The biological significance of the adenoma of
11 the olfactory nasal epithelium in one male at 6,000 is
12 unknown since it is from a different cell of origin. And
13 this type of tumor, also called an esthesioneural
14 epithelial neoplasm, should not be combined with other
15 tumors of the respiratory nasal cavity. In the 1990 NTP
16 report there was zero out of 4,000 males with adenomas of
17 olfactory epithelium.

18 In the female rats, there was an adenoma of the
19 respiratory epithelium at 6,000 parts per million and at
20 12,000 parts per million as compared to zero in the
21 controls. Both of these were in section five, the most
22 anterior section. The CARC II noted that these tumors

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1 were benign and only one at 6,000 parts per million was
2 at a non-excessive dose.

3 At the time of the CARC II meeting, we were
4 under the misconception that section five was the most
5 cuddle. Therefore, we did not consider the fact that
6 this section was not routinely sectioned in historical
7 control databases, or that this section would be the most
8 exposed to local irritation from feed.

9 An evaluation of the non-neoplastic nasal
10 lesions in section five showed that there was an increase
11 in inflammatory cells and cellular debris, sub-acute and
12 chronic inflammation, vestibular congestion and squamous
13 cell hyperplasia in both groups four and five. The
14 incidence of these nasal adenomas exceeded the historical
15 control incidence for the testing facility, which is zero
16 out of 240 females. In addition, the 1990 NTP indicated
17 that there were none reported in 4,000 females.

18 However, as I already mentioned, the section
19 that both tumors were observed in -- section five -- is
20 not routinely sampled by the NTP or the testing facility.
21 Therefore, there really is no appropriate control
22 database.

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1 Of the four rat nasal tumors, one in each sex at
2 the two highest dose levels, only the adenoma in the
3 females at 6,000 parts per million occurred at a non-
4 excessive dose. The female adenomas occurred most
5 rostrally, and the male adenoma occurred in the next most
6 rostral section.

7 The committee did postulate that direct contact
8 by malathion by volatilization from the feed or by
9 inhalation of the feed through the nose was possible as
10 an explanation for the nasal tumors. However, there was
11 no evidence to support or refute that the tumorigenicity
12 was due to exposure, either by inhalation of systemic
13 routes. The committee determined that a systemic effect
14 could not be unequivocally ruled out.

15 And I would like to point out that this last
16 point was made by the CARC II prior to learning that
17 section five was the most anterior and not the most
18 cudde section.

19 The committee concluded that it could not
20 determine whether nasal tumors were either treatment
21 related or due to random occurrence. On the one hand,
22 there was no dose response over a wide range of doses

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1 from 100 to 12,000 parts per million. There was no
2 statistical significance. There were only adenomas.
3 The high dose in both males and females was considered
4 ~~excessively~~ toxic.

5 These tumors occurred in section five for the
6 females where there was evidence of non-neoplastic
7 lesions in the nasal mucosa. In addition, although not
8 discussed by the CARC II, there is no historical control
9 data from section five. On the other hand, an adenoma of
10 the respiratory epithelium was seen in one female at
11 6,000 parts per million, which is not an excessive dose.
12 Spontaneous nasal tumors appear to be rare in rats, and
13 there were no nasal tumors in the concurrent controls and
14 the incidence exceed the NTP values.

15 CARC II also concluded that for males a
16 biological significance of the single olfactory
17 epithelial tumor at 6,000 parts per million, although an
18 adenoma is unknown, since it is different from the cell
19 of origin of the other tumors and cannot be combined.

20 The next tumors discussed were of the oral
21 cavity in rats. Since the oral cavity was not a protocol
22 tissue for this study, negative, gross and histologic

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1 observations were not routinely noted. However, the
2 cavity was always examined at necrose and abnormalities
3 were noted.

4 As can be seen in the diagram previously, the
5 section locations, oral palate and teeth, are part of the
6 routine nasal sections. Therefore, observation of oral
7 tumors was incidental to evaluation of the nasal cavity.
8 There is some uncertainty as to the actual incidence of
9 these tumors and how many animals had this issue
10 examined. It should be noted that the oral tumors in
11 both sexes were only observed histologically. There were
12 no gross notations of any tumors in the oral cavity.
13 Based on the above, CARC II determined that a re-cut
14 would not alter their conclusions.

15 In male rats there was one squamous cell
16 papilloma of the palate at the low dose, compared to zero
17 in all the other groups. This was located in section
18 three. In conclusion, the occurrence of the single low
19 dose tumor in males was considered by the CARC II to be
20 incidental background, since there were no additional
21 tumors at higher doses, even with the large dose spread.

22 In female rats, however, there was a squamous

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1 cell carcinoma of the alveolus of the tooth at the low
2 dose in section four, and a squamous cell papilloma of
3 the palate at 6,000 parts per million in section three,
4 and a squamous cell carcinoma of the palate at 12,000
5 parts per million in section four, compared to zero for
6 all three tumor types in controls.

7 Again, there is an uncertainty as to actual
8 incidence of these tumors and how many animals have this
9 tissue examined, since the oral mucosal was not
10 considered a routine tissue. It was difficult to judge
11 the significance of low dose alveolar tumor since the
12 oral cavity was not routinely examined and a tumor was
13 only seen in one low dose female.

14 Although it may be appropriate to combine all
15 squamous cell tumors of the oral cavity when determining
16 tumor incidence, it was difficult to interpret this data.
17 Therefore, the CARC II did not combine the alveolar tumor
18 with the palate tumors. Of the two oral palate tumors,
19 one at each of the high two doses, only one adenoma in
20 the 6,000 parts per million female was at a dose that was
21 not considered excessive.

22 This incidence of oral squamous cell tumors did

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1 exceed the historical control incidence for inhalation
2 studies at the testing facility. In an inhalation study,
3 the cavities were routinely sectioned, and that was zero
4 males and females.

5 In addition, the 1998 NTP historical controls
6 summary reported squamous cell papillomas in females at
7 .22 percent, two out of 900 animals. The squamous cell
8 carcinomas for females were zero percent out of 900
9 animals.

10 The committee concluded that it could not
11 determine whether the oral cavity tumors in females were
12 treatment related, or whether they were due to random
13 occurrence. On the one hand, there was no dose response
14 over a wide range. There was no statistical
15 significance. The high dose in the females was
16 considered excessively toxic.

17 On the other hand, squamous cell papilloma of
18 the palate was seen in one female at 6,000 parts per
19 million, a non-excessive dose. And spontaneous oral
20 tumors appear to be rare in rats. There were no oral
21 tumors in concurrent controls, and the incidence exceeded
22 the historical control incidence of the testing facility

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1 and NTP. And due to a lack of systematic pathologic
2 evaluation of the oral mucosa, there is uncertainty as to
3 the actual incidence of these tumors.

4 We would welcome any additional comments you may
5 have regarding the nasal and oral historical control
6 values.

7 And this ends my section two of the
8 presentation. Are there any questions?

9 DR. BRUSICK: I have one question. David
10 Brusick.

11 DR. COPLEY: Yes, David.

12 DR. BRUSICK: I would like to go back to the
13 mouse study in the 900 parts per million dose, which is
14 the highest dose that did not show excessive toxicity.

15 Would you consider -- or was there sufficient
16 data to conclude that that dose was an adequate high dose
17 to evaluate the carcinogenicity?

18 DR. COPLEY: We concluded that the 800 parts per
19 million dose was adequate to assess carcinogenicity.

20 DR. BRUSICK: I didn't see any information on
21 body weight change or survival on that table.

22 DR. COPLEY: Survival and body weight --

1 survival was not affected and body weight was not
2 affected, but there was an inhibition of cholinesterase.

3 DR. THRALL: Dr. McConnell?

4 DR. MCCONNELL: Yes, two questions for
5 clarification. First, do you have any insight as to why
6 in the mouse study 18 months was chosen as the end rather
7 than 24 months?

8 DR. COPLEY: Our guidelines require 18 months
9 for the mouse.

10 DR. MCCONNELL: Even for the B6C3F1? Okay.

11 Second question is, on that historical rate that
12 you have for the mouse liver tumors, is that for 18 month
13 animals?

14 MALE SPEAKER: Yes. They were all 18 month
15 studies.

16 DR. MCCONNELL: The other studies that you --

17 MALE SPEAKER: All the studies she cited --

18 DR. MCCONNELL: Right. Were all 18 months?

19 MALE SPEAKER: -- were all 18 month studies.

20 DR. MCCONNELL: Okay, thank you.

21 MALE SPEAKER: But historical data typically for
22 24 months if you go to the NTP files and look at those

1 values.

2 DR. COPLEY: This was the testing facility,
3 however.

4 DR. MCCONNELL: And their studies were all 18
5 months. Okay.

6 DR. THRALL: Could I ask you to identify
7 yourselves before you speak, please. Dr. Williams?

8 DR. WILLIAMS: Gary Williams. I have a question
9 about this piece on the bottom of page five, going over
10 onto page six of your document that deals with these 1998
11 guidelines -- or 1999 guidelines for adequate versus
12 excessive doses.

13 DR. COPLEY: Uh-huh.

14 DR. WILLIAMS: One of the criteria for an
15 excessive toxicity, which you mentioned, is a
16 perturbation of physiological function. Did the CARC
17 specifically conclude that inhibition of brain
18 cholinesterase was a perturbation of physiological
19 function?

20 DR. COPLEY: We discussed that.

21 DR. BURNAM: Bill Burnam. It was part of our
22 weight of the evidence, and usually for a cholinesterase

1 inhibitor such as malathion, we look at all three
2 parameters and see what is going on. And that was part
3 of the criteria.

4 DR. WILLIAMS: Okay. They fall under the
5 descriptor of a perturbation physiological function.

6 DR. BURNAM: Right.

7 DR. COPLEY: Yes.

8 DR. THRALL: Dr. Needleman?

9 DR. NEEDLEMAN: My question is similar to that.
10 When was that operational definition developed?

11 DR. BURNAM: It was in a definition of MTDs that
12 I think we brought to the SAP back in the late '80's.

13 DR. NEEDLEMAN: One other thing, Marion.

14 DR. COPLEY: Yes, Dr. Needleman?

15 DR. NEEDLEMAN: In all the tests of statistical
16 significance, where there any power analyses applied to
17 the samples? No?

18 DR. THRALL: I have a question. Mary Anna
19 Thrall. On the bottom of page three over on the left
20 hand side at the very bottom, the toxicity in the two
21 year malathion rat study? At the 6,000 part per million
22 dose in the females, what was the mortality?

1 DR. COPLEY: The bottom of page?

2 DR. BURNAM: What page?

3 DR. THRALL: The bottom of page three of our
4 handout. Do you have that -- the handout that we had.

5 FEMALE SPEAKER: Oh, you're on the slides.

6 DR. BURNAM: It's the overheads.

7 DR. THRALL: Uh-huh.

8 DR. COPLEY: I'm sorry. I was reading -- the
9 bottom of page three.

10 DR. THRALL: Slide number 15

11 DR. COPLEY: Okay. You're asking if I have the

12 --

13 DR. THRALL: On the 6,000 part per million dose
14 over on the females, the mortality is not listed, and I
15 just wondered if you knew what that was.

16 DR. CHEN: Sixty two percent. I have the
17 number. It's 62 percent.

18 DR. COPLEY: What is it?

19 DR. CHEN: Sixty two percent.

20 DR. COPLEY: Sixty two percent?

21 MR. LEWIS: Please identify yourself.

22 DR. CHEN: James Chen.

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1 MALE SPEAKER: I think you're talking about
2 survival. She asked for mortality.

3 DR. THRALL: I'm asking about mortality.

4 DR. CHEN: Mortality is 62 percent. Survival is
5 38 percent.

6 MALE SPEAKER: I think it's the other way
7 around.

8 DR. THRALL: We're in the rat study.

9 DR. COPLEY: It's listed at the top. At zero
10 the mortality was 31 percent.

11 DR. THRALL: Forty one -- about 41 percent?

12 MALE SPEAKER: Which group?

13 DR. THRALL: The next to the high dose. The one
14 that was not considered excessive.

15 MR. ROWLAND: Jess Rowland. It's 38 percent for
16 the group (inaudible).

17 DR. THRALL: Thirty eight? Okay.

18 DR. CHEN: This is James Chen. I have a
19 question about -- I have a question about how -- do you
20 have a set of criterion to determine what is adequate and
21 what is excessive? Like in the female rat study, which
22 OR statistical significance in all components -- all

1 three components -- is considered as adequate for the
2 mouse study which shows significant considered excessive.

3 Do you have kind of a set criteria how do you
4 determine adequate or excessive?

5 DR. COPLEY: They don't look only at
6 significance, but also about the percent inhibition as
7 well. And the percent inhibitions were approaching 90 or
8 more on the ones that we considered excessive.

9 DR. CHEN: So do you have a number, like 80
10 percent inhibition?

11 DR. COPLEY: We used the weight of the evidence.

12 DR. CHEN: Okay.

13 DR. COPLEY: Rather than being boxed into any
14 one bright line, because we didn't take any one number
15 out of context. We looked actually -- we put all the
16 mouse values up, and we put all the rat values up, and
17 they were all on the board at the same time, and we were
18 looking at them so we would be consistent --

19 DR. CHEN: Okay.

20 DR. COPLEY: -- in what we considered adequate
21 versus excessive. And we used the weight of the
22 evidence, which included not just the cholinesterase, but

1 body weight, mortality and all three compartments of
2 cholinesterase inhibition.

3 DR. CHEN: Yeah. That's why I question about in
4 female mice, the body weight decrease only 10 percent.

5 DR. COPLEY: A body weight decrease of 10
6 percent is actually a greater body weight change
7 decrease. The guidelines prefer for an adequate dose to
8 have less than a body weight change -- or body weight
9 gain decrease of 10 percent. And if the absolute weight
10 is 10 percent, that means the gain is going to be even
11 more -- or less.

12 MALE SPEAKER: I would like to comment on this.

13 DR. CHEN: Thank you.

14 MALE SPEAKER: I have a question. I'm sorry,
15 I'm not an expert in organophosphates.

16 DR. THRALL: What's your name?

17 DR. EVERITT: Oh, my name is Jeff Everitt. I
18 have a question. You showed the cholinesterase
19 inhibition at 18 months. Can you shed any light on
20 earlier time points? Obviously you get a lot of changes
21 in regulation of cholinesterase over time.

22 And I personally don't know in Fischer rats what

1 you would expect with OP's. But certainly data from the
2 pre-chronic studies and from early time points would be
3 useful for evaluating the cholinesterase stress, I would
4 imagine.

5 DR. COPLEY: Jess?

6 MR. ROWLAND: I don't know the answer.

7 MALE SPEAKER: They have the 90 day studies and
8 the two week studies. They have both of those in there.

9 DR. EVERITT: The reason I bring this up is
10 obviously these are extremely excessive doses by the
11 current guidelines. And I'm just wondering. As we start
12 to evaluate adequacy of study, we're going to be going
13 down quite a bit in concentration, and it's going to be
14 very, very important to properly interpret what 18 month
15 cholinesterase means.

16 DR. THRALL: Dr. Gaylor?

17 DR. GAYLOR: Yes. I have three or four
18 questions. On slide 10 talking about the mouse study --

19 DR. THRALL: Could you speak up just a bit,
20 please?

21 DR. GAYLOR: I'm talking about the mouse study
22 and 800 parts per million being an adequate dose. But

1 you're not implying that that is the MTD, right?

2 DR. COPLEY: No.

3 DR. GAYLOR: Okay. On that slide 10, you made
4 ~~the~~ statement: however, the 8,000 and 16,000 ppm doses
5 were considered excessive based on greater than 90
6 percent inhibition of plasma CHE greater than 92 percent
7 for RBC and from 20 to 40 percent for brain CHE
8 inhibition in both sexes.

9 Are you implying then that inhibition of
10 cholinesterase somehow influences tumor production?
11 Either increases or decreases tumor production?

12 DR. COPLEY: No.

13 DR. GAYLOR: Is that the implication?

14 DR. COPLEY: The implication is that the animal
15 is not a normal --

16 MR. LEWIS: Into the microphone, Dr. Copley.

17 DR. COPLEY: The implication is that the animal
18 is not a normal animal. It's physiological functions
19 have been compromised by the cholinesterase. I'm not
20 making a link between cholinesterase and tumor
21 production.

22 DR. GAYLOR: Are you making a link between some

1 physiological function and tumor production, and if so,
2 what is that?

3 DR. COPLEY: No, I'm not.

4 DR. GAYLOR: Okay.

5 DR. THRALL: All right. Are those all of the
6 questions?

7 DR. GAYLOR: I have a question about slide 11.

8 DR. COPLEY: But there were the body weight
9 changes.

10 DR. GAYLOR: Right.

11 DR. COPLEY: And there may have been association
12 there, but I'm not specifying that.

13 DR. GAYLOR: I don't know what statistical tests
14 were conducted on slide 11 when we're looking at the
15 tumor incidence. It just says at the bottom of the
16 slide, and our handout indicates statistical significance
17 at the 5 or 1 percent level.

18 What test was used for pair-wise comparisons?
19 Was this the Fischer exact test?

20 DR. COPLEY: Yes. It was not the --

21 DR. THRALL: Please use the microphone.

22 DR. COPLEY: This is the mouse, so there were no

1 survival problems so they would use the Fischer.

2 DR. GAYLOR: In other words, survival problems
3 at the high doses.

4 DR. COPLEY: In the mouse?

5 DR. GAYLOR: Right.

6 DR. COPLEY: Not in the mouse. In the rat there
7 was.

8 DR. GAYLOR: Oh, in the rat. Okay. But there
9 was some difference in survival across those groups,
10 though maybe not considered excessive, right?

11 DR. COPLEY: I --

12 DR. GAYLOR: It was just the pair-wise --
13 Fischer pair-wise test. There was no correction for the
14 number of animals in the test?

15 DR. COPLEY: No correction for that.

16 DR. GAYLOR: Okay.

17 DR. COPLEY: The only correction had to do with
18 in the tumor analysis with not considering animals that
19 were not at risk.

20 DR. GAYLOR: But those that die are not at risk?

21 DR. COPLEY: Right.

22 DR. GAYLOR: And that wasn't --

1 DR. COPLEY: Right. That is different.

2 DR. GAYLOR: And the trend test was what trend
3 test here? I mean, there are several trend tests. Is
4 this the Cochran Armitage Test --

5 DR. COPLEY: Yes.

6 DR. GAYLOR: -- based on crude data, or was it
7 the Peto's Hierarch Analysis? It doesn't indicate here
8 what statistical trend test was used.

9 DR. COPLEY: I don't -- there was no Peto's
10 correction.

11 DR. GAYLOR: So this was just a test based on
12 crude --

13 MR. BURNAM: Yeah. When our statistician
14 returns -- she just stepped out for a while -- we'll get
15 back to you.

16 DR. GAYLOR: Oh. We'll surprise her with a
17 question, then.

18 DR. COPLEY: Laurie, the question is what
19 statistics were used for the tumors in the mouse. Was
20 there any special corrections or anything? And was it
21 Cochran Armitage for trend and which was used for
22 pair-wise?

1 MR. LEWIS: Dr. Copley, can you ask the HED
2 person to come forward and identify herself? Thank you.

3 MS. BRUNSMAN: Laurie Brunzman from HED. Yes.
4 The question is, what statistics were used for the
5 malathion mouse study?

6 DR. COPLEY: Yes.

7 MS. BRUNSMAN: I believe that there were no
8 mortality issues with this, so it would have been the
9 Fischer's Exact Test and the Exact Test for trend. It
10 would be the Fischer's Exact Test for pair-wise
11 comparisons, and the Exact Test for trend.

12 DR. GAYLOR: By Exact do you mean Cochran
13 Armitage?

14 MS. BRUNSMAN: No. There is --

15 DR. GAYLOR: A crude test?

16 MS. BRUNSMAN: Yeah. There is a crude --

17 DR. GAYLOR: I mean just on the crude incidence?

18 MS. BRUNSMAN: There are two trend tests that
19 could be used, the Cochran Armitage or the Exact. And
20 the Exact Test for trend is much more precise. So
21 instead of using the Cochran Armitage, we used the Exact
22 Test for trend. And there was the Fischer's Exact Test.

1 The Fischer's Exact Test is what we used for the
2 pair-wise comparisons.

3 DR. GAYLOR: That Exact Trend Test, can you give
4 me a reference offhand or later, maybe?

5 MS. BRUNSMAN: Yeah. There is a -- I can give
6 you these references here off of the back of the -- would
7 you like for me to just bring these --

8 DR. GAYLOR: We can do that later.

9 MS. BRUNSMAN: Okay.

10 MR. LEWIS: Let's make sure it's added to the
11 docket. Anything you are providing to the Panel, make
12 sure the docket has it also.

13 MS. BRUNSMAN: Okay.

14 MR. LEWIS: Thank you.

15 MS. BRUNSMAN: Certainly.

16 DR. CHEN: It's Jim Chen. I have a question
17 about the Peto Prevalence Test.

18 DR. COPLEY: Uh-huh.

19 DR. CHEN: The Peto text require cause of death.
20 In your prevalence test, do you assume incidental tumor?

21 DR. COPLEY: I'm sorry. I don't understand.

22 DR. CHEN: In the rat study and a Peto

1 Prevalence Test, usually the Peto Prevalence Test would
2 have two compartments. One is the tumor is the cause of
3 death and tumor is not cause of death.

4 MS. BRUNSMAN: Okay.

5 DR. CHEN: And so when you say prevalence test,
6 which part do you mean, tumor is not cause of death? Is
7 that what you did?

8 MS. BRUNSMAN: We rarely ever have access to
9 information indicating whether or not the tumor was the
10 cause of death. We always consider the tumors to be
11 incidental findings, because in the pathology reports
12 that we receive, most of the time the pathologists do not
13 indicate a cause of death at all.

14 DR. CHEN: Okay. Thank you.

15 MS. BRUNSMAN: Uh-huh.

16 DR. COPLEY: Was there a question? If there are
17 no other questions for clarification, we'll continue.

18 DR. THRALL: There has been a request for a
19 break, so we will take 15 minutes.

20 DR. COPLEY: I have a presentation on
21 cholinesterase in the rat, if that might be useful.

22 MALE SPEAKER: Yeah, let's hear it.

1 DR. COPLEY: There was a 90 day neurotoxicity
2 study done. And it says that there was cholinesterase
3 inhibition of plasma and red blood cell, and it's ranging
4 up -- and also -- let's see. And brain cholinesterase.
5 Brain was about 20 percent and the others were between 20
6 and 50 percent, and they were inhibited at -- let's
7 convert the dose -- 300 milligrams, which was about 5,000
8 parts per million. So at 90 days, 5,000 parts per
9 million, had cholinesterase inhibition of all three
10 compartments.

11 Does that answer the question?

12 MALE SPEAKER: And below that?

13 DR. COPLEY: The next dose below that was only
14 50 parts per million. There wasn't any inhibition there,
15 but that's a very, very low dose.

16 DR. THRALL: All right. We'll take a break. I
17 have ten after. We will reconvene at 10:30.

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

19 DR. THRALL: We will reconvene and continue on
20 with the weight of the evidence and cancer classification
21 discussion. Dr. Copley?

22 DR. COPLEY: I would now like to discuss other

1 factors that are part of the weight of the evidence.
2 Aside from the two cancer studies with malathion, other
3 factors considered in the weight of the evidence included
4 mutagenic potential and structure activity relationship.

5 The CARC II has re-analyzed the genetic
6 toxicology information on malathion. Over a decade ago,
7 it was concluded by the Cancer Peer Review Committee that
8 there was some evidence from mutagenicity studies
9 suggesting that a genetic component for malathion and
10 malaaxon was possible.

11 Although the submitted FIFRA guideline
12 mutagenicity studies were acceptable and negative, this
13 conclusion was primarily based on evidence from the
14 published literature of in vitro and in vivo chromosomal
15 aberration studies.

16 The field of mutagenesis is very -- is a very
17 active area of toxicology testing. Since 1990 there has
18 been substantial research developments that have
19 contributed to data evaluation and interpretation of
20 genetic toxicology findings. For example, high treatment
21 doses of certain benign agents can elicit positive genal
22 toxic responses due to changes in PH, osmolarity or

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1 severe cytotoxicity.

2 Moreover, the agency has emphasized in its
3 proposed revisions of the guidelines for carcinogen risk
4 assessment the draft '96 and '99, the importance of
5 distinguishing between direct DNA reactive mechanisms and
6 indirect or secondary mechanisms leading to DNA damage.
7 Because of these advances, the genetic toxicology
8 database for malathion was reexamined in depth when the
9 bioassay tissues and slides were being reevaluated in '99
10 and this year.

11 Although the genetic toxicology database has not
12 changed significantly, the manner in which we evaluate
13 genetic toxicology today has evolved. The CARC routinely
14 considers all the available data, both submitted and
15 published, in the weight of evidence approach.

16 The recent re-analysis revealed that clastogenic
17 responses were found only in published studies and at
18 doses that caused severe cytotoxicity. Therefore, while
19 the agency has high confidence in the malathion
20 acceptable guideline studies, it has reservations, which
21 were first noted in 1999, regarding the published
22 results.

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1 These concerns with the published articles
2 include lack of purity information, the testing with
3 commercial or less than 50 percent malathion, and
4 positive responses at precipitating or severely cytotoxic
5 doses. The agency noted these areas of concern and/or
6 uncertainties with these data in the February 2000
7 document. However, the April 2000 document more fully
8 articulates the reasons that in vitro and in vivo
9 findings from the open literature should be interpreted
10 with caution.

11 In summary, results of the guideline genetic
12 toxicology studies of malathion indicate that the test
13 material did not cause gene mutation in bacteria or
14 unscheduled DNA synthesis in cultured rat habitat sites.
15 Similarly, malathion was neither clastogenic nor
16 agenogenic up to doses that showed clear cytotoxicity for
17 the target tissue in vivo.

18 The CARC II concluded that in vitro and in vivo
19 findings from the open literature should be interpreted
20 with caution. However, the only area where a positive
21 response is clearly seen is in the induction of sister
22 chromatid exchanges, also called SCE's. Based on our

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1 experience with this pest system and organophosphates, we
2 have found no correlation between organophosphate
3 induction of SCE's and carcinogenicity.

4 Although the structure of malathion suggests
5 electrophilicity, the committee concluded that the weight
6 of the evidence supports neither a mutagenic hazard nor a
7 role for mutagenicity in the carcinogenicity associated
8 with malathion.

9 Next I'll discuss the structure activity
10 relationship. Malaoxon is the oxygen analog and
11 cholinesterase inhibiting metabolite of malathion. As
12 you can see, the structures are similar, except for the
13 oxygen replacing sulphur at the yellow arrow.

14 One of the required, new two year
15 carcinogenicity studies was conducted with malaoxon in
16 rats at doses of 0, 20, 1,000 and 2,000 parts per
17 million. The committee concluded that 2,000 parts per
18 million dose was excessive because of increased
19 mortality, which was 53 percent in males and 49 percent
20 in females, compared to controls which was 29 percent in
21 males and 13 percent in females. There was also an 83 to
22 96 percent inhibition in plasma, 54 to 66 inhibition in

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1 red blood cell, and 11 to 78 percent inhibition in brain
2 cholinesterase activity for both males and females.

3 The dose level of 1,000 was considered adequate,
4 because it was on half the dose causing the excessive
5 toxicity and there was some inhibition of --

6 (END OF TAPE 1, SIDE B)

7 DR. COPLEY: -- proposed cancer guidelines are:
8 carcinogenic to humans, likely to be carcinogenic to
9 humans, suggestive evidence of carcinogenicity but not
10 sufficient to assess human carcinogenic potential, data
11 are inadequate for an assessment of human carcinogenic
12 potential, and not likely to be carcinogenic to humans.
13 In April of this year the CARC II classified malathion as
14 suggestive evidence of carcinogenicity by all routes.

15 Next slide, please. The CARC II considered the
16 following weight of evidence for malathion. The benign
17 liver tumors in male and female mice -- in male and
18 female rats, I'm sorry -- occurred only at excessive
19 doses, were statistically significant and outside the
20 historical control range. There were a few rare tumors
21 of the oral palate mucosa in females, and nasal
22 respiratory epithelium in male and female rats. However,

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1 the CARC II could not determine whether they were either
2 treatment related or due to random occurrence. This is
3 talking about the nasal and oral tumors.

4 With the exception of one nasal and one oral
5 tumor in female rats, all other tumor types were
6 determined to have occurred at excessive doses or were
7 unrelated to treatment with malathion. The evidence for
8 mutagenicity is not supportive of a mutagenic concern in
9 carcinogenicity and malaaxon, a structurally related
10 chemical, was not carcinogenic in male or female rats or
11 mice.

12 The suggestive classification was supported by
13 11 out of 16 members -- next slide, please -- members
14 present at the meeting. Four of the 16 members, however,
15 thought that the evidence for malathion's cancer
16 potential was weaker than the suggested classification.
17 Two voted for data are inadequate for assessment of human
18 carcinogenic potential, and two voted for not likely to
19 be carcinogenic to humans.

20 These opinions were based in part on the
21 consideration that the increase in liver tumors was due
22 to hepatocellular adenomas which are benign. The

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1 increase was only in the presence of excessive toxicity.
2 They did not consider the oral and nasal tumors to be
3 treatment related. In addition, they believed that the
4 dose range for malathion's cancer effects was well
5 defined and limited to excessive or near excessive doses.
6 There was one abstaining.

7 And that is the end of part three. If there are
8 any questions on the weight of the evidence?

9 DR. THRALL: Yes, Dr. Gaylor?

10 DR. GAYLOR: In your first slide, slide 31, it
11 wasn't clear to me. Was cytotoxicity seen at the two
12 high doses? I couldn't tell from the discussion. You
13 were talking about public studies, but I wasn't clear
14 what those public studies were.

15 DR. COPLEY: Slide 31 pertains to the cancer
16 bioassay. Cytotoxicity pertains to mutagenicity studies.
17 Two different issues.

18 DR. GAYLOR: So we have no -- okay. So we have
19 no information on whether the two high doses caused cell
20 death in the cancer studies? We don't have that
21 information, is that right?

22 DR. COPLEY: We don't usually look at that in

1 the cancer studies. The cancer study is an in vivo study
2 where you're looking at the animal themselves.

3 DR. GAYLOR: Right. Well, you answered my
4 question.

5 DR. COPLEY: Okay.

6 DR. GAYLOR: And then let's see. On Slide --
7 that's all right now.

8 DR. THRALL: Yes, Dr. Roberts?

9 DR. ROBERTS: Steve Roberts. What role, if any,
10 did the original five studies play in the weight of
11 evidence decision?

12 DR. COPLEY: The role of the original five
13 studies was to let us know we needed additional studies,
14 because they didn't have much confidence in the original
15 results. And since the new studies were done using new
16 techniques and following the new guideline requirements,
17 the data from the new studies was used for the analysis.

18 DR. THRALL: Dr. Needleman?

19 DR. NEEDLEMAN: I'm still stuck on using an
20 assay of acetyl cholinesterase to evaluate the
21 carcinogenic potential of an agent. If this definition
22 -- this operational definition was made in the '80's, and

1 you knew what the dose response relationship was between
2 malathion and ACHE activity, why were 8,000 and 16,000
3 ppm used in the second round of studies?

4 DR. COPLEY: I wasn't here at the time. But
5 from what I've read, the reason why they had required
6 those doses is they wanted to see if the NTP data -- or
7 NCI data would be duplicated. Those were the doses that
8 were in the original studies.

9 DR. NEEDLEMAN: Well, it sounds like there is a
10 post hoc definition of what was excessive.

11 DR. COPLEY: A what?

12 DR. NEEDLEMAN: Post hoc. After you saw the
13 results and you determined that the two upper dose ranges
14 were excessive. That's what stopped me.

15 MR. BURNAM: Let's see. Bill Burnam. I think
16 the mouse studies -- I don't think they had a whole lot
17 of cholinesterase data in the mouse. And that was the
18 one that we wanted a replicate of the original NTP
19 studies that went up to 16,000, just to see if -- because
20 they had gone that high, we knew it was possible to go
21 that high. So we wanted to see what was going on at that
22 dose, even though that was above the limit dose of that

1 7,000 ppm for mice.

2 And in terms of being excessive or adequate,
3 those are the terms we used for the study that has been
4 done. And in terms of predicting an MTD, we use a sub-
5 chronic study for that. So to a certain extent, once a
6 study has been done and we have all the cholinesterase
7 data, we can determine and make a judgment about the dose
8 as either being excessive or adequate.

9 DR. NEEDLEMAN: Well, let me return to that
10 question one more time. What is the biological rationale
11 behind determining that an agent that effects a
12 neurotransmitter activity, to a certain extent, is
13 excessive in the measurement of carcinogenic potential?
14 How do you link those two different -- somewhat different
15 biologic systems?

16 DR. COPLEY: Yeah. I just heard Penny say what
17 I was going to say. The general overall well being of
18 the animal has been altered. The body doesn't handle
19 things the same way. And in the rat, you have mortality
20 as well, not just cholinesterase. And in the mouse, you
21 have body weight changes, not just cholinesterase.

22 So cholinesterase, as I said earlier, was only

1 one part of the weight of the evidence to determine where
2 the MTD actually was -- or not MTD. Where the adequate
3 dose level or excessive dose level border was.

4 And I think Penny wants to say something.

5 DR. FINNERCRISP: I want to ask a question of
6 Bill -- this is Penny Finnercrisp -- in part and in
7 response to Dr. Needleman's question.

8 I suspect and would want to confirm that when
9 the NCI studies were done with these chemicals,
10 cholinesterase was not measured in either of the species.

11 DR. NEEDLEMAN: That's true.

12 DR. FINNERCRISP: It was the standard pathology
13 and perhaps some clinical stuff. But I suspect they
14 didn't make any of the cholinesterase measurements. But
15 when we asked that the studies be repeated, we did ask
16 that the cholinesterase measures be included.

17 DR. DEMENTI: Can I say one thing? I'm Dr.
18 Dementi. I agree with the question that you're asking,
19 and I have a great deal of concern with using
20 cholinesterase inhibition as a rationale for discounting
21 positive findings. And I hope this committee will debate
22 that subject further, because that's a very important

1 question.

2 DR. THRALL: All right. If there are no other
3 questions for clarification, we'll continue.

4 DR. COPLEY: Okay. The CARC and CARC II had
5 discussions about several other tumor types and
6 determined that their occurrence was not due to
7 treatment.

8 Liver adenomas at low doses in male mice was
9 already discussed previously when I discussed the female
10 mouse liver tumors. The CARC and CARC II concluded that
11 these tumors were not related to treatment at the two low
12 doses in the male mice. The following tumors were
13 observed in the rat study. Since there was a disparity
14 in mortality, as I have mentioned earlier, the Peto's
15 Prevalence Test was used. And I'll start with the males
16 first.

17 The significance of oral tumors in the male was
18 discussed previously with the oral tumors in the females.
19 To reiterate, the single occurrence of a low dose tumor
20 in males was considered by the CARC II to be incidental
21 of background since there were no tumors at higher doses
22 even with the large dose spread. This was incorrectly

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1 listed as male rat nasal tumors in question three of the
2 background document.

3 Thyroid gland follicular cell tumors. As can be
4 seen on the table, there was a numerical increase in
5 adenomas and combined tumors at the high two doses and in
6 carcinomas at 500 and 6,000 parts per million.
7 Historical control data from the testing facility were
8 from six studies: three dietary and three inhalation.

9 The mean for adenomas was about 1.3 with a range
10 from zero to 2 percent, and the mean for carcinomas was
11 1.7 with a range from zero to 4 percent. Historical
12 control data from the NTP in the 1998 report indicate the
13 mean for adenomas was 12.3 percent with a range from 2 to
14 24 percent, and a mean for carcinomas of 1.1 with a range
15 of zero to 4 percent.

16 Although these values are outside the historical
17 control ranges, the committee concluded that the
18 follicular cell tumors are not treatment related, since
19 there is neither a pair-wise significance nor a dose
20 response relationship for any tumor. Only a trend was
21 seen for combined tumors. Additionally, there was no
22 evidence of malathion induced thyroid toxicity in the

1 database, and there was no supportive pre- or non-
2 neoplastic lesions in the thyroid glands of male or
3 female rats.

4 In the thyroid C-cell tumor table, you can see
5 that there was statistical significance by pair-wise
6 comparison for thyroid C-cell carcinomas at 500 parts per
7 million. This is true both when you consider the two
8 high doses and when you don't consider them. In
9 addition, the incidence of carcinomas at 50 and 500 parts
10 per million exceeded the mean historical control
11 incidence, which was about 2.5 percent for carcinomas in
12 male rats.

13 The CARC did consider the possibility that the
14 excessive mortality in males at the top dose, which was
15 74 percent -- the top two doses, 74 percent at 6,000 and
16 100-percent at 12,000, may have compromised the
17 expression of this tumor at these higher doses. Along
18 this line of reasoning, though, they observed that when
19 the top two doses were excluded from the analysis, there
20 was also a dose related increase in carcinomas.

21 However, this was discounted, because at 6,000
22 parts per million there were still 43 rats considered to

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1 be at risk, which means that they were alive after the
2 occurrence of the first carcinoma. And that they
3 considered to be an adequate number for evaluation.
4 Therefore, the CARC considered that there was no dose
5 response for carcinomas in males, and the increase at 500
6 parts per million was due to variability rather than to
7 malathion.

8 The incidence of combined thyroid C-cell tumors
9 were determined to be the most appropriate tumor values
10 for the final evaluation. There was no statistical
11 increase, either by pair-wise or by trend, or combined
12 tumors -- or for the combined tumors. Additionally,
13 there was no evidence of malathion induced thyroid
14 toxicity in the database, and there was no supportive
15 pre- or non-neoplastic lesions in the thyroid glands of
16 male or female rats.

17 Based on the above information, the committee
18 concluded that the thyroid C-cell tumors are not
19 attributable to treatment based on the combined tumor
20 adenoma and carcinoma incidence.

21 Nest slide, Kathy. The next tumor for
22 discussion is the testicular interstitial cell tumor. As

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1 with the previous tumors in the male rat, Peto's
2 Prevalence Test was used. The table of interstitial cell
3 tumors in rats indicates a significant trend for the
4 study that can be seen at the control group. There was
5 also a significant pair-wise comparison at 500, 6,000 and
6 12,000 parts per million.

7 Statistical analysis of this tumor in the study
8 report concluded that increases in testicular tumors were
9 significant at all dose levels. Statistical analysis by
10 HED obtained essentially the same results, except for the
11 low dose which did not show pair-wise significance.
12 However, a statistical evaluation should not be
13 considered the final word without any consideration of
14 the biological relevance of the data. Historically for
15 this tumor type, the spontaneous occurrence often
16 approaches 100 percent by the end of the study.

17 Therefore, the committee concluded that in spite
18 of the above statistical evidence, testicular tumors are
19 not treatment related since this is a nonlethal tumor.
20 It was observed in nearly 100 percent of the male rats,
21 including controls.

22 The apparent statistical significance of the

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1 tumor incidence in the two high doses could be attributed
2 to the high mortality at these doses resulting in earlier
3 observations of the tumor. And significance was
4 considered to be an artifact of the Peto's Prevalence
5 analysis protocol.

6 Sufficient data are not available to determine
7 if there was a decrease in latency period. For example,
8 there were no serial sacrifices to determine latency. In
9 fact, the first tumor occurred in the control group
10 during week 54. Also, this tumor is not useful in the
11 overall evaluation, since its occurrence is similar in
12 all dose levels.

13 The committee also discussed the significance of
14 liver tumors in male rats. As can be seen, there was no
15 evidence of treatment related increased or a statistical
16 significance in hepatocellular tumors, either adenomas or
17 carcinomas at any dose level in male rats. The incidence
18 of adenomas ranged from one to three, and for carcinomas,
19 zero to two tumors per group with no dose response or
20 statistical significance.

21 Therefore, the CARC concluded that
22 hepatocellular tumors were not related to treatment in

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1 male rats at any dose. It should be noted that there was
2 excessive toxicity at the two high doses.

3 Next is mononuclear cell leukemia, also called
4 MCL. As can be seen in the table, there is no
5 statistical increase in MCL in the male rats. However,
6 the committee also evaluated the possibility that there
7 is an increase in leukemic animals dying from leukemia
8 with increasing dose. It was suggested that this may
9 indicate an increase in severity of MCL, which would
10 indicate an increased carcinogenic response.

11 Also presented at the meeting was the week when
12 the first several rats with MCL were diagnosed and which
13 group they appeared in. Note that this tumor was only
14 diagnosed when animals died or were sacrificed. The
15 first MCL occurred in the 12,000 parts per million group
16 during week 64. The second one was in the 500 parts per
17 million group at week 72. The third one occurred at
18 6,000 parts per million at week 74. The fourth, again at
19 500 parts per million, at week 82. The fifth and sixth
20 occurred during week 83 in groups 500 and 6,000. And the
21 seventh occurred in the controls at week 84. There
22 didn't appear to be a strong temporal association with

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1 dose.

2 The committee concluded that there was no
3 evidence for increased carcinogenicity based on MCL,
4 because this tumor commonly occurs in Fischer 344 rats
5 and the incidence were within historical control ranges.
6 There was no statistical significance at any dose. There
7 was no dose response. There was no indication of early
8 onset or increased incidence.

9 It was noted that attributing the cause of death
10 to MCL is subjective and not a reliable indicator of
11 increased severity, because establishing a cause of death
12 is subjective in older rats with possible multiple aging
13 processes.

14 In general, for many of the previously discussed
15 male rat tumors, it was noted that the potential for
16 tumor induction may have been compromised by competing
17 toxicity, particularly at 6,000 and 12,000 parts per
18 million, where mortality was 74 and 100 percent
19 respectively. There is, however, no evidence to either
20 support or refute this supposition. In addition, the
21 next lower dose of 500 parts per million was considered
22 adequate by the CARC for carcinogenicity testing.

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1 The next group of tumors occurred in the female
2 rat. The first are tumors of the pars distalis (phonetic)
3 of the pituitary gland. The CARC originally noted that
4 not all female pituitary glands had been examined
5 microscopically. Therefore, histopathology examination
6 and peer review of microscopic slides of the pituitary
7 glands from all females were required. This evaluation
8 resulted in values presented on this table. Although
9 this table includes the interim sacrificed animals, there
10 were no tumors present in these animals.

11 As you can see, the tumor incidence and types
12 observed in the treated groups were comparable to those
13 seen in the concurrent control group. There was neither
14 statistical nor biological significance, and there was no
15 dose response relationship. Therefore, the committee
16 concluded that pituitary tumors are not attributable to
17 treatment.

18 Uterine tumors are the final tumor type I'll
19 discuss from the malathion rat study. The CARC noted the
20 presence of some rare unusual uterine tumors in the
21 original submission. Although individually the incidence
22 of the uterine tumors were low, collectively the

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1 incidence of the uterine tumors were of concern to the
2 committee. Therefore, they again required histopathology
3 examination and peer review of microscopic slides of the
4 uterus, since not all the low and mid doses had been
5 examined. This evaluation resulted in the following
6 tumors as noted on the slide.

7 As can be seen, the individual tumor incidence
8 remained low. The tumor incidence and types in the
9 treated controls were comparable to those seen in the
10 concurrent control group. And there was neither
11 statistical nor biological significance and there was no
12 dose response relationship. The committee therefore
13 concluded that the uterine tumors are not treatment
14 related.

15 Now I'll move on to the malaaxon male rat.
16 There was a question about MCL in male rats treated with
17 malaaxon. There was a statistically significant increase
18 in mononuclear cell leukemia in male rats at the highest
19 dose, which was 2,000 parts per million. There was also
20 a statistically significant trend for these tumors.

21 However, the committee concluded that
22 mononuclear cell leukemia was not treatment related,

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1 since statistical significance was only seen in males at
2 a dose that was determined to be excessive. There was no
3 dose response and the incidence were within historical
4 control range, which was 15 to 36 percent for the testing
5 facility.

6 Although there was a 35 percent increase at
7 1,000 parts per million, a value higher than that
8 observed at 2,000 parts per million, this was not
9 statistically significant using the Peto's Prevalence
10 Test to account for the survival disparity.

11 And I thank you for your attention. We would
12 appreciate any guidance that you can provide regarding
13 the cancer classification of malathion. But I would like
14 to add that since Dr. DeGeorge will have to leave after
15 the morning session, the SAP might wish to address any
16 questions regarding FDA's interpretation of our data at
17 this point.

18 Thank you.

19 DR. THRALL: Thank you, Dr. Copley. Are there
20 questions for clarification, or questions of Dr. DeGeorge
21 at this time?

22 Dr. Gaylor?

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1 DR. GAYLOR: We were supplied a lot of
2 information. I could have missed it, but I take it on
3 the thyroid there were no measurements made at T3, T4 or
4 TSH, is that correct? I didn't see anything in the
5 packets.

6 DR. COPLEY: It would have been in the DERs if
7 they had been measured.

8 DR. DEGEORGE: I don't think so.

9 DR. COPLEY: And I don't think so.

10 DR. GAYLOR: Okay.

11 DR. THRALL: Dr. Roberts?

12 DR. ROBERTS: Yes, Steve Roberts. As I look
13 back at the original five studies, one of the things that
14 came out of those was thyroid tumors from malaoxon in
15 Fischer 344 rats. That was one of the things that was
16 sort of highlighted, although the NTP did -- in their
17 reevaluation did consider those equivocal.

18 In the second study on malaoxon, the newer
19 study, the CARC is silent about thyroid as an endpoint.
20 I mean, they discuss leukemia. What were the results
21 with thyroid from malaoxon in the new study? I'm sure
22 it's in this pile of documents somewhere. But since that

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1 was presumably a finding that prompted a reexamination of
2 malaoxon, it might be useful to at least state what that
3 result was. Presumably there were no increases.

4 DR. DEGEORGE: Yeah.

5 DR. COPLEY: Yeah.

6 DR. ROBERTS: You might want to state that
7 explicitly or kind of give us a feeling for what happened
8 there.

9 DR. COPLEY: Do we have that DER? The malaoxon
10 DER? Okay. There was no treatment related increase.
11 But you're right. We could put that in, making it an
12 obvious statement saying there was no increase.

13 DR. DEMENTI: Wasn't there a slight numerical
14 increase?

15 MR. LEWIS: Please identify yourself and speak
16 into the microphone.

17 DR. DEMENTI: I seem to recall there was a
18 slight numerical increase.

19 DR. THRALL: Dr. Williams?

20 DR. WILLIAMS: Gary Williams. I would like to
21 hear FDA's evaluation.

22 DR. THRALL: Dr. DeGeorge?

1 DR. DEGEORGE: Thank you, Gary. Actually, we
2 have not completed our report on this. We had our
3 carcinogenicity assessment committee meeting a while ago,
4 and we are evaluating in relation to a product for acute
5 infrequent use. So there are some different issues in
6 terms of how risk management decisions might be reached.

7 But we would not -- as I just said, we would
8 look at not just the existing studies or the most recent
9 study, but in fact look at those findings in light of the
10 other findings justifying, perhaps, that the doses
11 originally selected were appropriate and should be
12 considered in the analysis.

13 We would not -- and, again, I can't speak about
14 the specific findings in the sense of telling you that we
15 think this tumor is significant or we think this tumor is
16 not significant. I'm just not free to do that at this
17 point.

18 But we would look at the toxicity, for example,
19 in liver in some of those findings and say that that does
20 play into the role for potential tumorigenic responses.
21 We would look at the effects on liver and consider
22 whether or not, as Dr. Gaylor pointed out, those might

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1 actually be related to particular thyroid effects and not
2 necessarily a consequence of direct treatment with the
3 product on the thyroid.

4 And then we would look at the genal toxicity
5 data, or absence of genal toxicity information, and
6 conclude that there may not be a risk for acute use based
7 on that kind of an assessment.

8 So I really can't go into the specifics. If you
9 want to try to go through every tumor, I don't think I
10 could go through it for you and give you a definitive
11 answer. I can only tell you what our approach would be,
12 that we do not look at tumor findings in organs in which
13 there is excessive toxicity, particularly if that organ
14 is a target site for the toxicity, unless we see a trend
15 in lower doses where that toxicity is not so obvious and
16 where the tumor findings would not be attributable to
17 that endpoint of the toxicity itself.

18 I don't know if I can be any clearer about it
19 than that.

20 DR. THRALL: Dr. McConnell?

21 DR. MCCONNELL: Yeah. I had the same comment,
22 but since you've given me the mic, I have another one.

1 Could you briefly go over with us the metabolism of
2 malathion. Is it primarily in the liver, or is it in all
3 tissues, or what?

4 DR. DEMENTI: That's a very complicated subject.
5 We do have a metabolism study, and I don't have that with
6 me. But I can tell you that one of the metabolic
7 concerns that I have is the comparison between the liver
8 metabolism and that in the nasal tissues. But there is
9 good indication that there are carboxyl esterases in the
10 nasal tissues, and there is good reason to think there
11 may be a similar toxicological effect in the nasal
12 tissues as in the liver.

13 Malathion is metabolized malaaxon, which is the
14 active cholinesterase inhibitor. There are carboxyl
15 esterases in the blood stream and in the liver, which
16 detoxifies malaaxon by cleaning off the two carboxyl
17 groups so that they no longer bind the cholinesterases.
18 And there are other various metabolites. I don't have
19 all of them at my fingertips.

20 DR. MCCONNELL: But in the totality of the
21 metabolism of a given dose of malathion, is most of it in
22 the liver? That's what I assume from my reading, but I

1 couldn't find any definitive statement in that regard.

2 DR. DEMENTI: I don't know the answer. I mean,
3 I don't think I can definitively answer that question.
4 ~~It~~ may be notable, just that I don't have the answer
5 right here.

6 MALE SPEAKER: One quick question on the
7 toxicity profile. I noticed in the clinical findings on
8 the rat study that there was yellow anal genital
9 staining as a clinical finding. Was this interpreted as
10 evidence of a cholinergic effect?

11 And my second question relates to OPs and
12 rodents again. At these extremely high concentration
13 levels on the dose feed study in mice, no clinical
14 effects are listed, even at the outset of the study. Is
15 this unusual or was this in the previous five bioassays?

16 I'm just curious. Would we expect to see
17 cholinergic effects, or is the clinical assessment in the
18 laboratory at a level that perhaps it couldn't be
19 detected in these rodents? Because at some point, we're
20 going to have to make a determination of at the non-
21 excessive dose selection are these animals under
22 substantial cholinergic stress, which I would interpret

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1 they may be. But it's going to be that issue on
2 cholinesterase levels of how to biologically interpret
3 cholinergic stress and setal cholinesterase levels.

4 DR. COPLEY: Marion Copley. I'll start off the
5 answer, and then I'll turn it over to Bill. But in a lot
6 of studies we don't see actual clinical signs now. They
7 don't do a lot of the routine neurologic testing that is
8 required in some of the special neurotoxicity studies.

9 But the other thing is that you may not see it
10 routinely in the animal, unless the animal is stressed
11 and goes through certain types of procedures that might
12 aggravate it. And then you would start seeing signs. So
13 just because we're not seeing clinical signs, I'm not
14 sure if that is a good indicator that the animal has no
15 cholinergic stress, since we're not actually evaluating
16 specifically for that.

17 Bill, do you want to --

18 DR. DEMENTI: I would say, you know, that if you
19 evaluated such neurological impairments as learning and
20 memory, that you probably found that these animals don't
21 perform normally. And also I think that --

22 MALE SPEAKER: Excuse me one second. Is that

1 your opinion, or have they done studies for that?

2 DR. DEMENTI: That's my opinion based upon --
3 not on malathion particularly. But based on my work with
4 cholinesterase I would say that's likely. Also, it's my
5 understanding that as cholinesterase inhibition
6 increases, there are adaptations of the nervous system.
7 Down regulation of cholinergic neurons, the cholinergic
8 receptors, that enable the animal to adapt to the point
9 where he looks fairly normal, you know, under extreme
10 levels of cholinesterase inhibition.

11 But if challenged pharmacologically, that animal
12 would be found to be flawed. He will have lost a lot of
13 his adaptability to cholinesterase inhibition. In other
14 words, it's my understanding that there are extensive
15 neurological changes that occur.

16 MALE SPEAKER: Yeah.

17 DR. DEMENTI: Even though the animal appears
18 normal.

19 MR. BURNAM: If I could add something, too,
20 Brian. If you could look at the sub-chronic neurotox
21 study of the rats, that's the usual specie of choice. We
22 don't have the mouse type of data for that same thing.

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1 They have the doses of 50, 5,000 or 20,000 parts per
2 million. And only at the highest dose, the 20,000 parts
3 per million which is over a thousand milligrams per
4 kilogram, were they getting cholinergic signs.

5 So it looks like the signs weren't really
6 kicking in until the very high doses. But we have
7 cholinesterase inhibition down at lower doses. That's
8 sort of -- we've seen everything. We've done a survey of
9 all the OPs. Sometimes you see the signs just don't
10 happen. You have a lot of cholinesterase inhibition and
11 nothing going on with the signs. And then you have some
12 other cases where you're getting signs, and like Marion
13 said, sometimes you have to challenge the animal to see
14 these things.

15 DR. DEMENTI: Often a precipitous decline in
16 cholinesterase will elicit -- to a certain level
17 inhibition will elicit clear signs that don't appear with
18 a gradual decline in cholinesterase because of the
19 adaptation that takes place in a gradual setting.

20 DR. THRALL: Dr. Williams?

21 DR. WILLIAMS: Gary Williams. Yes. I have a
22 couple of questions about the malaoxon studies. First

1 off, is malaoxon a commercial product?

2 DR. DEMENTI: No.

3 DR. WILLIAMS: No.

4 DR. DEMENTI: Um -- no.

5 DR. WILLIAMS: Okay. What was the degree of
6 purity of the malaoxon that was used in these studies?

7 MR. BURNAM: We should have that here.

8 FEMALE SPEAKER: Could somebody explain to him
9 what malaoxon is?

10 DR. WILLIAMS: I know what it is. And I also
11 know that only 4 percent of malathion goes to malaoxon in
12 the rat.

13 DR. COPLEY: Right. That's true. And that
14 information is in slightly more detail in the cancer
15 document, which is your number one and your number two in
16 the package that you received. It has metabolism blurbs
17 in it. This was a 96.4 percent active.

18 DR. WILLIAMS: Okay.

19 DR. COPLEY: And there was -- it showed toxicity
20 and mortality at lower doses in the rat than malathion,
21 because you didn't get death until 8,000 in the
22 malathion, and here you're having deaths at 2,000.

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1 DR. WILLIAMS: Sure. Well, it's the
2 cholinesterase inhibition, right.

3 DR. COPLEY: Yes.

4 DR. WILLIAMS: Well, then the last question is
5 why was this study done? What was the thinking that it
6 was going to contribute?

7 MR. BURNAM : Normally for most of the OPs those
8 chemicals that have an auction analog, we do not ask for
9 a separate study, because we assume if you test the
10 parent compound with the PES bond, the animal will
11 metabolize it to the auction analog. And the animal sees
12 the auction analog, so any effects of that will be taken
13 care of. Again, I think this is part of this
14 reproduction of the original NCI/NTP studies where they
15 used the malaixon.

16 DR. WILLIAMS: Okay.

17 MR. BURNAM: And, again, we accepted the mouse
18 malaixon, and we wanted them to repeat the rat malaixon.

19 DR. WILLIAMS: Okay. Then a question about the
20 mononuclear cell leukemia, because there seems to be some
21 concern over whether there is an increase in this tumor.
22 Now this tumor starts in the spleen, but then involves

1 eventually other organs. And that is often used as an
2 indicator of the extent of the disease.

3 Do you know whether the mononuclear cell
4 leukemia was confined to the spleen in the treatment
5 groups? Did they involve more other tissues than in the
6 controls?

7 DR. COPLEY: They were in other organs. And
8 I'll tell you what. I saw in the report -- and it was
9 difficult to interpret to a large extent. In a lot of
10 the animals that died with mononuclear cell leukemia --
11 actually most of them -- the pathologist attributed death
12 to mononuclear cell leukemia, which from what I can tell
13 from talking to other pathologists is frequent. If you
14 see mononuclear cell leukemia in the animal, particularly
15 if it's in several organs, and you don't have another
16 obvious cause, then you put down mononuclear cell
17 leukemia as the cause of death.

18 And as far severity -- as far saying the fact
19 that it caused death means an increase in severity, I
20 called several pathologists and I read several articles,
21 and wasn't able to find anything that really indicated
22 that there was any confidence in that, and the severity

1 staging was not done on this.

2 DR. WILLIAMS: Okay.

3 DR. THRALL: Gene?

4 DR. MCCONNELL: Yes.

5 DR. THRALL: Dr. McConnell?

6 DR. MCCONNELL: These two studies, the malathion
7 and the malaaxon, were they done in the same laboratory
8 and in a contemporary fashion?

9 DR. COPLEY: Okay. Malaaxon was done --

10 DR. THRALL: Dr. Copley?

11 DR. MCCONNELL: Yeah, but were they contemporary
12 to each other, do you think?

13 DR. COPLEY: They were --

14 DR. THRALL: Dr. Copley?

15 DR. COPLEY: They were within two years of each
16 other.

17 DR. MCCONNELL: Why I ask that question was that
18 in the malathion study, Dr. Williams, the incidence in
19 the controls was 42 percent. And if that were in the
20 malaaxon, of course, we wouldn't be discussing it.

21 DR. THRALL: Dr. Dementi?

22 DR. DEMENTI: Yes. I had a response to the

1 question Gary Williams had about leukemia. I looked at
2 the pathology sheets from the malathion study, and
3 according to my observation there was a general tendency
4 for the more pervasiveness of leukemia in the animals
5 that were diagnosed as having died as leukemia being the
6 cause of death.

7 In other words -- and I did talk with the
8 pathologist at NTP myself, who is an expert in the field.
9 And he said, you know, that pervasion into the liver, the
10 lung and so forth would support diagnosing that as the
11 cause of death, and also as an assessment of the
12 severity. And there was in this study. The obvious
13 tendency would be for there to be a more severe response
14 among animals that were diagnosed as having died from
15 leukemia.

16 DR. THRALL: Yes, Dr. Chen?

17 DR. CHEN: Yeah. I have kind of two statistical
18 questions. The first one is the leukemia. That's on
19 page 48. And you have a table of kind of the cause of
20 death information, and also, too, an analysis of time to
21 first tumor in different groups. An average of the
22 tumors in the different groups.

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1 Have you conducted the Peto fatal tumor
2 analysis?

3 DR. COPLEY: The first row on the table, a Peto
4 analysis was done on that row.

5 DR. CHEN: But those on prevalence test.
6 Usually the prevalence test, we kind of assume tumor is
7 not cause of death.

8 DR. COPLEY: But in this case -- okay.

9 DR. CHEN: Tumor is the cause of death. So one
10 of my questions is, have you conducted cause of death
11 test?

12 MR. BURNAM: Yes, they did.

13 DR. CHEN: And what is the P value?

14 MS. BRUNSMAN: Laurie Brunsmann. The only test
15 that we ran on this was the Peto Prevalence Test with the
16 assumption that the animals were in fact, you know, dying
17 from this mononuclear cell leukemia. But actually the
18 fatal test, I'm not familiar with it. What exactly are
19 you referring to?

20 DR. CHEN: Okay. The Peto Test, as I said, has
21 two parts. One is for incidental analysis, which assumes
22 tumor is not cause of death, or the prevalence test. And

1 the other part is called the fatal tumor analysis. It's
2 equivalent to the lab table test or Cochran Test.

3 And so if tumor is the cause of death, what
4 ought to be done would be assume tumor is the cause of
5 death and then do the Peto test. And it will give you
6 equivalent to the Cochran Test or lab table test.

7 MS. BRUNSMAN: The analyses were run with taking
8 the time of death into consideration. Is that your
9 question?

10 DR. CHEN: Yes.

11 MS. BRUNSMAN: Yes.

12 DR. GAYLOR: Dave Gaylor. There is more to it
13 than just taking the Peto fatal tumor test. It's based
14 on the Ararch (phonetic) Monograph that was published in
15 1980. And the NTP quite often runs two tests. If they
16 don't know the cause of death, they run it assuming
17 they're all incidental tumors or they're all fatal
18 tumors. But now they're using a Poly-3. A so-called
19 Poly-3 analysis.

20 So it doesn't sound to me like you've conducted
21 a test that takes into account the animals that are at
22 risk properly. You have done what's called the fatal

1 tumor analysis.

2 DR. THRALL: Dr. Gaylor, could you speak up a
3 little bit?

4 DR. GAYLOR: All you've done is a prevalence
5 test assuming they are incidental tumors, correct? We
6 don't have anything other than that?

7 MS. BRUNSMAN: That's correct.

8 DR. GAYLOR: Okay.

9 DR. CHEN: And it seems to me, according to the
10 kind of percentage of increase, if you do the Peto fatal
11 tumor analysis, you will get a very highly significant P
12 value.

13 MS. BRUNSMAN: For?

14 DR. CHEN: For MCL for the cause of death.

15 MS. BRUNSMAN: Are you talking about the MCL
16 incidence itself?

17 DR. CHEN: No. I'm talking about cause of
18 death.

19 MS. BRUNSMAN: Oh, that's correct.

20 DR. CHEN: Yeah. If you do the Cochran test or
21 Peto fatal tumor test, you will get a highly significant
22 P value.

1 DR. COPLEY: You need to make -- you need to
2 make sure that you understand what that -- oh, this is
3 Marion Copley. What that row is. That row is -- and I
4 can't read it. MCL is the cause of death only with
5 animals that were diagnosed as having MCL.

6 DR. CHEN: Yeah.

7 DR. COPLEY: That's not animals with the cause
8 of death with MCL, period. It's only the animals that
9 had MCL as a diagnosis that caused the death. Of all the
10 animals diagnosed with it, there were several animals
11 that the pathologist attributed to other causes, and
12 those were subtracted from this thing.

13 (END OF TAPE 2, SIDE A)

14 DR. CHEN: -- which MCL is not cause of death.
15 Then do the prevalence test and combine together with the
16 time two tumor test. And each one give you a different
17 individual P value.

18 DR. COPLEY: Well, wouldn't you consider all the
19 animals at risk, not just the animals that had the tumor?

20 DR. CHEN: Yeah.

21 DR. COPLEY: What that one does, it only
22 considers the animals that had the tumor, and which ones

1 of those animals that had the tumor died from the tumor.
2 It's not looking at the total population of animals that
3 were tested.

4 DR. CHEN: Yeah. I know that. The point is
5 that it seems to me they're not conducting the Peto fatal
6 tumor test. And maybe what you say -- maybe I'm
7 guessing. But if you just do the prevalence test, I
8 think the result was what you have.

9 DR. COPLEY: Yes.

10 DR. CHEN: But my point is that they should have
11 a prevalence test since some of the tumors does cause the
12 death.

13 MS. BRUNSMAN: Laurie Brunsman again. The
14 prevalence test was run on the first row there, the MCL
15 where you have the number of tumors over the number of
16 animals at risk. We did not run the fatal tumor, as you
17 are suggesting, on that second line there, the MCL is
18 cause of death over the number with MCL. It seemed
19 obvious, I suppose, that there was a very significant
20 increase there, if you look at those ratios on the bottom
21 line, the percent of rats with MCL dying from MCL.

22 DR. CHEN: Yeah. I did not mean you just based

1 on second. They're based on the whole group when they
2 are still alive. That's the Peto's. They're based on
3 the whole animals when still alive.

4 MS. BRUNSMAN: Right. And that second and third
5 rows aren't based on that.

6 DR. CHEN: Okay.

7 MS. BRUNSMAN: Those are just visualization of a
8 point that was trying to be made.

9 DR. CHEN: Okay. I have second question about
10 page 46, testicular tumor. Slide 46, sorry. About the
11 interpretation of the Peto test. The way what Peto test
12 would be the Peto Prevalence Test. Usually in toxicology
13 study what we want to test would be whether the tumor
14 incidence -- whether there is different tumor incidence.

15 Also, want to know whether the chemical kind of
16 reduced the latency period. And even testicular just is
17 kind of the end of study. Maybe four animals get 100
18 percent tumor. But the Peto test would give you a
19 different -- kind of tell you like some group have a
20 different time for tumors.

21 So what slide 46 tells you, the trend test is
22 highly significant. It tells you the test animal, the

1 test group, the time to tumor onset. They can show even
2 it does not have internal sacrifice, because the animal
3 during the period dying during the experiment, are they
4 (inaudible) animal where kind of serve the same purpose
5 of the sacrifice?

6 DR. COPLEY: I don't think so, because if all
7 the animals have the tumor at 18 months -- this is not a
8 fatal tumor and you don't diagnose it until the animal is
9 sacrificed. So if all -- this is an exaggeration. If
10 all the animals had the tumor at 18 months, but the high
11 dose animals all died at 19 months, you would see a
12 positive here because all of the animals would see it at
13 19 months in the high dose, and none of the others would
14 be seen until 24 months.

15 DR. CHEN: The Peto test would tell you --

16 DR. COPLEY: It wouldn't tell you, because you
17 don't have any idea when the animals are getting the
18 tumor. You just know when you're seeing it. And
19 something else is killing these animals.

20 DR. CHEN: Right. Because something else
21 killing the animal. So the way it would be like a
22 different time interval would become kind of the time

1 would be used as the denominator where harming an animal
2 already at risk. So those -- the animal died during the
3 course of experiment. It would serve you as kind of a
4 denominator for the tumor rate during the course of
5 experiment period.

6 DR. COPLEY: That doesn't make sense to me. I
7 don't understand.

8 DR. THRALL: All right. Well, let's move on.

9 DR. CHEN: Okay.

10 DR. THRALL: Dr. DeGeorge, did you have a
11 comment or a question a while ago?

12 DR. DEGEORGE: Well, I just going to comment
13 that there are others -- David made the point about the
14 Poly-3 test, which does not require any analysis of
15 whether or not the tumor was fatal or incidental. And
16 that is a test which the NTP usually uses now, because
17 you don't have to make a decision about the tumor
18 incidence and whether it was fatal. And you can do the
19 analysis that way and you don't have to worry about the
20 pathologist.

21 DR. THRALL: All right. If there are no other
22 questions? There is one other question. Dr. Williams?

1 DR. WILLIAMS: Well, yeah, a question about
2 these interstitial cell tumors in case we have to
3 deliberate on them later. It would be informative to
4 know how many of these were apparent grossly and how many
5 are only microscopic diagnoses. Because the criteria for
6 this tumor is really, I think, minimal. The STP criteria
7 -- they classify a tumor as a lesion the size of three
8 tubules. And a lot of us think that's just hyperplasia.

9 So I don't expect you to produce these numbers
10 now, but if you could have them for us later, that might
11 be helpful.

12 DR. THRALL: All right. We need to make a
13 decision here. We can go on and have Dr. Dementi's
14 presentation now, which will last about an hour, or we
15 can break for lunch now for an hour and reconvene earlier
16 than scheduled. And probably I should ask Dr. Dementi
17 what he prefers.

18 DR. DEMENTI: I would prefer getting it over
19 with now.

20 DR. THRALL: All right.

21 DR. DEMENTI: But I will go along with whatever
22 you decide.

1 DR. THRALL: All right. Dr. McConnell?

2 DR. MCCONNELL: Yeah. I think that Dr.
3 Dementi's presentation is going to generate a lot of
4 questions, even for clarification, and I'm not sure an
5 hour will be fair to him. And I certainly wouldn't want
6 to cut him off in the middle and then go to lunch and
7 come back. That's just my own view.

8 DR. THRALL: All right. In that case, if there
9 are no other questions for clarification -- just a
10 moment. Dr. DeGeorge, you're leaving. Do you have
11 anything else to add at this time?

12 DR. DEGEORGE: Well, I can stay until 1:45,
13 which is -- so I don't know. That was my comment, that I
14 will be back, but I won't be here. If you're back, I
15 wouldn't mind commenting a little bit.

16 But I have to point out that from the
17 pharmaceutical perspective, we are not using technical
18 grade material. The pharmaceutical perspective is
19 pharmaceutical grade material, which is greater than 98
20 percent pure. So there are some differences in the
21 quality of the material that is being used in the
22 different applications.

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1 DR. THRALL: All right. In that case --

2 FEMALE SPEAKER: (Inaudible).

3 DR. THRALL: No, because that doesn't have
4 anything to do with the carcinogenicity.

5 FEMALE SPEAKER: (Inaudible).

6 DR. THRALL: And he will be back after lunch for
7 a short time. So let's plan on reconvening after lunch
8 at 12:40.

9 (Whereupon, a lunch recess was taken.)

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AFTERNOON SESSION

1
2 DR. THRALL: All right. We will reconvene and
3 we will now have a presentation by Dr. Brian Dementi on
4 an alternative approach.

5 DR. DEMENTI: Good afternoon. I have a prepared
6 statement here that I'll be reading to you. I regret
7 having to read it to you, but to keep on track, we have
8 to do it that way.

9 In announcing this SAP meeting to consider the
10 CARC's assessment of the cancer database for malathion,
11 management offered me the opportunity to express my
12 views, which I couldn't turn down. As a toxicologist I
13 have had a principal role in reviewing and presenting the
14 database to the committee. I found that I disagree with
15 many of the conclusions of the committee and have made my
16 concerns clear in my comments on several draft CARC
17 reports and memoranda to the CARC Chairman. The office
18 has agreed to include these various comments as
19 attachments to the final CARC report.

20 I have developed a written presentation for
21 today's meeting. That document, dated July 27th, was
22 submitted to the Panel members earlier this month. It

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1 best represents my views as I have been able to assemble
2 them in a constricted time frame. That written
3 statements and the attachments to the CARC report
4 represent my views, only part of which I am able to speak
5 to at this moment.

6 I should say that much of the disagreement
7 between myself and the committee centers on the
8 interpretation of information, including statistics
9 before us, and over the language in which the various
10 findings are couched in the CARC reports. We're all
11 evaluating the same data. It is how the data should be
12 interpreted and represented that is at issue.

13 During this entire period of review of data
14 submissions, I have taken the opportunity to study many
15 authoritative publications pertinent to interpretation of
16 data derived from cancer bioassays, and have engaged
17 experts in discussions of interpretation of specific
18 neoplastic findings.

19 Principal documents I have employed as guides in
20 the interpreting process include EPA's draft cancer
21 assessment guidelines; the White House, Office of Science
22 and Technology Policy document entitled, Chemical

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1 Carcinogens: A Review of the Science and the Associated
2 Principles; the Interagency Regulatory and Liaison Group
3 report entitled, Scientific Basis for Identification of
4 Potential Carcinogens and Estimations of Risk, and
5 others.

6 I have also read many publications focussed on
7 the understanding and interpretation of more specific
8 neoplastic response findings at issue in the malathion
9 database.

10 Am I speaking loud enough?

11 MALE SPEAKER: Yes.

12 DR. DEMENTI: A major concern has to do with the
13 science of pathology itself. I stand amazed over the
14 differences of opinion expressed by different
15 pathologists examining the very same slides. We have
16 expert pathologists performing the original diagnoses of
17 lesions. We have expert pathologists performing
18 pathology peer reviews. And then we have expert
19 pathologists on PWGs, all looking at the same slides.
20 For example, one nasal tissue section, three different
21 diagnoses were rendered on the very same slide.

22 Among lesions examined by peer review or PWG, in

1 the case of the male mouse liver, of an original 16 mice
2 diagnosed with liver carcinoma, all in dose groups only,
3 eight were downgraded to adenomas. In the rat pituitary,
4 sufficient numbers of carcinomas were downgraded to
5 adenomas by peer review to change the interpretation of
6 the neoplastic response from positive to negative.

7 In female rats, the original pathology
8 assessment identified five carcinomas among dose groups
9 only, with a peer review confirming four of these to be
10 carcinomas, only to have the subsequent PWG downgrade all
11 five carcinomas to adenomas, while also downgrading six
12 of the eight original adenomas to hepatocellular
13 alterations. Those of us who evaluate this data have no
14 way of knowing whether peculiarly restrictive diagnostic
15 criteria were used in these cases, or how historical
16 control lesions would fair under review of the same PWG.

17 Furthermore, it is only the initially positive
18 neoplastic responses -- that is, those that pose a
19 potential problem for the cancer classification of
20 malathion -- that are subjected to peer reviews and/or
21 PWG assessments. We naively accept that all originally
22 diagnosed negative findings are truly just that, absent

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1 any further inspection. In the overall pathology
2 assessment, there is in my opinion a bias, perhaps
3 unwitting, directed against positive findings.

4 Now under principles of interpretation, I would
5 at this point like to focus on certain principles of
6 interpretation as obtained from authoritative sources,
7 and follow that with an example of the application of
8 these principles in the interpretation of one particular
9 malathion data set. Time does not permit me to discuss
10 interpretation of the neoplastic findings in the
11 database, although these are discussed in my July 27th
12 written presentation.

13 In all three of the recent cancer bioassays,
14 CARC has concluded that certain of the high dose levels
15 were excessive, and has declared certain lower dose
16 levels in each case to be acceptable. Indeed, the
17 differences of opinion between myself and the committee
18 center on the questions of whether the studies are
19 acceptable, and whether neoplastic findings should be
20 considered acceptable even if dosing is considered
21 excessive, and what constitutes an acceptable negative
22 study.

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1 Certainly one essential element in interpreting
2 cancer bioassays is that of the definition of carcinogen.
3 Among many authoritative sources I have read, while the
4 assessment of neoplasia may be discussed at length, I do
5 not often find a definition of carcinogen. OSTP employs
6 the following language. It's up there.

7 A chemical carcinogen may be a substance which
8 either significantly increases the incidence of cancer in
9 animals or humans or significantly decreases the time it
10 takes a naturally occurring spontaneous tumor to develop
11 relative to an appropriate background for control data.
12 Either phenomenon is said to represent the effects of a
13 carcinogen.

14 In my evaluation of the malathion database, I
15 have been conscious of both aspects of evidence that
16 would indicate a neoplastic response under this
17 definition, namely increased tumor incidents and evidence
18 of enhanced stage of tumor development as characterized
19 by such factors as decreased latency, progression, tumor
20 multiplicity, malignancy, tumor size and macroscopic
21 pathology. The case for a neoplastic finding is
22 obviously more compelling when both types of evidence are

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1 present.

2 In my letter of November 12, 1999, to the
3 committee, which is Attachment 18 to the CARC report, I
4 set forth certain principles of interpretation of cancer
5 bioassays that appear to have application in this case.
6 Particularly relevant from among quotations cited in
7 Attachment 18 are the following.

8 The EMTD -- and this is a quote now -- the
9 estimated maximum tolerated dose, is determined on the
10 basis of pre-chronic tests and other relevant
11 information. If the test reveals that the EMTD is too
12 high to meet the conditions defined here, positive
13 results -- I note that positive results -- obtained above
14 the EMTD are acceptable as evidence of carcinogenicity
15 unless there is convincing evidence to the contrary.

16 Alternatively, negative results obtained above
17 the EMTD are considered inadequate unless particularly
18 strong and specific scientific reasons justify their
19 acceptance as negative. Positive results obtained at or
20 before the EMTD provide evidence of carcinogenicity.

21 I found that in very important cases, CARC's
22 decisions run counter to this interpretation in

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1 discounting positive evidence at doses considered
2 excessive, while accepting as negative the absence of or
3 less remarkable finding of doses considered excessive.

4 ----- In negative studies the absence of neoplastic
5 findings as excessive doses does not mean the neoplastic
6 effect would not be seen at lower doses considered
7 acceptable. Early mortality resulting from excessive
8 toxicity may cut short full expression of certain tumor
9 types, particularly those which are later cured, such as
10 leukemia among males in the present malathion F344 rat
11 study, particularly exemplified at the 12,000 ppm dose
12 level where incidence dropped to but one in 55 animals.

13 Also, with increasing dose of a carcinogen there
14 may be an optimal dose of tumor induction depending upon
15 each tumor type. Yet like most cells, neoplasm through
16 tox...free environments for them nurture such that would
17 increase in dose, the neoplastic response may be
18 compromised.

19 Now slide seven. This is another quotation.
20 Animal studies are conducted at high doses in order to
21 provide statistical power, the highest dose being one
22 that is minimally toxic at the maximum tolerated dose.

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1 Consequently, the question often arises whether the
2 carcinogenic effect at the highest dose may be a
3 consequence of cell killing with compensatory cell
4 replication or general physiological disruption rather
5 than inherent carcinogenicity of the test agent.

6 There is little doubt that this may happen in
7 some cases, but skepticism exists among some scientists
8 that it is a pervasive problem. If adequate data
9 demonstrate that the effects are solely -- and I
10 emphasize that -- solely the result of excessive toxicity
11 rather than carcinogenicity of the tested agent per se,
12 then the effects may be regarded as not appropriate to
13 include an assessment for the potential of human
14 carcinogenicity of the agent. And that's from EPA's 1999
15 guidelines.

16 In my view, several positive neoplastic findings
17 occurring at the higher doses in these studies have been
18 discounted without evidence that the effects were in
19 fact, quote, solely the result of excessive toxicity.

20 And then another quotation, slide number nine.
21 A negative study is ordinarily accepted by regulatory
22 agencies if survival of all groups per sex per dose is no

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1 less than 50 percent at 104 weeks for rats. That's from
2 the Office of Science and Technology Policy.

3 I should note that negative findings in dose
4 groups where survival is less than 50 percent should not
5 be accepted as negative, nor used to discount positive
6 findings at lower doses considered acceptable. This has
7 particular application to interpretation of neoplastic
8 responses among males in the F344 rat malathion bioassay,
9 where survival was but 26 at 6,000 ppm and zero percent
10 at 12,000 ppm.

11 In my view, to the extent that CARC concludes
12 the malathion F344 rat study to be a negative cancer
13 bioassay, this study should be considered unacceptable,
14 principally due to the survival problem and possible
15 competing toxicity.

16 Now I would like to go through an example of how
17 I apply these principles to one set of data, that of the
18 mouse liver tumor data. Historically, based upon
19 equivocal hepatocellular and neoplastic response in the
20 1978 NCI mouse bioassay, the agency required a new study
21 at the same dose levels, 8,000 and 16,000 ppm, in the
22 same strain of males, B6C3F1.

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1 Liver tumor incidence from that earlier NCI
2 study are presented in the following slide. That is from
3 the old NCI study. NCI concluded the pair-wise
4 comparison for males at 16,000 ppm -- P equals .031 --
5 was not significant by their criterion of significance,
6 which they used as P equals .025.

7 While HED concluded it was significant by the
8 agency's criterion, which is .05, the trend test was also
9 positive, .019. You should note the absence of any
10 evidence of a positive response among females. And
11 that's a very notably finding.

12 Now in the new required study, it is clear there
13 were positive neoplastic findings in both sexes at both
14 of the high test dose levels, 8,000 and 16,000 ppm.
15 Particularly noteworthy is the remarkable 84 percent
16 response in females at 16,000 ppm, as well as the nearly
17 tenfold increased incidence at 8,000 ppm, as contrasted
18 with the absence of response in the NCI study at both
19 doses. We have no explanation for this disparity for
20 females, which is of considerable concern to me.

21 Parenthetically I should note that the NCI study
22 was an in-life study conducted for 95 weeks where dosing

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1 was for 80 weeks. The animals were then allowed to live
2 for 15 additional weeks, while the current study was a
3 protocol 18 month, 78 week study. Also, different
4 malathion was used in the two studies: American Cyanamid
5 malathion was used in the NCI study, while Kemy Nova
6 malathion was employed in the recent study.

7 In the original study submissions, statistically
8 significant increases in combined tumor incidence were
9 seen in males at 100 ppm, at dose level incorporated in
10 search of a no effect level for cholinesterase
11 inhibition, 8,000 and 16,000 ppm dose levels, but not at
12 the 800 ppm dose level, though there was a greater than
13 four-fold numerical increase of tumor incidence at that
14 level versus the control. The tumorigenic response in
15 males was characterized by a highly significant trend
16 test, .000.

17 In consideration of the apparent and perhaps
18 questionable neoplastic response in the low dose male
19 group, the agency required a PWG be performed on the male
20 histopathology.

21 And now we're going to slide 13. Resulting from
22 the PWG, the male histopathology tumor incidence remained

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1 highly significantly increased at 8,000 and 16,000 ppm
2 levels, but no longer so in the opinion of the committee
3 -- that is the SAP committee -- at 100 ppm, where the P
4 value was .075 for pair-wise. Nor was it significant at
5 800 ppm. The trend test remained highly positive if P
6 was .000.

7 The principle reason accounting for the lack of
8 significance at the .05 level for the 100 ppm group
9 following the PWG was the increased incidence of adenomas
10 in the control, from one in 54 to four in 54, while the
11 actual number of mice affected in the 100 ppm group
12 remained unchanged at 19 percent -- 10 in 54.

13 In a very important decision, CARC concluded
14 that the top two dose levels were excessive and
15 discounted use of the neoplastic findings at these doses
16 in quantitative risk assessment. The CARC also concluded
17 findings at 100 ppm to be negative, and the 800 ppm dose
18 level to be an acceptable dose level for this study.

19 So in effect, post-PWG this study has for all
20 practical purposes been determined by CARC to be an
21 acceptable negative mouse carcinogenicity bioassay. Now
22 I have many problems with that interpretation.

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1 By contrast, in my view this study should be
2 considered acceptable as providing positive evidence of
3 carcinogenicity across the full dose range and should be
4 employed as such in the risk assessment.

5 I would proceed at this point to present my
6 rationale. Okay. Now first I will be discussing the
7 rationale for not discounting the high dose group
8 findings, the first being based upon cholinesterase
9 inhibition.

10 And now if you could put up the next slide, the
11 cholinesterase data. This is the cholinesterase data
12 from the two year study. I mean -- yeah, from the 18
13 month study.

14 The de facto discounting for risk assessment
15 purposes of the remarkable tumorigenic responses in both
16 sexes at the top two dose levels, based upon an argument
17 of excessive dosing as evidenced by pronounced inhibition
18 of cholinesterase in the absence of cholinergic clinical
19 signs, increased mortality or other evidence that MTD was
20 significantly exceeded, is unacceptable in my view.

21 This is, in my opinion, without scientific
22 justification, particularly at 8,000 ppm where brain

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1 cholinesterase inhibit was but 23 percent in males and 20
2 percent females, not statistically significant and very
3 close to the limit of detection of cholinesterase
4 inhibition under current methodology.

5 It cannot be said with certainty that brain
6 cholinesterase was even inhibited in either sex at 8,000
7 ppm, but if so, it was marginal. In my witness, brain
8 cholinesterase inhibition of 37 to 43 percent, as
9 recorded for the 16,000 ppm group, does not qualify as
10 severe or excessive for a cancer bioassay, particularly
11 in the absence of cholinergic signs.

12 Furthermore, there is no evidence that I am
13 aware of that high levels of inhibition of the blood
14 borne cholinesterase is alone. In the absence of
15 cholinergic clinical signs, it's particularly toxic.
16 That is, in the sense of exceeding an MTD for a cancer
17 bioassay.

18 In considering dosing as excessive, one should
19 also observe that in the same study at 800 ppm, plasma
20 and red cell cholinesterases in females were
21 significantly inhibited by 36 percent and 58 percent
22 respectively. One might ask, in CARC's experience what

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1 degree of cholinesterase inhibition qualifies as
2 excessive. One might ask, are there any guidelines.

3 Living organisms incorporate a host of enzymes
4 never evaluated in cancer bioassays. Are we prepared to
5 say that if any one of these should be discovered to be
6 severely inhibited, we would discount neoplastic findings
7 in the absence of clinical signs or increased mortality?
8 Obviously, we cannot assay all enzymes. And I maintain
9 there is no reason for singling out cholinesterase
10 inhibition for this purpose in the absence of cholinergic
11 clinical signs.

12 In my view, the discounting of the top dose
13 groups on the basis of cholinesterase inhibition, the
14 blood enzymes no less, represents an abuse of the
15 cholinesterase data and consequently runs counter to the
16 agency's responsibility for the protection of the public
17 health in removing the study from a risk assessment role.

18 Earlier during the course of consideration of
19 the database, CARC calculated a Q* for cancer based upon
20 the tumor incidence for females in the study, only to
21 drop this from its final report, now proceeding without
22 any quantitative risk assessment.

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1 And this is parenthetical. I should acknowledge
2 there was other evidence that the MTD was somewhat
3 exceeded at 8,000 and 16,000 ppm. Mainly decreased body
4 weight, increased liver weight and liver hyperplasia.
5 Yet there was no accompanying liver necroses or other
6 liver histopathology. In my view these reasons were not
7 of sufficient magnitude or importance to justify
8 discounting the positive neoplastic findings, even if the
9 MTD was thus exceeded.

10 Also, in assessing the effects in both sexes at
11 the top two dose levels, these should not be lumped
12 together as the effects in females at 8,000 ppm were less
13 remarkable although the neoplastic response was clearly
14 positive for that group. At 8,000 ppm among females,
15 body weight decrease was but 9.7 percent. There was no
16 liver weight increase, and liver hyperplasia, although
17 present, was of a low order on the scale. One point
18 seven was its rate.

19 Again, in my view these effects do not rise to a
20 level sufficient to discount the neoplastic responses of
21 the top two dose levels, and particularly so in the case
22 of females at 8,000 ppm.

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1 And now the next slide is concerning the
2 decision to discount positive neoplastic findings at
3 doses deemed excessive. I do not accept that the
4 positive findings at these doses should be discounted,
5 even if dosing could be accepted as excessive based on
6 cholinesterase inhibition.

7 Again, there was no increased mortality, no
8 clinical signs and no other reason to conclude, in the
9 words of EPA's guidelines as cited previously, that the
10 tumorigenic findings were due to anything other than the
11 tumorigenicity of the test material.

12 Furthermore, as cited earlier the IRLG says if
13 the test reveals that the EMTD is too high to meet the
14 conditions defined herein, positive results obtained
15 above the EMTD are acceptable as evidence of
16 carcinogenicity unless there is convincing evidence to
17 the contrary. In my view there is no evidence to the
18 contrary in this study.

19 So in my view the bottom line is that
20 cholinesterase inhibition is not a legitimate basis for
21 discounting the high dose findings, particularly so for
22 the 8,000 ppm dose level. But even if dosing were

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1 accepted as excessive for that reason, then in this case
2 the liver neoplastic findings nonetheless constitute
3 acceptable positive evidence of carcinogenicity for use
4 in risk assessment.

5 I would now like to talk a little about my
6 rationale for accepting the low dose finding as real. So
7 slide 16. All right. I'm going to speak of two things.
8 The first aspect concerns the increased enzymes. You
9 remember the OSTP definition of incidence and development
10 -- tumor development. So under the topic of increased
11 enzymes, concerning the first aspect of the OSTP
12 definition, I consider as particularly persuasive
13 evidence of a positive neoplastic response at the lowest
14 dose level, 100 ppm, in male mice.

15 Slide 17. The rationale is essentially a
16 conservative one as the agency is expected to be
17 conservative. Even post-PWG the pair-wise comparison
18 equals .075 for this group, taken in concept with the
19 remarkable positive trend, 0.000, and indicates a
20 positive neoplastic response across all doses and should
21 not be discounted as real even in the statistical sense.

22 This conclusion takes into consideration

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1 quantitative evidence of a more remarkable neoplastic
2 response which is simply not factored into the
3 statistical analysis, such as multiple tumors in affected
4 animals in the low dose group versus the absence of
5 multiplicity in the control group.

6 And in this I'm seeking the help of our
7 statistician on the Board. What does our statistician
8 say when you have a P value of .075 and a trend of .000.
9 And I feel comfortable myself saying that is sufficient
10 reason to consider it real statistically.

11 Concerning the second aspect of the OSTP
12 definition, the rationale for concluding an earlier, more
13 advanced neoplastic response in the low dose group
14 consists of the following: (A), more advanced stage in
15 the elements of the natural history of neoplasia. So if
16 we could put up the next slide, the natural history of
17 neoplasia.

18 The scientific literature supports the concept
19 of the natural history of neoplasia for the development
20 of hepatocellular tumors, wherein the neoplastic response
21 proceeds through the three indicated stages. I do not
22 have time to discuss this concept further.

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1 In the mouse study before us, arguably the
2 response from the control group is in the hepatocellular
3 focus to abnormal stage, while the response in the low
4 dose group is in a more advanced adenoma to carcinoma
5 stage of development, explained as follows.

6 The PWG upgraded and initially diagnosed three
7 hepatocellular foci plus one adenoma to four adenomas in
8 the control. Debate among pathologists centered upon
9 whether these four lesions were foci or adenomas. The
10 study pathologist had identified three foci and one
11 adenoma. The reviewing pathologist had identified two
12 foci and two adenomas, while the PWG said there was zero
13 foci and four adenomas. Carcinoma was not identified or
14 debated in this control, to my knowledge.

15 While in the low dose group the discussion of
16 the PWG was focused on adenoma versus carcinoma
17 diagnoses, where two carcinomas were upgraded to adenoma
18 -- excuse me. Downgraded to adenoma, leaving eight mice
19 with adenomas and four with carcinomas, one, possibly
20 two, which had two carcinomas and the other two had an
21 adenoma in addition to the carcinoma.

22 In my view there is clear contrast between the

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1 control and the low dose group in terms of their relative
2 stage of advancing along this course in the natural
3 history of neoplasia, with the low dose group being more
4 advanced. Arguably the control group is in its infancy
5 in terms of neoplasia. The three adenomas, resulting
6 from upgrade of a hepatocellular foci, likely are small
7 and just emerging as tumors, given the conflicting
8 diagnoses and absence of further countermanding
9 information.

10 And so now I would like to go on to further
11 rationale and discuss the natural history of neoplasia.
12 Now (B), the presence of carcinomas. Carcinomas exceeded
13 the historical control in the database which is small and
14 inadequate. NTP's large database is for two year studies
15 and is useless in this case.

16 Carcinomas may be rare in 18 month mouse
17 studies, especially those that could survive the criteria
18 of this PWG. Recall that eight of the originally
19 diagnosed 16 carcinomas in dose groups only survived this
20 PWG. It is noteworthy that but a total of four
21 carcinomas exist in the entire historical control
22 database for the performing laboratory. We don't know

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1 what would happen to these carcinomas under the scrutiny
2 of the PWG in question. Since the historical control
3 dose diagnoses were from the same performing laboratory,
4 one might guess half of these would likely be downgraded.

5 Furthermore, in my view the historical control
6 group is virtually useless. The database is somewhat
7 old. It contains too few animals, in addition to not
8 having the benefit of characterization by this PWG. The
9 historical control incorporates but five study groups
10 consisting of a total of 205 mice. Under such
11 circumstances, the contemporaneous control clearly takes
12 precedent as controlling the interpretation of this
13 study.

14 There is also evidence of multiplicity in the
15 low dose group. That is, livers having more than one
16 tumor. There were four -- three and possibly four such
17 cases. Large tumors. The dimensions of lesions in the
18 low dose group was substantially larger than those in the
19 control group. Liver masses were identified
20 macroscopically in eight low dose group mice as opposed
21 to none in the control.

22 Male mice appear more responsive than females in

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1 both the NCI and the more recent studies, which is
2 somewhat supportive of a finding extending into the lower
3 dose range for males.

4 At one CARC meeting our consulting pathologist
5 said something to the effect that there is something
6 different about that low dose group, but I don't know
7 whether it's due to malathion. My response would be,
8 this is a controlled study to evaluate the effects of
9 malathion, and findings in dose groups should be
10 contributed to treatment absent a definitive explanation.

11 This has led me to suggest a possible change of
12 mechanism for neoplasia with a dose in this study. So if
13 we could put up slide 20, evidence for change of
14 mechanism.

15 There is an apparent positive dose response
16 across the control in the 800, 8,000 and 16,000 ppm
17 groups, suggesting a different mechanism of neoplasia in
18 this range versus that of the lower dose groups and the
19 presence of carcinomas in the low dose group, which are
20 absent in the control and in the 16,000 ppm dose group,
21 despite the latter group's 96 percent adenoma incidence,
22 plus multiplicity. In my view, this suggests that the

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1 high dose actually mitigates tumor progression.

2 Multiplicity involving benign and malignant
3 tumors, and multiplicity involving malignant tumors, it
4 ~~is~~ not unreasonable to consider that a different
5 mechanism of carcinogenicity operates across such a vast
6 dose range of 100 ppm to 16,000 ppm, which CARC has not
7 acknowledged.

8 The Pathology Working Group discounted carcinoma
9 in the lower dose range because of the absence at the
10 high dose, an argument which imposes -- in my view
11 imposes the condition of a single mechanism across all
12 doses. In my view, such reasoning presumes one mechanism
13 applies, which has not been established in any scientific
14 manner.

15 All right. Then the next point I would like to
16 discuss is the question whether the 800 ppm dose groups
17 should be considered acceptable. Slide 21.

18 In discounting the 8,000 and 16,000 ppm dose
19 levels as excessive, CARC characterized 800 ppm as
20 acceptable and thus declared the study acceptable.
21 However, to the extent the study is considered acceptable
22 based upon a conclusion that 800 ppm is an acceptable

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1 dose level, is problematical for the following reasons.

2 One, absent the top two dose levels, the power
3 of the study has been severely compromised. Acceptable
4 studies should incorporate at least three well spaced
5 dose groups with the highest dose being an MTD. The 100
6 ppm dose level is very low for malathion. For
7 comparative purposes the prevailing food tolerance is
8 eight part per million.

9 The 100 ppm level is essentially at the
10 interface of cholinesterase inhibition and was chosen in
11 the hope of identifying a NOEL for cholinesterase
12 inhibition. Such a low dose level likely, in my view,
13 would not otherwise be chosen for a cancer bioassay.
14 Furthermore, for malathion cancer testing, 800 ppm is not
15 that much higher and would not be suitable as an MTD. In
16 other words, the 100 and 800 ppm dose levels, if negative
17 for neoplasia, would not provide dose levels sufficiently
18 toxic to satisfy requirements for cancer bioassays.

19 The fact that a neoplastic response may not be
20 observed at these levels is that the test animal
21 population may be too small to detect low, but real
22 response, and is the reason for high dose testing, the

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1 results of which have been extrapolated to lower doses.
2 The 800 ppm is well below the limit dose claimed at the
3 CARC meetings to be about 7,000 ppm.

4 But by contrast, the limit dose is said to be 5
5 percent or 50,000 ppm in the draft cancer guideline. The
6 limit dose argument really should not apply in this case,
7 as 8,000 ppm especially, and 16,000 ppm is not -- are not
8 that out of range in terms of limit dose as variously
9 characterized.

10 The public deserves the benefit of a bioassay
11 that is sufficiently challenged. The EPA's
12 carcinogenicity testing guidelines require that
13 histopathology -- this is item four now. EPA's
14 carcinogenicity testing guidelines require that
15 histopathology be performed on all protocol tissues in
16 the control and high dose groups.

17 In my view, to the extent the dose level of an
18 existing high dose group is declared excessive and hence
19 neoplastic findings from that group are deemed useless
20 for risk assessment purposes, a lower dose level must
21 satisfy the role of a high dose group before the study
22 can be accepted.

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1 All tissues must be examined histopathologically
2 as required by OSTP's guidelines for the high dose group.
3 This was not done for any dose group below the 16,000 ppm
4 level in the mouse study. The liver was examined in all
5 groups, because it along with certain other select
6 tissues is required for all groups.

7 In summary, CARC concluded dosing was excessive
8 at the high dose levels, and in so doing discounted the
9 use of liver tumorigenic findings in risk assessment.
10 While affirming the 800 ppm as an adequate dose level,
11 the conclusion that dosing was excessive at the top dose
12 levels was based primarily upon cholinesterase
13 inhibition.

14 In contrast to this conclusion, I do not support
15 the use of cholinesterase inhibition in and of itself as
16 sufficient reason to conclude dosing was excessive, and
17 therefore maintain as acceptable for use in risk
18 assessment the liver neoplastic responses at the higher
19 dose levels.

20 Secondly, even if dosing were excessive, I
21 maintain that in accordance with the principles I have
22 cited here, that positive results are acceptable as

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1 evidence of carcinogenicity and should not be discounted
2 for use in quantitative risk assessment.

3 The CARC concluded there was no effect in terms
4 of liver neoplasia in the low dose group based upon the
5 absence of statistical significance. In my view, when
6 considering all the factors the finding in this dose
7 group satisfies both aspects of the OSTP definition of a
8 carcinogen, i.e., increased incidence and more advanced
9 tumor development, and hence constitute positive evidence
10 for neoplasia that cannot be discounted on the grounds of
11 any evidence thus far put forward, especially having been
12 through the PWG.

13 The evidence for a neoplastic response extending
14 to the lowest dose level, particularly the low dose 100
15 ppm, is a considerable concern. Conclusions of the EPA
16 must be conservative in fulfilling its role of the
17 protection of the public health. Where there is doubt or
18 uncertainty, default must be on the side of the public
19 health protection. I do not see any of that concern
20 reflected in CARC's conclusion.

21 And now there are additional neoplastic
22 responses which I consider to be positive by similar

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1 reasoning. Today I really just presented the sort of
2 reasoning of my view, but I think it applies to these
3 other types as well. I trust the Panel will consider
4 each on its own merits.

5 To the extent these neoplastic findings are not
6 considered to provide positive evidence of
7 carcinogenicity, the studies themselves should be
8 declared unacceptable according to the principles and
9 interpretations I've cited. Discussions on each of these
10 endpoints is presented in my written submission.

11 And lastly, the definition of suggestive
12 evidence of carcinogenicity that I have to offer, which
13 comes out of our guidelines -- EPA's guidelines -- is not
14 quite the same as the one the committee offered. Here,
15 if you read that definition, I find that the sort of
16 criteria that triggered that classification far exceeded
17 in the malathion database. And furthermore, I would be
18 curious to know whether the EPA contemplates any further
19 testing as would indicate in that characterization of
20 suggestive evidence of carcinogenicity.

21 Our different philosophies and what we believe
22 should be the interpretation. Let me back up. Our

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1 different philosophies, the CARC's and mine, and what we
2 believe should be an interpretation may explain some of
3 the disparity between the committee and myself. Thank
4 you for considering my assessment.

5 That's it.

6 DR. THRALL: Thank you.

7 DR. DEMENTI: That's enough.

8 DR. THRALL: Thank you, Dr. Dementi. Are there
9 questions of clarification for Dr. Dementi?

10 DR. BRUSICK: I have one. David Brusick. I
11 would just like to go back to the OSTP definition of
12 carcinogen that you use, and ask you whether or not you
13 feel that that definition, which does not in any way
14 specify anything about the environment in which that
15 compound is administered, how much, and what state the
16 animal might be in and so on.

17 Would you say those are unimportant bits of
18 information that might be necessary to put perspective on
19 the result of the study?

20 DR. DEMENTI: Excuse me. Which definition are
21 you speaking of, please?

22 DR. BRUSICK: You said a chemical carcinogen may

1 be a --

2 DR. DEMENTI: Oh, the chemical carcinogen.

3 DR. BRUSICK: -- substance which significantly
4 increases the incidence of cancer in animals or humans.

5 But there is nowhere in here that specifies at what
6 level, at what exposure, what kind of animal and what
7 kind of condition the animal may be in.

8 Are you saying that those conditions are
9 unimportant in the definition or should be added to this
10 definition?

11 DR. DEMENTI: Oh, all I know, sir, is this was
12 the definition that prestigious group offered. And this
13 is a small statement within a much larger text that goes
14 into depth into how to evaluate these bioassays. But I
15 think what they're saying is there are two basic
16 endpoints that are critical in defining a carcinogen.
17 One is increased tumor incidence and the other is
18 increased progression or development of the tumor.

19 DR. BRUSICK: But what do you -- what is your
20 opinion?

21 DR. DEMENTI: My opinion is that many factors
22 weigh into the decision as to whether those conditions

1 have been met. Is that the answer to your question?

2 Maybe I missed the point. I'm sorry.

3 DR. THRALL: All right. Dr. McConnell has a
4 question of Dr. DeGeorge. If you would come up to the
5 table, please.

6 DR. MCCONNELL: Thank you. Why I'm doing this
7 is that he has to leave, so I wanted to find out what he
8 had to say before he left.

9 You know this data probably as well as the
10 people on this Panel. You are aware of the oral tumors
11 and the nasal tumors in those Fischer rat studies. How
12 would the FDA, if you can speak for the FDA, view those
13 in terms of a treatment related effect?

14 DR. DEGEORGE: Okay. First of all, I can't
15 speak for the FDA.

16 DR. MCCONNELL: I understand that.

17 DR. DEGEORGE: I can only speak for myself. But
18 in looking at the nasal tumors, we would evaluate whether
19 or not there was evidence of toxicity, particularly in
20 the conditions of the test that might have contributed to
21 those tumors. And particularly given the low frequency
22 in the study and, in fact, also some data about

1 background rates, recognizing, of course, we don't have
2 any historical background rate for the sections that were
3 particularly evident, in the section five, for example.

4 ----- But in the oral tumor data, we would again look
5 at the historical control data. And we actually have
6 some data from NTP that indicates that those tumors are
7 at somewhat higher spontaneous frequency than has been
8 represented. I think there are three in the upper range
9 of responses. Somewhere around three out of 50 animals
10 for those tumors.

11 So that would really not be -- the findings as
12 reported would not be outside the historical control
13 range, recognizing, of course, that they are not -- those
14 are not section tumors. Those are based on observation
15 generally and following up based on clinical gross
16 observation.

17 ----- DR. DEMENTI: Can I ask you a question? You say
18 the incidence at NTP are higher than what we've said they
19 are?

20 DR. DEGEORGE: The answer is yes. What we have
21 is we have a more -- I think maybe a more recent database
22 than NTP has available. And I think someone else here

1 may also have some access to that database to report that
2 the incidence is somewhat higher than was in the report
3 as presented.

4 DR. DEMENTI: Well, we have the latest 1998
5 historical control data. I don't know how recent yours
6 is. But when you speak of the oral cavity tumors, are
7 you speaking of the oral cavity in totality, or are you
8 speaking in terms of the palate which is where these
9 tumors were found?

10 DR. DEGEORGE: This is based on gross
11 observation of the oral cavity where they would be
12 combined. And it is a database from 1999. September of
13 '99 I think is the most recent data set.

14 DR. DEMENTI: I have one response. And that is,
15 these tumors in this study were identified in the palate.
16 One in the alveolus of a tooth, which in one case that
17 particular tumor was diagnosed -- one of the palate
18 tumors was diagnosed that way and then revised to that of
19 a palate. So these tissues are right next to each other.
20 That is the alveolus of a tooth and the palate.

21 But in any case, in NTP's database I cannot find
22 a single incidence of a palate tumor. Now there are oral

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1 cavity tumors. But the point is, in this study the other
2 tissues in the oral cavity were not examined
3 histopathologically. We have not looked at the tongue,
4 the oropharynx and other regions of the mouth. And we do
5 not even have an official palate histopathology
6 assessment. All we have is what incidentally happened to
7 come out of a nasal tissue assessment.

8 And these four that we found are utterly rare.
9 I talked with Joe Hasman at NTP, who pulled out three of
10 these studies to see if we could further localize three
11 squamous cell tumors that were just reported in the oral
12 cavity as to whether the pathologist had said whether or
13 not they were located in any particular place. And he
14 said two of them were in fact further localized to the
15 oropharynx. The third was not further localized. It was
16 just an oral tumor.

17 So as far as I can tell after examining this
18 database very thoroughly, there is not a single incidence
19 of a palate squamous cell tumor with that possible
20 exception. That one which could be, but in all likely
21 isn't. So, I mean, I have studied this very thoroughly.

22 DR. DEGEORGE: And weren't those detected based

1 on histopathology and presence in sections and not based
2 on gross lesions? They were based on observation in
3 sections?

4 DR. DEMENTI: All I know is that they're from
5 the NTP report.

6 DR. DEGEORGE: No, no. I was talking about the
7 tumors that are in this study.

8 DR. DEMENTI: Oh.

9 DR. DEGEORGE: I believe they came out of the
10 histopathology sections, not based on gross observations.
11 These are both -- the tumors in the NTP database are of
12 such a size they are based on gross observation.

13 DR. DEMENTI: But are they of the palate?
14 That's the whole point. That's the only --

15 DR. THRALL: Okay. This has kind of become a
16 personal thing because we can't hear you.

17 DR. DEGEORGE: The point is that we don't have
18 the data on where specifically they were located. I
19 think as Brian pointed out, at least one of them it's
20 unreported as its site, but it is part of the oral
21 cavity.

22 DR. DEMENTI: I acknowledge there are like six

1 reported in the oral cavity. But they're on the tongue
2 and the oropharynx, and we haven't looked at either of
3 those tissues in the study. Okay.

4 DR. THRALL: Dr. Boorman, did you have a
5 comment?

6 DR. BOORMAN: A couple of things. One is that
7 I'll bring some data which I think Dr. Brian Dementi
8 mentioned. And that's a 1998 report of Hasman. There
9 are a few more tumors of the oral cavity in that report
10 than on the earlier reports.

11 I also pulled all of the reports that came out
12 in 1999 and there are some tumors there. Part of the
13 problem is that the oral cavity is examined on the nasal
14 sections, and some of the pathologists will report the
15 source of the tumor as the oral cavity. I talked to Rick
16 Haley, who is in charge of hepatic pathology as to how
17 often they may arise from like the alveolus of the tooth,
18 which is one of the questions. And it's difficult,
19 because when these tumors become large squamous cell
20 carcinomas, the exact origin is difficult and sometimes
21 they're just noted as oral cavity.

22 So I think what Dr. Dementi raised is a

1 difficult issue, and I think it will require some debate.
2 But I would agree with Dr. DeGeorge that it is probably
3 slightly more common than in the older data, and that's
4 probably hopefully because we're getting better at
5 examinations.

6 DR. THRALL: All right. Other questions?

7 DR. EVERITT: I have a question for Dr. Dementi.
8 Jeff Everitt. I would like to know your feelings on the
9 toxicity manifested in the 8,000 and 16,000 ppm group as
10 far as the body weight changes, liver weight changes,
11 absolute kidney weight changes, etc., and the food
12 consumption changes.

13 Because although it is not completely reflective
14 of percent body weight change as we typically think of
15 assessing maximum tolerated dose, the way I look at it in
16 my professional opinion, in a lab animal. That is, I
17 look at what has gone on in the food consumption, for
18 instance, at 16,000 ppm and it's astounding to me, the
19 difference.

20 DE. DEMENTI: The body weight change is real,
21 and the change in body weight was not calculated in this
22 study. I mean in the review. It's not available to us

1 right now.

2 But I think the point I'm making is that all of
3 these -- both of these groups and both sexes should not
4 be lumped together and treated as a unit. In other
5 words, on body weight change in females at 8,000 ppm, the
6 body weight change -- excuse me. The body weight deficit
7 was 9.7 percent. And the higher dose female group and
8 both male groups were higher and probably would be in a
9 range that you might say would exceed the MTD.
10 I don't think that's characteristic of the female in the
11 8,000 ppm group.

12 DR. BOORMAN: I'm interested in what you think
13 of the liver to brain rate ratios in the high
14 concentration groups. I mean, in your experience how do
15 you assess what is the degree of hepatocellular
16 hypertrophy which was reported by the pathologist as
17 being the major non-neoplastic effect. How do we assess
18 that?

19 You made an opinion that there was no
20 hepatocellular necrose, etc., but certainly you don't
21 find hepatic necrose as the only manifestation of non-
22 neoplastic hepatic pathology. So I'm interested in how

1 you assessed the size of the liver and what your
2 assessment of that hepatic to brain rate ratio is.

3 DR. DEMENTI: All right. You're asking multiple
4 questions. But in the case of hypertrophy it's my
5 understanding that it was -- that hypertrophy was there
6 for males at both doses, and the females at the high dose
7 level. But for females at the 8,000 ppm, the hypertrophy
8 -- although it was there, was of a lower score and in my
9 opinion not sufficient to disqualify the group as
10 meaningful in its carcinogenic response.

11 But as far as the body weight, what are you
12 talking about? You were mentioning the liver?

13 DR. BOORMAN: Well, I'm saying when you do liver
14 to brain rate ratios, those kinds of things, what in your
15 professional opinion would be the kind of ratio that
16 would tell you you had an excessive size of the liver?

17 DR. DEMENTI: Oh, it's what guideline would I
18 use?

19 DR. BOORMAN: Yes.

20 DR. DEMENTI: I don't know what it would be.
21 That's a judgment call like the committee often uses.
22 It's a judgment call. But I think that it is less

1 obviously a problem in the 8,000 ppm female group.

2 DR. BOORMAN: Well, yes, there is obviously a
3 concentration response. But I guess I'm asking where are
4 you drawing your line and how are you making that
5 assessment? I mean, we're going to be faced with a lot
6 of subjective opinions here, and here we have some
7 quantitative data.

8 DR. DEMENTI: Well, then I guess --

9 DR. BOORMAN: I'm asking in your opinion with
10 other compounds, what would be a significant brain rate
11 ratio?

12 DR. DEMENTI: I don't know. I guess we need to
13 get out the data and have you all debate it. What you
14 think.

15 DR. THRALL: Dr. Williams?

16 DR. WILLIAMS: If I could ask you a question
17 about the OSTP guidelines which you relied heavily on.
18 Those guidelines, I notice, as well as the EPA
19 guidelines, for the weight of evidence approach use the
20 word cancer. And cancer is in its ordinary meaning a
21 malignant tumor.

22 Now were you using cancer that way, or does OSTP

1 use cancer that way?

2 DR. DEMENTI: No. I think it uses the
3 neoplastic response, benign and malignant. I mean, as I
4 read that document they combine them, and they talk about
5 progression and so forth. And I think when they speak of
6 cancer, they're talking about adenomas and carcinomas of
7 the liver.

8 That's my opinion.

9 DR. WILLIAMS: Yeah. But would you agree that
10 most of the tumors we're talking about here are actually
11 benign tumors?

12 DR. DEMENTI: You're talking about the mouse
13 now?

14 DR. WILLIAMS: I'm talking about all of them.

15 DR. DEMENTI: Well --

16 DR. WILLIAMS: The rat.

17 DR. DEMENTI: I mean, in the liver. You're
18 talking about the liver?

19 DR. WILLIAMS: No. I'm also talking about the
20 olfactory neoplasms, the hard palate neoplasms. They're
21 all diagnosed mainly as adenomas.

22 DR. DEMENTI: No. Two of the palate tumors, the

1 squamous cell carcinoma --

2 DR. WILLIAMS: Oh, yes. No, I said mainly.

3 DR. DEMENTI: Okay.

4 DR. WILLIAMS: And my question is, aren't we
5 looking at predominately benign tumors here?

6 DR. DEMENTI: Yes.

7 DR. WILLIAMS: Okay.

8 DR. DEMENTI: But not so much in the low dose
9 groups of the males.

10 DR. THRALL: Dr. McConnell?

11 DR. MCCONNELL: Well, I don't know whether you
12 want to get into the debate on this business yet or not.

13 DR. THRALL: I think we're still on
14 clarification.

15 DR. MCCONNELL: Okay. So I did do some math on
16 the liver weights, and I would point out one thing. I
17 think it can be misleading to look at liver weights in an
18 18 month study in mice when you have liver weights at 12
19 months. I would rely more on those, because of the
20 problems of aging that occur later in life.

21 And looking at those liver weights in the male
22 mice, if my colleague's calculator's battery is working,

1 was that on a liver to body weight basis -- Jeff, I
2 didn't do it for liver to brain, but in looking at the
3 numbers, it looks like it would be about the same --
4 there was a 34 percent increase in male mice at 8,000,
5 and a 61 percent at 16,000. For female mice the number
6 for liver to body weight was 19 percent increase at 8,000
7 and 45 percent at 16,000.

8 In addition, in those animals at 12 months that
9 were sacrificed, they already had showed hypertrophy of
10 the liver. So I think we can assume that the livers were
11 enlarged at 12 months and significantly so, and that it
12 probably related to hypertrophy.

13 And I'll wait until tomorrow to discuss what
14 that might mean earlier in life in terms of cell
15 proliferation, etc. And probably Dr. Williams is better
16 qualified to speak to that anyhow than I am.

17 DR. THRALL: Thank you, Dr. McConnell. Are
18 there any other questions of clarification from Dr.
19 Dementi?

20 Yes, Dr. Boorman?

21 DR. BOORMAN: I just wanted to make one point
22 that Dr. Dementi made that I thought we shouldn't forget.

1 And he mentioned that there were four carcinomas in the
2 historical database in the lab, and that the study we're
3 comparing with those that had gone through the PWG where
4 some of the carcinomas had been changed to adenomas.

5 And I think his -- and I hadn't picked up on
6 that. I just want to remind us. I think that's a good
7 point that the historical database might look different
8 if the results were subject to PWG. And I think that was
9 a point that we just need to keep in mind as we discuss
10 comparisons.

11 DR. THRALL: Dr. Boorman, before you came in,
12 Dr. Dementi was wondering why pathologists don't agree on
13 their assessment of tissues.

14 DR. BOORMAN: Oh, boy. Usually we get the
15 questions from the statisticians as to why we can't
16 agree. I think there are several things. One is when
17 you're looking at a large number of tissues in animals
18 over a six month or eight month period, it's difficult
19 with changes in the weather, changes in the family and
20 changes in everything to be consistent.

21 And one thing that we found with the pathology
22 review process is a reviewing pathologist looks at all of

1 the tissues in question, often in a two to three week
2 period. So that person has the opportunity to see the
3 first carcinomas and the last carcinomas that were
4 diagnosed within a few days and look for consistency.

5 And many times when we bring the study
6 pathologist in, and the reviewing pathologist in, and
7 they look at it as a group, they will come to a consensus
8 that it is perhaps more uniform and will remove some of
9 the inconsistencies. I think as long as it is done in a
10 blind fashion, where there is no awareness of doses and
11 so forth and so on, that it is perfectly acceptable.

12 And we find in our experience that tumors are
13 both upgraded and downgraded, and what we hope is that at
14 the end of the process it's closer to the truth.

15 DR. THRALL: Thank you.

16 DR. BOORMAN: You notice I didn't answer why we
17 disagree.

18 DR. THRALL: All right. Other questions or
19 comments before we go to the public comments?

20 Yes, Dr. Gaylor?

21 DR. GAYLOR: I would just like to make one
22 comment. I thought the EPA did a excellent job this

1 morning of summarizing an enormous amount of data and
2 information. I'm not saying that I necessarily agree
3 with all the statements, but they did a great job of
4 presenting the data. I appreciate Brian's comments,
5 also. This was very helpful.

6 DR. THRALL: Okay. All right. Our first public
7 commenter, then, is Dr. Judy Housworth.

8 DR. HOUSWORTH: I think we need to --

9 DR. THRALL: If you would just go ahead and tell
10 us who you represent?

11 DR. HOUSWORTH: I'm Judy Housworth, and I'm
12 making this presentation on behalf of Kemy Nova. And up
13 here with me is Dr. Jerry Hardesty, who was the Chairman
14 of the PWGs, both of them, for the male mouse liver and
15 the female rat liver, and Dr. Don O'Shaughnessy, who is
16 of Kemy Nova -- who is at Kemy Nova. And Mina Sanawanee
17 from Jellinek, Schwartz & Connally.

18 DR. THRALL: Thank you.

19 DR. HOUSWORTH: That's the overhead.

20 FEMALE SPEAKER: They used to work for EPA.

21 DR. THRALL: Pardon me?

22 FEMALE SPEAKER: They used to work for EPA,

1 didn't they?

2 DR. HOUSWORTH: Yes, I did use to work for EPA,
3 and so did Mina.

4 MR. LEWIS: Just give us a moment in getting the
5 overhead projector ready.

6 DR. HOUSWORTH: Well, conveniently I guess I
7 didn't bring it up here with me, even though I have
8 several volumes of data here. There was an increased
9 incidence of hepatocellular hypertrophy at 10,000 and
10 20,000 ppm.

11 Mina, can I have the next overhead? I have done
12 that one already. I wanted to comment on the mortality
13 in the 24 month study. This is the mortality for males
14 and females at each of the dose levels. At 6,000 ppm in
15 females there was a very slight increased mortality. I
16 don't think we can call it significant, but there was a
17 slight increase.

18 MALE SPEAKER: May I ask a question?

19 DR. HOUSWORTH: Uh-huh.

20 MALE SPEAKER: Do you know what the mortality
21 was in control groups in the laboratory for concurrent
22 studies?

1 DR. HOUSWORTH: No, I don't. Also, on the two
2 year study, this overhead indicates percent inhibition of
3 cholinesterase in each of the compartments over the time
4 of the study, three months, six months and 12 months. So
5 you can have an idea of what was happening over the
6 course of the study.

7 May I have the next overhead, Mina? We also did
8 a weight of the evidence on the data. In B6C3F1 mice the
9 incidence of liver tumors is shown in the next overhead
10 and agrees with what EPA has presented and with what
11 Brian has presented.

12 The historical control data from the performing
13 laboratory for adenoma in males ranged from 14.29 to
14 21.74 percent. In females the range was 9.52 to 10.64
15 percent. So at 8,000 and 16,000 ppm the incidence of
16 adenoma is definitely outside of the historical control
17 range of the performing laboratory, but it is within the
18 historical control range of NTP, at least the data that
19 we have and are using. In males the range was 20 to 56
20 percent. In females the range was 12 to 50 percent.

21 Back to the weight of the evidence, there was an
22 increase in benign tumors only, and we conclude that the

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1 tumors occur only at dose levels that are excessive and
2 above a limit dose which is 7,000 ppm for studies of this
3 type.

4 Just to give you an idea of what the actual dose
5 levels on a milligram per kilogram basis were in that
6 study, 8,000 ppm in males was 1.4 grams per kg per day,
7 and 16,000 ppm was 2.9 milligrams per kilogram per day.
8 In females, 8,000 ppm was 1.7 milligrams per kilogram per
9 day, and at 16,000 ppm the dose level equated to 3.44
10 grams per kilogram per day. I'm sorry.

11 MALE SPEAKER: These are all grams, right?

12 DR. HOUSWORTH: These are all grams. I'm sorry.
13 Could I have -- you already did it. In the Fischer study
14 liver tumors occurred in female rats which are shown on
15 the next overhead. And the incidence that is given is
16 that--that was determined by the pathology working group.
17 So there was only an increased incident at 12,000 ppm.
18 There were no liver tumors seen at 6,000, and one or two
19 in the other dose groups.

20 The historical control data that we relied on
21 was that from Hasman and not the most recent. But I
22 present that for adenomas the range being zero to 10

1 percent from NTP. The performing laboratory was zero to
2 5.4 percent. And comparing the incidence in the study to
3 that of the historical control range of the performing
4 laboratory, the incidence in the malathion study is
5 outside of the range.

6 Moving on to the nasal cavity tumors in the next
7 overhead, if you only look at the top half of this slide,
8 the top half is the nasal tumors and the bottom half is
9 the oral cavity tumors. There is one benign tumor each
10 observed in the 6,000 and 12,000 ppm groups for males and
11 females. We agree with EPA that we cannot rely on any
12 historical control data because there were five sections
13 cut of these tissues, and NTP cuts three and the
14 performing laboratory only cuts two.

15 We do note, however, that these tumors have been
16 seen in control animals in several studies conducted by
17 NTP, and some of these studies include epinephrin,
18 phenathalene (phonetic), resorcinol and anthracranon
19 (phonetic).

20 On the oral mucosal tumors in male and female
21 rats, one squamous cell papilloma was seen at 6,000 ppm
22 in females, one squamous cell carcinoma at 12,000 ppm in

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1 females, one squamous cell papilloma at 100/50 ppm in
2 male rats. And the incidence of these tumors is shown on
3 the slide that we had up previously.

4 Our historical control data indicates that the
5 range for the occurrence of these tumors in both males
6 and females is zero to 2 percent in the NTP database.
7 And looking at individual studies -- the results of
8 individual studies -- I found that there were zero to two
9 malignant tumors in males and females in controls, and
10 from zero to three of these tumors, carcinomas or
11 adenomas, in males.

12 We concluded from this that treatment -- there
13 is no treat -- there is only a treatment related increase
14 in benign liver tumors in female rats, and that is at
15 12,000 ppm, which we considered to be an excessive dose.
16 Kemy Nova agrees with EPA that no other tumors observed
17 in the rat studies are related to malathion
18 administration.

19 Our weight of the evidence on the mutagenicity
20 of malathion is the same of that of EPA. Kemy Nova
21 concurs with EPA's conclusion that the evidence is not
22 supportive of a mutagenic concern in carcinogenicity. In

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1 our oncogenic classification the factors that we
2 considered were that malathion is not mutagenic. Tumors
3 are seen at doses that overwhelm the metabolic capacity
4 of experimental animals.

5 Treatment related increases in tumors in mice
6 and female rats were limited to benign liver tumors. No
7 increase in neoplasms was observed in male rats. Only
8 one benign nasal tumor was observed in each of the two
9 high dose groups in male and female rats.

10 Kemy Nova does not consider the nasal tumors to
11 be treatment related for the following reasons. There
12 was no dose response, there was no statistically
13 significant increase, and these tumors have been observed
14 at a similar incidence rate in control rats in NTP
15 studies. And the tumors were seen at excessive dose
16 levels. One oral tumor, benign, was observed at 6,000
17 ppm in rats, one oral malignant tumor in females at
18 12,000 ppm, and one oral benign tumor in males at 100/50
19 ppm.

20 Kemy Nova does not consider the oral palate
21 tumors or mucosal tumors to be treatment related for the
22 following reasons. There was no dose response, there was

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1 no statistically significant increase, and these tumors
2 have been observed at a similar incidence rate in control
3 rats in NTP studies.

4 I would like to note going back to the nasal
5 tumors that there was no increase in hyperplasia observed
6 in the sections in which tumors were observed. There was
7 an increased incidence of epithelial hyperplasia in
8 section two, but no tumors were observed there.

9 I'm going to go through EPA's 1999 proposed
10 classification scheme and indicate what Kemy nova
11 believes to be the correct classification for malathion.

12 Carcinogenic to humans. Appropriate when there
13 is convincing epidemiologic evidence demonstrating
14 causality between human exposure and cancer. That
15 descriptor is not met. Under the same classification,
16 there is a second descriptor. There is an absence of
17 conclusive epidemiologic evidence to clearly establish a
18 cause and effect relationship between human exposure and
19 cancer.

20 But there is compelling evidence of
21 carcinogenicity in animals and mechanistic information in
22 animals and humans demonstrating similar modes of action.

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1 We do not have mechanistic information indicating a
2 similar mechanism between experimental animals and
3 humans, and there is not compelling evidence of
4 carcinogenicity in experimental animals.

5 The second classification -- possible
6 classification -- likely to be carcinogenic to humans.
7 This is appropriate when the available tumor effects and
8 other key data are adequate to demonstrate carcinogenic
9 potential to humans. The descriptors range from evidence
10 for an association between human exposure to the agent
11 and cancer, which we do not have, and strong experimental
12 evidence of carcinogenicity in animals. We do not have
13 that, either.

14 The third classification is suggestive evidence
15 of carcinogenicity but not sufficient to assess human
16 carcinogenic potential. According to the guidelines,
17 this is appropriate when the evidence from human or
18 animal data is suggestive of carcinogenicity, which
19 raises a concern for carcinogenic effects but is judged
20 not sufficient for a conclusion as to human carcinogenic
21 potential.

22 Kemy Nova does not believe that the two benign

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1 tumors, one oral and one nasal, seen at dose levels that
2 are not excessive, is suggestive of carcinogenicity.

3 The fourth category, data are inadequate for
4 assessment of human carcinogenic potential. This is
5 appropriate when available data are judged inadequate to
6 perform an assessment, there is a lack of pertinent or
7 useful data or there are conflicting data.

8 Kemy Nova believes that after having conducted,
9 or at least there have been conducted, six chronic
10 oncogenicity studies on malathion that that is sufficient
11 to determine the oncogenic potential of malathion.

12 The last category, not likely to be carcinogenic
13 to humans. This is appropriate when the available data
14 are considered robust for deciding that there is no basis
15 for human hazard. The descriptors are extensive human
16 experience that demonstrates lack of carcinogenic effect
17 -- we do not have extensive human experience -- and
18 animal evidence that demonstrates lack of carcinogenic
19 effects in at least two well designed and well conducted
20 studies. We have two benign tumors at two different
21 sites that are seen at dose levels that are not
22 excessive.

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1 Extensive experimental evidence showing that the
2 only carcinogenic effects observed in animals are not
3 considered relevant to humans. We cannot comment on
4 that. We don't have information.

5 Evidence that carcinogenic effects are not
6 likely by a particular route of exposure. We do not have
7 information other than oral or dietary exposure.

8 Evidence that carcinogenic effects are not
9 anticipated below a defined dose range. That is a
10 criteria that we definitely meet. Tumors are only seen
11 at doses that are excessive or very high. We're talking
12 about doses that are above one gram per kilogram per day.

13 Based on the factors discussed above, Kemy Nova
14 concludes that malathion should be classified as unlikely
15 to be a human carcinogen.

16 DR. THRALL: Dr. McConnell, you have a question
17 of clarification?

18 DR. MCCONNELL: Yes. You used the term that the
19 doses that caused the liver tumors were those that
20 overwhelmed metabolic capacity. Could you tell me more
21 of what you mean by that?

22 DR. HOUSWORTH: In the rat study the highest

1 dose level that we used was 800 milligram per kilogram
2 per day, and there was indication of saturation at that
3 dose level. And we are testing dose levels in the study
4 that are higher than that.

5 DR. MCCONNELL: Saturation of what?

6 DR. HOUSWORTH: We're reaching a plateau. It's
7 plateauing.

8 DR. MCCONNELL: In its metabolism?

9 DR. HOUSWORTH: Yes. Mina, do you want to
10 comment on that?

11 DR. SANAWANEE: I'm Mina Sanawanee from
12 Jellinek, Schwartz & Connally.

13 MALE SPEAKER: Get closer to the mic.

14 DR. SANAWANEE: We have seen effects in the rat
15 metabolism study that at 800 milligram per kilogram dose
16 level the metabolic system is saturated. Meaning, you
17 know, it reached plateau in its plasma under the core
18 concentration.

19 DR. EVERITT: I have a question. Jeff Everitt.
20 Dr. Dementi brought up the possibility that in the liver
21 there was a shift and a concentration dependent mechanism
22 might be at work and we might in fact have two separate

1 mechanisms at work. One at high dose and one at low
2 concentration.

3 Is there any indication from the saturation of
4 metabolism that there is a qualitative shift in the
5 metabolism when you saturate? In other words, is it
6 known, do you shift pathways when you go to high
7 concentration, or do you in fact just saturate existing
8 metabolic pathways and change it quantitatively?

9 DR. SANAWANEE: We have seen -- we didn't see
10 the differences between the low and the high dose group.
11 Only thing, you know, the concentrations are higher in
12 the high dose group.

13 DR. THRALL: Dr. Roberts?

14 DR. ROBERTS: Just a little more clarification.
15 Concentrations of -- what are you measuring? Are you
16 measuring specific metabolites or parent compound? Are
17 you measuring the blood or tissues? I don't need a big
18 explanation, but I just want a little bit more
19 information.

20 DR. SANAWANEE: Yeah. We measure plasma
21 concentrations as well as metabolites at high and low
22 dose levels.

1 Judy?

2 DR. HOUSWORTH: We're actually identifying
3 urinary metabolites and fecal metabolites. We also have
4 some information on plasma and at least the amount of
5 radioactivity that concentrates in various tissues of the
6 rat.

7 Does that help?

8 DR. ROBERTS: Yeah. You're saying that becomes
9 non-linear, then, above a certain dose?

10 DR. HOUSWORTH: Yes. That's what I'm trying to
11 say.

12 DR. ROBERTS: Okay.

13 DR. EVERITT: One more question. Jeff Everitt.
14 Is that regarding the liver and olfactory mucosa, or just
15 the liver?

16 DR. HOUSWORTH: This is just in general. I
17 can't specifically say that it was the liver or olfactory
18 tissues. Those types of studies have not been done.

19 DR. THRALL: Yes, Dr. Dementi?

20 DR. DEMENTI: Yes. Judy, I have two questions.
21 You mentioned historical control data for the squamous
22 cell tumors. Was that specifically for the palate, or

1 was that for the oral cavity?

2 DR. HOUSWORTH: It was for oral mucosa.

3 DR. DEMENTI: Right. In other words, you really
4 don't have historical control data?

5 DR. HOUSWORTH: On the separate -- no. On the
6 palate, no.

7 DR. DEMENTI: And then I think you also
8 mentioned NTP's historical control data for the mouse
9 liver tumor?

10 DR. HOUSWORTH: Uh-huh.

11 DR. DEMENTI: Was that for 18 months --

12 DR. THRALL: Dr. Dementi, could you speak up?

13 DR. DEMENTI: Yes. In the case of the mouse
14 liver historical control data that Judy cited, I'm asking
15 her was it 18 month data or two year date. Because it's
16 my understanding that all of NTP's data is two year data.

17 DR. HOUSWORTH: It's two year data.

18 DR. DEMENTI: Then do you think that's relevant
19 in an 18 month study?

20 DR. HOUSWORTH: Well, my immediate reaction is
21 no. What troubles me about the NTP study is they stopped
22 dosing it at 80 weeks. And I'm not an expert in what

1 happens when you stop dosing at 80 weeks and then you
2 carry out a study to 24 months. But I think there are
3 problems with both of the studies as far as that is
4 considered.

5 DR. DEMENTI: Do they all stop at 80 weeks? I
6 mean I cited the NCI study that was done on malathion.

7 DR. HOUSWORTH: I'm talking about the studies
8 that were -- the mouse study that was conducted on
9 malathion.

10 DR. DEMENTI: But I'm talking about NTP's
11 historical database. It's the full two year, not run for
12 80 weeks and then finished. It's two years.

13 DR. HOUSWORTH: The early NCI studies followed
14 the malathion protocol. The early malathion NCI studies
15 followed the typical protocol that was used at that time,
16 and dosing was stopped at 80 weeks. I can cite other
17 compounds for which that protocol was used.

18 DR. DEMENTI: But, I mean, I thought you were
19 citing the data in reference to -- okay.

20 DR. HARDESTY: The NTP study is a 24 month
21 study.

22 DR. THRALL: Dr. Hardesty.

1 DR. HARDESTY: This is Dr. Hardesty.

2 MR. LEWIS: Thank you.

3 DR. HARDESTY: The NTP studies are conducted for
4 24 months, so the historical control data for NTP studies
5 conducted are 24 month data. And it's not relevant for
6 18 -- compared to 18 month data.

7 DR. HOUSWORTH: That was my immediate reaction.

8 (END OF TAPE 3, SIDE A)

9 MALE SPEAKER: -- its lack of mutagenicity or
10 mode of action?

11 DR. HOUSWORTH: No mode of action data
12 specifically on malathion. And just judging from the
13 levels at which the tumors were observed in the studies,
14 they were all very close to one gram per kilogram per
15 day. And no tumors seen at lower dose levels that humans
16 would be expected to be exposed to. We're not going to
17 be exposed to a gram of malathion at one given time over
18 a long period of time.

19 DR. THRALL: Dr. Williams?

20 DR. WILLIAMS: Gary Williams. I have a question
21 that concerns the nature of the test substance that was
22 used in the early NCI bioassays and what was used in the

1 current bioassays.

2 Now apparently the early ones were done with an
3 American Cyanamid product?

4 DR. HOUSWORTH: That's correct.

5 DR. WILLIAMS: Yeah. And your studies were done
6 with a --

7 DR. HOUSWORTH: Kemy Nova technical product.

8 DR. WILLIAMS: Right. Now are they following
9 the same -- is that going by the same production process?
10 Do you have any reason to believe that there would be the
11 same or different impurities in these two test materials?

12 DR. HOUSWORTH: I should let Don O'Shaughnessy
13 address that. But I do know that the American Cyanamid
14 material is less pure than the Kemy Nova material.

15 DR. O'SHAUGHNESSY: Yes. We've got more than
16 just reason to believe. We know for a fact at the time
17 that Kemy Nova acquired that business, literally we
18 bought the entire business from Cyanamid. Initially we
19 used their production and then switched over to Kemy
20 Nova's own plant in Denmark. And the American Cyanamid
21 material, if I recall correctly -- I don't have the
22 figures in front of me. I believe it averaged around 93

1 percent or 94 percent malathion. Kemy Nova's production
2 is nominally 96.5.

3 So immediately you see that there is a much
4 higher purity. I don't recall exactly if there are any
5 different impurities, but certainly I am certain that the
6 levels of those impurities are quite a bit lower in the
7 Kemy Nova material.

8 DR. WILLIAMS: Okay. Thank you.

9 DR. HOUSWORTH: I can recall that there are
10 several impurities. I shouldn't say several. Maybe at
11 the most two or three in the American Cyanamid product
12 that are not present in the malathion product.

13 DR. WILLIAMS: I've got a couple more questions.
14 But one more on this, because there are studies in the
15 literature on metabolism and genal toxicity of malathion.
16 Now I assume in all of these cases, because the authors
17 are not specific, that they're probably using technical
18 grade malathion.

19 Can you tell me at what -- around what year did
20 Kemy Nova introduce its process?

21 DR. HOUSWORTH: 1990.

22 DR. O'SHAUGHNESSY: 1990?

1 DR. HOUSWORTH: I think it was around 1990 or
2 1991.

3 DR. O'SHAUGHNESSY: Okay. That sounds about
4 right.

5 DR. WILLIAMS: Yeah. Now that would lead me to
6 believe that a lot of the older work is on the American
7 Cyanamid product?

8 DR. O'SHAUGHNESSY: Now going back to that
9 point, though, certainly I'm sure in most cases that
10 would be true that it was technical material. However,
11 we are aware of some of the studies where in fact
12 formulated material was used in some sort of organic,
13 xylene based solvent in some of the older studies.

14 DR. WILLIAMS: Okay, thank you. And I have a
15 question for Dr. Hardesty concerning the effects in the
16 nasal mucosa. We learned from the PWG review of those
17 neoplasms that there was also marked toxicity in a nasal
18 mucosa, at least at the -- what was it -- the eight and
19 16,000 ppm dose.

20 Can you tell us anything about the condition of
21 the nasal mucosa at lower doses?

22 DR. HARDESTY: There wasn't a PWG of the nasal

1 cavity. There was a peer review and I did not conduct
2 that. Jim Swenberg did.

3 DR. WILLIAMS: Right. That's what I was
4 referring to.

5 DR. HARDESTY: And so I really don't know. I
6 know that at higher doses there was atrophy of the
7 olfactory epithelium and some hyperplasia respiratory
8 epithelium. To the best of my knowledge, I don't think
9 there was anything going on at lower doses, but I would
10 have to look at Jim's report.

11 DR. WILLIAMS: Well, no. I'm talking about the
12 -- obviously the nasal cavity was sectioned in all
13 animals.

14 DR. HARDESTY: That's correct.

15 DR. WILLIAMS: So the study pathologist would
16 have-- would they have recorded degeneration and
17 disclamation at this lower doses --

18 DR. HARDESTY: Yes.

19 DR. WILLIAMS: -- if it was present?

20 DR. HARDESTY: Yes, they would if it was
21 present.

22 DR. WILLIAMS: And we don't have any information

1 that suggests there was anything like that?

2 DR. HARDESTY: No, not at lower doses.

3 DR. WILLIAMS: Okay.

4 DR. DEMENTI: Could I respond to that? I think
5 the EPA's review of that study concludes that 500 ppm was
6 a low effect level, and it possibly extends even to the
7 lowest dose. But I think Kemy Nova has argued that it
8 all ends at the 6,000 ppm.

9 DR. HOUSWORTH: Can I comment on that? The
10 severe nasal toxicity is definitely seen at the higher
11 dose levels, but at 500 ppm there is some nasal toxicity
12 as well.

13 DR. THRALL: Dr. Gaylor?

14 DR. GAYLOR: The phrase was used, no clear
15 evidence of carcinogenicity. Does that mean you're
16 leaving the door open for suggestive or equivocal
17 evidence?

18 DR. HOUSWORTH: That was the NTP's conclusion.
19 I believe that was one of their category -- no? I took
20 that out of the NTP reports directly.

21 MALE SPEAKER: That was the old report, yes.

22 DR. HOUSWORTH: Right.

1 MALE SPEAKER: That was the old way we used to
2 do things before we got smart.

3 DR. THRALL: Dr. Chen?

4 DR. CHEN: I have a question about the two low
5 dose. The two high dose in my study was required by the
6 EPA. And two low dose, according to what you described
7 in order to determine NOEL.

8 DR. HOUSWORTH: Yes.

9 DR. CHEN: But NOEL is what endpoint? Because
10 the NCI study are negative. So what kind of NOEL
11 endpoint?

12 DR. HOUSWORTH: Well, it's our experience that
13 EPA wants a NOEL in any chronic study that is conducted,
14 so that's why we did that. We were looking for a NOEL as
15 well for cholinesterase inhibition.

16 DR. CHEN: In the -- okay.

17 DR. HOUSWORTH: Yes. The lowest dose level is
18 suppose to be a NOEL. The mid dose, you're suppose to
19 see some toxicity.

20 DR. CHEN: But NOEL on cholinesterase?

21 DR. HOUSWORTH: Yes.

22 DR. CHEN: Okay.

1 MALE SPEAKER: I have one question. Is there
2 anything known about malathion impregnated feed that you
3 can shed any light on as far as what it might do in the
4 nasal cavity when inhaled or volatilization from the
5 feed?

6 I mean there's always a question about what the
7 concentration response is in the nasal cavity, whether
8 it's systemic or whether it's some local thing. And I
9 note that there is an increase in nasal fringel
10 (phonetic) hyperplasia that is concentration dependent.

11 Can you shed any light on the physical
12 properties of malathion impregnated feed?

13 DR. HOUSWORTH: I really can't, except to note
14 that in the malathion study you didn't see as many food
15 particles in the nasal passages. But in the malaaxon
16 study, for some reason, there was a lot of food debris in
17 the nose. But not in the malathion study.

18 We really can't say whether or not it's a local
19 irritant effect due to inhalation or if it's a systemic
20 effect, which could also be an irritation since malathion
21 is metabolized to a dye acid in the nasal turbinates.

22 MALE SPEAKER: And just following up on that

1 since we just got this latest diagnosis on the olfactory
2 tumor, is malathion metabolized in Bowman's glands?

3 DR. HOUSWORTH: I don't know.

4 MALE SPEAKER: But presumably malathion is
5 metabolized via carboxyl esterases?

6 DR. HOUSWORTH: Right.

7 MALE SPEAKER: And that's in Bowman's glands.

8 DR. HOUSWORTH: But we haven't done any of those
9 studies.

10 DR. THRALL: All right. Are there other
11 questions of clarification?

12 DR. BRUSICK: I have one.

13 DR. THRALL: Yes.

14 DR. BRUSICK: David Brusick. Just -- this
15 question would go to both EPA and to Kemy Nova. There
16 has been a lot of discussions during the day about the
17 mutagenicity data being suggested as playing no role in
18 any tumors that might be seen even at excessive dose
19 levels.

20 If you just take the data that is available --
21 and I've got a review. I haven't looked at the details
22 of these papers. I'm only taking them at face value.

1 But there were about six studies done looking at in vivo
2 chromosome aberration induction ranging somewhere between
3 150 and 300 milligrams per kilogram. In acute doses
4 there may be multiple day doses which are approximately
5 one fourth the dose levels that have been given in the
6 feeding studies on a milligram per kilogram basis, which
7 would suggest to me that the high doses up in the range
8 of 12,000 parts per million would be in excess of those
9 dose levels that give rise to chromosome aberrations.

10 On what basis is EPA and Kemy Nova saying that
11 mutagenicity could not in any way, or shouldn't be, or
12 they don't believe it's playing any role in the
13 production of this tumors?

14 MR. O'SHAUGHNESSY: Well, of course we --

15 DR. THRALL: Would you identify yourself?

16 MR. O'SHAUGHNESSY: Oh, sorry. It's Don
17 O'Shaughnessy from Kemy Nova. Just first of all, I can't
18 really speak to the exact paper, because I'm not aware of
19 exactly what one it is. However, answering the question
20 to the best of the knowledge we have is that we concur
21 with the EPA CARC assessment that -- CARC II, I guess,
22 just to be specific. That of the published studies that

1 they had evaluated and which we subsequently had looked
2 at, there were a number of concerns.

3 We had no information about the purity or the
4 source of the material. We had some of those studies
5 conducted at levels that were cytotoxic. There is at
6 least one of those that I am aware of that was using a
7 solvent based formulation rather than technical.

8 On the other hand, Kemy Nova did do full and
9 proper GLP set of genal toxicity studies. And the weight
10 of the evidence there is that in well conducted GLP
11 studies, there is no evidence with our own material of
12 known purity that there is any genal toxic effect.

13 DR. BRUSICK: Well, just to indicate, the
14 manuscript was published in 1993, and it's basically
15 coming out of the California Occupational Health Group
16 and also at Berkeley. I don't know either. I don't know
17 because I haven't looked at these studies.

18 But I just thought that it's kind of difficult
19 to dismiss any possible implication because of this.
20 These studies do have malathion purity for each of the
21 studies. They were all done in mice -- or one in a
22 hamster -- ranging from 30 percent to greater than 99

1 percent purity.

2 MALE SPEAKER: What was the route of exposure?
3 Was this a Gavage study, per chance?

4 DR. BRUSICK: No. Most of these -- again, I
5 would say the predominant route was interparietal
6 injection. There was a dermal study and a couple of oral
7 studies.

8 MR. BURNAM: Bill Burnam. Is that article from
9 the Hoper in California, I believe?

10 DR. BRUSICK: Yes. It's a review of the genetic
11 toxicity of malathion.

12 MR. BURNAM: Right. Okay. Our mutagenic people
13 have been over that. They have taken that into
14 consideration when they did their mutagenicity
15 presentation. Most of those studies were -- are the ones
16 that they were talking about where they were flawed in
17 various ways, of being too high of concentrations and
18 unknown impurities.

19 DR. THRALL: Dr. Dementi?

20 DR. DEMENTI: Yes. Back to the purity issue for
21 the two products, the Kemy Nova product may be 96 percent
22 malathion, but the composition of the remaining four

1 percent may be quite different than what the composition
2 of the six percent impurity is in the American Cyanamid
3 product.

4 I really think we should get the statement of
5 formulations and bring them here so you can see for
6 yourself what the difference is between the two products.
7 We can do that tomorrow, I think.

8 And then I have another question about the
9 tumorigenic response in the nasal cavity. If indeed the
10 tumor that arose in the olfactory epithelium is somehow
11 not combinable with those that arose from a respiratory
12 epithelium, in the sense that both epithelial are
13 responding to a traumatic insult, and in the sense that
14 maybe the olfactory epithelium could not generate the
15 same kind of tumor that would come from the respiratory
16 epithelium, do they nonetheless share something in
17 common, in that both are listing a tumorigenic response
18 to a common insult and therefore should not be separated
19 and somehow, you know, divide -- the divide and conquer
20 approach in the blithe of those four tumors?

21 DR. THRALL: Dr. Hardesty?

22 DR. HARDESTY: This is Dr. Hardesty. You know,

1 I regard all four of the tumors as spontaneous, so
2 they're not responding to any kind of a tumorigenic
3 response. But the epithelial tumors arise in the
4 anterior portion, or rising from the surface respiratory
5 epithelium, which is a pseudo stratified ciliated
6 respiratory epithelium.

7 The tumor arising in the olfactory region is
8 arising from Q-border epithelium. It's not ciliated.
9 It's not suta stratified in the glands, so that the thing
10 that they have in common is their epithelia. But that's
11 about all, you know. So I think that there is not any
12 reason to believe that the spontaneous tumors that are
13 occurring there, you know, are responding to the same
14 tumorigenic response, because I don't feel like those
15 tumors are induced.

16 DR. DEMENTI: I guess I also feel that out of
17 the nasal histopathology we have four extremely rare
18 squamous cell tumors in the oral cavity and four
19 extremely rare in nasal tumors.

20 Now just the fact that we have eight extremely
21 rare tumors in this nasal histopathology, does that raise
22 any concern in anyone's mind, even though they are of

1 different tumor types? Do they share anything in common?

2 DR. O'SHAUGHNESSY: I would like to make a
3 comment on that. We'll get into this tomorrow, I'm sure,
4 when we start discussing some of the tumor types in the
5 nose. But I think you should be cautioned saying
6 extremely rare. These are infrequent findings, but there
7 are many bioassays for which sporadic oral neoplasms
8 arise.

9 And one can go to the TDMS on the Internet on
10 the NTP database and just look at compounds that are not
11 known to induce tumors. The nasal organ is a targeted
12 organ of toxicity. And throughout low concentration in
13 control groups, you'll see a finding of oral tumors.
14 It's well known in rats that when you get irritation of
15 the oral kind of periodontal influence, you can get
16 squamous cell carcinomas of the root of the alveolus,
17 such as we have in this study. You can also get nasal
18 tumors.

19 And so I just caution in how we use the
20 database. This is a problematic area of toxpath -- of
21 rodent toxpath. This area has not been historically well
22 evaluated, and I would caution how we use the database.

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1 But these tumors do occur probably more frequently than
2 have been reported in the past in the database.

3 And there in fact are reports in the literature
4 of rats that have had extremely rough feed. Where rats
5 in Europe have been on barley diets, for instance, where
6 there is a very high incidence of oral neoplasms. There
7 have been associations of malocclusion syndrome with the
8 development of oral neoplasms.

9 And I should point out that it's not common to
10 compare incidence in dose feed diets such as this with
11 inhalation studies where the nasal cavity has been
12 extremely well evaluated.

13 So we have to take database information very,
14 very cautiously for this particular site. And I'm sure
15 we'll get into that discussion more tomorrow when we get
16 into the methodology of these individual responses.

17 DR. THRALL: All right. Are there any more
18 questions of clarification at this point?

19 Yes, Dr. Williams?

20 DR. WILLIAMS: Gary Williams, yes. Just a
21 moment ago Dr. Dementi was I think arguing that there
22 would be some rationale to combining all the nasal

1 tumors. If you do that, what does that get you? I mean,
2 do you get something more than you had with three plus
3 one?

4 DR. DEMENTI: Well, it just seems as though my
5 colleagues in the EPA think it's a less serious effect if
6 they're different. I mean --

7 DR. WILLIAMS: I'm just asking what your opinion
8 is.

9 DR. DEMENTI: Well, my opinion is --

10 DR. WILLIAMS: I'm willing to consider them all
11 nozomas (phonetic) for the purpose of discussion here.
12 So we've got four nozomas. What does that give us?

13 DR. DEMENTI: Well, you know, as I evaluate them
14 -- have been able to evaluate the historical control
15 database from NTP, these are indeed extremely rare
16 tumors. And if there are four of them there, then that's
17 very significant. It's less significant if there are
18 three and you count the other one as something else.

19 But then when you've got four squamous cell
20 tumors, coming incidentally out of a nasal tissue, then
21 without even examination of the full oral cavity, just
22 the rareness of these.

1 DR. WILLIAMS: Yeah. Okay.

2 DR. THRALL: All right. At this point we're
3 going to take a 15 minute break, and we will reconvene at
4 3 o'clock.

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

6 DR. THRALL: Our next public commenter is Dr.
7 David Berkston from the Animal and Plant Health
8 Inspection Service, USDA.

9 Dr. Berkston?

10 DR. BERKSTON: Compared to some of the comments
11 today, I'm probably going to be a little bit lighter and
12 a little more general. A lot of the issues we've been
13 talking about actually I have on my paper here, and I'll
14 just kind of express some concerns that I have and go
15 from there.

16 I would just like to thank everyone for the
17 opportunity to address concerns about the malathion
18 cancer risk assessment. As a toxicologist for the U.S.
19 Department of Agriculture over the last 11 years, I have
20 watched closely the debates and proceedings regarding the
21 potential for carcinogenic risk from malathion exposure.

22 I have observed conditions under which data from

1 chronic studies are accepted and rejected. I have also
2 noted the changing politics and proposed changes in
3 classification of carcinogenic potential.

4 The present deliberations raise several concerns
5 that have not been clearly addressed. It's hoped that
6 the Scientific Advisory Panel can provide insights on
7 these issues for the EPA reviewers.

8 First I would like to -- and we discussed this a
9 little bit earlier -- point out there is no real clear
10 mechanistic evidence provided for initiation or promotion
11 of carcinogenesis for malathion exposure. The EPA cancer
12 committee acknowledges that the weight of evidence
13 supports neither a mutagenic hazard nor a role for
14 mutagenicity in carcinogenesis. No alternate mechanism
15 for carcinogenesis is proposed. The chronic study of
16 malathion suggests that at least one primary metabolite is
17 not carcinogenic, but other mechanisms are neither
18 supported nor refuted.

19 Regulating a compound as a carcinogen without
20 mechanistic evidence could be considered arbitrary and is
21 tenuous at best. And I would suggest that maybe we need
22 to look a little bit closer at mechanisms.

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1 The proposed and interim guidelines for
2 carcinogenic risk assessment gives specific explanations
3 of what constitutes an excessive dose and the lack of
4 appropriateness for the use of this data in regulatory
5 decisions, particularly when frank toxicity, reduction in
6 body weight, clinical signs of intoxication and
7 saturation of absorption in toxic mechanisms are evident.

8 The decision to use this type of data from
9 chronic malathion bioassays as justification for a
10 regulatory decision about carcinogenic potential is
11 contrary to the intent of the guidelines and raises some
12 serious questions about the regulatory flexibility being
13 taken in this EPA review.

14 If results from excessive doses were considered
15 acceptable for carcinogen risk assessment for other
16 compounds, then many additional chemicals, including
17 drugs, food additives, natural compounds and other
18 pesticides, would be comparatively regulated. And this
19 really isn't being done right now. Consistency is
20 important to the regulatory process. If there is a
21 justifiable reason for accepting data from excessive
22 doses of malathion in this carcinogen risk assessment,

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1 that justification should be clearly and unequivocally
2 stated.

3 The importance of concurrent controls and
4 historical controls cannot be overstated. If test
5 results do not reveal statistical differences in tumor
6 incidence and control data are lacking for a given tumor
7 type, is it appropriate to assume cancer causation by the
8 test agent? When given test results -- when should
9 given test results be discounted due to uncertainty over
10 treatment association or random occurrence? These are
11 all questions we should be asking ourselves.

12 Lastly, I would like to point out concerns about
13 the lack of clear risk communication. If someone tells
14 me that a compound has suggested evidence of
15 carcinogenicity, but the data are not sufficient to
16 assess human carcinogenic potential, it suggests that
17 either inadequate testing had been done to determine
18 carcinogenic potential or there was inadequate evidence
19 to verify whether or not an agent could cause cancer or
20 not.

21 The public is then likely to assume that
22 malathion is carcinogenic and of higher risk due to lack

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1 of data. This assumption will affect public perception
2 of malathion cancer risk and use patterns, in that any
3 uses of malathion for public health or governmental
4 actions resulting in negligible exposure will not be
5 acceptable to the public.

6 Any final decisions should provide a clear
7 explanation of the meaning of the decision to prevent
8 such misinterpretations, rather than strictly provide a
9 classification terminology.

10 Thank you for the opportunity to speak.

11 MR. LEWIS: Please wait a minute, sir.

12 DR. THRALL: Just a moment.

13 MR. LEWIS: Thank you.

14 DR. THRALL: Are there questions of Dr.

15 Berkston? Yes?

16 MALE SPEAKER: Are you expressing your personal
17 views or the views of the U.S. Department of Agriculture?

18 DR. BERKSTON: I'm speaking strictly for my
19 agency, the Animal and Plant Health Inspection Service.

20 MALE SPEAKER: Okay. But these are official
21 views of that Service?

22 DR. BERKSTON: These are views of the

1 organization.

2 MALE SPEAKER: Okay.

3 DR. BERKSTON: These are concerns that they have
4 about the risk assessment.

5 DR. THRALL: Other questions of Dr. Berkston?
6 All right. Our next public commenter is Joyce Shepherd,
7 who represents the Citizens Action Network for Change.

8 MS. SHEPHERD: Good afternoon. I'm sure you've
9 heard me react back there. Almost six hours of sitting
10 and not saying anything for me is quite a lot. I think I
11 have been behaving quite nicely.

12 I had so much to say, so I'll start with I am
13 appalled that the U.S. EPA relies on the registrant in
14 regard to what their chemical is all about. I'm appalled
15 that they would not let us know what the inert ingredient
16 is of malathion. I'm really concerned that their top gun
17 toxicologist testified when asked questions, I don't
18 recall. I don't remember. I don't think so.

19 We're talking -- and we talked today about women
20 and men, but we're also talking about the children out
21 there. Nobody has focussed on the children. The EPA has
22 not. I don't know. I asked earlier are there toddler

1 mice that they can do tests on.

2 So if these test results are coming up in the
3 cholinesterase levels of men and women, what the heck is
4 happening to our children out there? What is happening
5 to their cholinesterase? Are they being diagnosed with
6 attention deficit disorder because their central nervous
7 system is being affected? Are they hyperactive acting
8 out? What is going on out there with our children?

9 Last year when New York City sprayed malathion,
10 people panicked. I didn't even know how to pronounce it.
11 I want to make it clear, I'm not a chemophob (phonetic).
12 Before last year I would get quite concerned when my
13 exterminator missed me on a Saturday morning. However,
14 when I started checking out and doing research, my own
15 taxpaying research on malathion, I started becoming
16 panic, too.

17 The research coming from -- and I don't know if
18 this Panel has this research -- from a Dr. Plasiak in
19 Poland, who showed that the DNA is damaged in vitro
20 irreversibly. That children get leukemia from malaaxon
21 and malathion. That studies show -- and the Army did
22 studies of tumors in children.

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1 They say here we do not have human exposure
2 studies. Well, let me tell you. I have some human
3 exposure studies that I did last year. I'm a psychiatric
4 social worker. And when I found that the city was not
5 doing data on how many people were being affected by the
6 malathion, I started a malathion hot line in New York.

7 When it was advertised, the phone started
8 ringing off the hook. And I purposely did not give the
9 symptoms of what to expect. I got over 300 calls from
10 mostly women who are concerned about their own symptoms.
11 But mothers with children. Children who were in
12 hospitals with rashes and the doctors couldn't diagnose
13 the rashes. They kept giving them Benadryl.

14 Because I then found out that M.D.'s are not
15 mandated to take toxicology courses in medical school.
16 And so what's been happening with the malathion diagnoses
17 is upper respiratory, skin rash, dermatology, rash,
18 postnasal drip.

19 But I have a friend who lives in Sussex County,
20 New Jersey. Four years ago she had a tumor removed from
21 her liver, and the tumor was benign. And I think you,
22 Dr. Williams, said and stressed to Dementi, well, they

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1 were benign, weren't they, Dr. Dementi. Her family at
2 that time didn't care whether they were benign or not.
3 She had a tumor and it took her whole family -- it
4 encompassed the whole family unit and scared them. And
5 do you know, it was benign. But every time they spray
6 malathion in her small town, in Watchung, New Jersey,
7 every summer her liver swells and she experiences extreme
8 pain.

9 I think it's important to put a face on this
10 chemical. I did not drive here from New York to spend
11 two days for no reason. This is serious business. This
12 is not having your foot in the door of Kemy Nova. This
13 is not thinking of gee, maybe I'll testify for Kemy Nova
14 and make 10,000. Or maybe I'll become a lobbyist for
15 Kemy Nova and make 200,000. This is not about us. This
16 is about the public health.

17 Now when Dr. Dementi mentioned his concern about
18 the public health, I applauded, and I got some looks
19 like, what are you, out of your mind? That's what this
20 whole thing is about. You are all responsible. You all
21 have it on your shoulders about the public health and
22 what your decision will be made.

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1 And every time those helicopters, and every time
2 those trucks come into a municipality and spray the kids
3 playing because they think it's safe -- the applicators.
4 Well, the EPA tells us it's safe. It's going on right
5 now in Jew Jersey. Mayor Julianne was smart enough to
6 stop the spraying until there was some basis for him
7 saying that it's safe.

8 The Mayor of New York was saying it's safe. The
9 Commissioners of the pesticide applicators in New Jersey
10 are telling me, we're going to spray it until the EPA
11 tells us we can't. And so what do they do? They say
12 they're going to spray at 5 o'clock at night, but it's 7
13 o'clock they're spraying when people are barbecuing and
14 the kids are out in the street riding their bikes. They
15 don't notify anybody.

16 I called the Health Department of the Sussex
17 County to tell them that 10 people in the complex that I
18 live in got ill from the malathion spraying: vomiting,
19 rash, irritation of eyes, itchy throat, dry cough. I
20 said I would like to report these incidence, and they
21 said what incidence. We don't know what you're talking
22 about. Call the CDC in Atlanta, Georgia. That's where

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1 this town referred us to report our incidence.

2 So we now have a malathion hot line in New
3 Jersey. It started last week. We've got 25 calls from
4 people who said, gee, I didn't realize my husband having
5 diarrhea. My grandchildren having this upper
6 respiratory. And we're raising the consciousness.

7 But our job as taxpayers, we're not getting paid
8 to do this. We're paying people to do this. Now I see
9 all the paperwork, and somebody says you're bogged down
10 with paperwork. That's a good way if you're not getting
11 information. Because I did a FOIA request of the EPA,
12 and last week I received over 10 pounds -- literally my
13 UPS driver could hardly carry this amount of paperwork
14 that was sent to me. I sent it back. It was useless.
15 Because to go through all of this is useless. Send me
16 the essentials.

17 We met with the EPA on the 28th. Ms. Marcia
18 Mulkey couldn't make it that day. She wanted to make it
19 for July 4th. I said I doubt if I could get the people
20 to attend a July 5th meeting. Ms. Mulkey was here today.
21 She introduced herself, introduced people and left. What
22 message is that to me, the taxpayer, that the head of the

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1 pesticides unit doesn't care enough to sit here and to
2 listen to both sides, to listen to what's going on to the
3 people outside that are working and paying very high
4 federal taxes.

5 I truly do not believe that I'm getting my
6 money's worth in this agency. I don't like it when I
7 hear that people from this agency leave here and become
8 lobbyists for Kemy Nova. Because what message is that to
9 the people that remain? Well, let's be nice to the
10 chemical companies. Maybe when we leave, we'll get a job
11 with Jellinek and what other names of the lobbyist firm.

12 I beg all of you here -- and you know what's
13 interesting? The woman asked the question about the
14 cancer in the uterus. But we're surrounded by men here
15 and one woman on the Panel, and a couple of women from
16 EPA. Where are the women to sit here, other than the one
17 woman that asked about the cancer in the uterus, to say
18 women and children are the most vulnerable. Because you
19 men, you may get testes. Maybe, but it's benign, you
20 know.

21 But women and children are mostly at risk,
22 because children's immune systems are not developed and

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1 women's immune systems are weaker. And think about your
2 mothers and your fathers out there. Their immune systems
3 are compromised. They're weaker.

4 So all of this science gobbly gook I've heard
5 today, you don't have human exposure studies. And I
6 think the EPA or somebody should start doing them,
7 because there are enough people out there that have
8 become ill. There are enough people out that have
9 cholinesterase blood tests. I'm asking people now to get
10 baseline studies.

11 There are going to be lawsuits, because there
12 are two lawsuits already, one I think in Tampa, Florida.
13 And what about the 123 people that got ill in Manatee
14 County in Sarasota, Florida? And what about Roys v.
15 Travellers?

16 This is just to me, just a little ole gal who
17 pays taxes and is a social worker, this is going to
18 become the tobacco industry scandal. Exactly what
19 happened with the tobacco industry with their paid
20 honchos and with their internal memos. And I don't know
21 if any of you doctors heard of Dr. Omar Shafee from the
22 Department of Health in Florida. He came out, as Dr.

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1 Dementi did, and said no, something is wrong here. You
2 cannot spray this. It's not good for the people. Maybe
3 for the met flies.

4 And why are you doing studies on prisoners
5 without the public knowing about it? Dr. Shafee got
6 fired because of a \$12 expense account, and of course
7 he's suing the Department of Health on the
8 whistleblower's law.

9 So there are Dr. Shafee's and Dr. Dementi's, and
10 then there is the Dr. Demented. And it's the Dr.
11 Demented that I am concerned about. It's the sociopathic
12 guy or woman that doesn't have a conscious, that is
13 political, that doesn't really go to bed at night and
14 think about the women and children that the trucks are
15 spraying.

16 So I'm reaching out to your conscious, and I'm
17 asking you that when you determine this chemical, go on
18 chem-tox.com tonight before you come back tomorrow.

19 Chem-tox.com. You'll see the studies and the research
20 that was done on children. You'll see what they report.

21 Go on safetouse.com. You'll see the research
22 there. You may not have it in front of you. But I ask

1 you to please, before you make any decision on the women
2 and children out there, to do a lot of homework and not
3 to listen to everything the EPA tells you.

4 And if you know Jerry from Kemy Nova, and if you
5 know Jim from Kemy Nova, don't let that get in your way.
6 Let your conscious and your heart be your guide with this
7 one. Because remember Dursban and remember DDT and
8 remember thalidomide when you determine this product.

9 Thank you.

10 DR. THRALL: Thank you, Ms. Shepherd. Are there
11 any questions of clarification for Ms. Shepherd? Yes?

12 DR. EVERITT: Jeff Everitt. I've got a
13 question. I guess, you know, not wanting to go on the
14 Internet for this because that's not a peer reviewed MOE,
15 can you provide us with the papers for which Malathion
16 has induced leukemia?

17 MS. SHEPHERD: In children, yes.

18 DR. EVERITT: Yeah. I mean, all I'm saying is
19 this is a scientific panel that is solely dealing with
20 the issue of carcinogenicity here. I think anybody here
21 will be willing to look at any publication that deals
22 with the carcinogenicity in malathion.

1 So are there papers that you are aware of --

2 MS. SHEPHERD: Yes.

3 DR. EVERITT: -- that we may or may not have
4 access to that we should see?

5 MS. SHEPHERD: Yes. Yes. And it's on chem-tox
6 -- I can't provide it, because I really didn't bring it
7 with me. I don't have a lap top, but if somebody has
8 access to a computer, you can go on chem-tox.com -- maybe
9 the EPA can do that -- and bring in these studies that
10 were done on leukemia and other studies that the Army did
11 on cancer in children and women. It's on this web site.

12 DR. THRALL: Other questions? Comments? Mr.
13 Williams?

14 DR. WILLIAMS: Yeah. Well, relating to that, I
15 mean, could I ask the EPA -- I mean normally you would
16 make a search for this kind of information, wouldn't you?
17 I mean, are you aware that such information exists?

18 MALE SPEAKER: We do have an epidemiologist who
19 is not here today.

20 MS. SHEPHERD: You know, also Dr. Robert Simon,
21 a toxicologist from Fairfax, Virginia, has presented
22 Patricia Moe with the DNA evidence in vitro that was done

1 by Dr. Plasiak in Poland. So the EPA does have that.
2 And also the carcinogenicity of the liver that was
3 presented. So I think that Ms. Moe has it. You can ask
4 the EPA to provide you with what Dr. Simon presented to
5 them.

6 Silence is golden.

7 MALE SPEAKER: We'll look at the web site
8 tonight, and if there is something that seems appropriate
9 to copy off for the Panel, we'll do that.

10 MS. SHEPHERD: Okay. And what about -- I'm sure
11 that NCAMP can bring in some. Greg, do you have some
12 stuff that you can bring in tomorrow for them on the
13 carcinogenicity and leukemia?

14 MR. KIDD: I may have.

15 MS. SHEPHERD: Okay. Well, we'll try and get
16 that. And I'll call New York and see if I can get some
17 faxed to me. But what Dr. Simon had presented by Dr.
18 Plasiak -- P L A S I A K -- in Poland on the
19 carcinogenicity in the liver and the DNA damage in vitro
20 irreversibly. I think that's important to look at, and
21 Patricia Moe has that.

22 DR. THRALL: All right. Perhaps you and the EPA

1 can provide the Panel with this material by tomorrow
2 then.

3 MS. SHEPHERD: Okay.

4 DR. THRALL: Thank you very much.

5 MS. SHEPHERD: Thank you for the opportunity.

6 DR. THRALL: Our next public commenter is Greg
7 Kidd from the National Coalition Against the Misuse of
8 Pesticides.

9 MR. KIDD: Good afternoon, members of the
10 committee. My name is Greg Kidd. I'm the Science and
11 Legal Policy Director with Beyond Pesticides, NCAMP.
12 I'll be brief this afternoon.

13 It seems clear that there is an ongoing
14 controversy about whether or not malathion is cancer
15 causing. There is, for instance, a 1992 study published
16 in cancer research that links the use of malathion by
17 Iowa and Minnesota farmers to increased risk of
18 non-Hodgkin's lymphoma. Another study published in the
19 American Journal of Epidemiology found a similar
20 increased risk in Nebraska farmers using malathion.

21 Adding to that controversy are things like a
22 letter that was received by Dr. Simon, who was mentioned

1 earlier by Joyce. He received a letter from a Dr. Harold
2 Smith of the U.S. Department of Agriculture. He had
3 originally written to the USDA regarding an EIS on the
4 use of malathion against met fly.

5 In the return letter from Dr. Smith, Dr. Smith
6 says that the preliminary information received from EPA
7 indicates that EPA is considering changing the
8 registration status of malathion because of studies that
9 suggest that it could be a low liver carcinogen. Such a
10 change would require a review of protection and
11 mitigation measure.

12 Again, adding to the controversy would be the
13 fact that Reuters News Wire on May 10th reported that an
14 anonymous source -- which obviously it's an anonymous
15 source from the EPA -- revealed that EPA's scientist's
16 risk assessment found that malathion was a suspected
17 carcinogen. Shortly after that EPA -- when the risk
18 assessment was subsequently published by EPA, the EPA
19 stated that there was insufficient evidence to assess
20 malathion's cancer causing potential.

21 EPA documents reveal that the CARC downgraded
22 its original diagnoses of tumors found in lab animals

1 exposed to malathion as a result of a report created by
2 the PWG. As I understand it, the PWG was established as
3 a result of the manufacturer, Kemy Nova's, concern about
4 the analysis of the data.

5 What we're really asking for is that a credible
6 peer review from academia be conducted, as opposed to a
7 peer review by an industry chosen panel, in an effort to
8 avoid any biased conclusions about the potential
9 carcinogenicity -- cancer causing of malathion.

10 So in closing I would like to say that we urge
11 EPA to revert back to its original diagnosis, subject
12 that to public comment and answer Dr. Dementi's questions
13 about the adequacy of the PWG's and CARC's review.

14 Thank you.

15 DR. THRALL: Thank you, Mr. Kidd. Are there
16 questions of Mr. Kidd?

17 MR. KIDD: Okay. Thanks again.

18 DR. THRALL: Yes, Dr. Williams?

19 DR. WILLIAMS: Gary Williams. Can I assume that
20 the papers referred to in your presentation here are
21 going to be provided to us?

22 MR. KIDD: You know, I'm not sure that we have

1 those in the office. But I'll certainly see if we do,
2 and if we do, then I will bring them in tomorrow.

3 DR. WILLIAMS: I would appreciate it.

4 MR. KIDD: Yes.

5 DR. WILLIAMS: Thank you.

6 DR. THRALL: Other questions or comments?

7 MR. KIDD: Thanks.

8 DR. THRALL: Okay. Are there any other public
9 commenters in the audience that would like to speak to
10 this issue?

11 All right. If not, does the Panel have any
12 questions of anybody who presented today before we
13 adjourn?

14 Mr. Lewis, do you have any closing?

15 MR. LEWIS: I just want to say --

16 DR. THRALL: Oh, wait just a minute.

17 MALE SPEAKER: Yeah. Unless maybe somebody
18 skipped me, I know they submitted some comments -- Kemy
19 Nova. But could we have copies of those overheads?

20 FEMALE SPEAKER: I could provide them tomorrow.
21 They did not pass out the copies today.

22 MALE SPEAKER: You'll pass them out tomorrow?

1 FEMALE SPEAKER: Well, Kemy Nova will bring
2 copies tomorrow.

3 MALE SPEAKER: Okay.

4 DR. THRALL: So we'll get copies of Kemy Nova's
5 overheads tomorrow.

6 Dr. Needleman? I'm sorry.

7 DR. NEEDLEMAN: Yes. I see that Mr. Kidd did
8 supply us with two specific references. And rather than
9 leave it up to him to perhaps be able to get it, EPA
10 should be able to supply us with those two reprints.
11 Kidd, et al. in volume 52 in the American Journal of
12 Epidemiology?

13 MALE SPEAKER: On cancer research.

14 DR. NEEDLEMAN: Oh, cancer research, and the
15 other is in the American Journal of Epidemiology. Could
16 we ask for those?

17 DR. THRALL: Can the EPA provide the Panel with
18 copies of those?

19 (END OF TAPE 3, SIDE B)

20 DR. THRALL: -- the Panel discussion.

21 MALE SPEAKER: Let's just keep going.

22 DR. THRALL: Well, we kind of need one of the

1 people that's not quiet.

2 All right. Issue number one? I think what
3 we'll do, Dr. Copley, is just have you reiterate issue
4 number one and read question one, and then we'll open
5 that up for discussion.

6 DR. COPLEY: Okay. We're asking the SAP for
7 advice regarding the following issues and questions. The
8 actual questions are identified with a question mark to
9 the left of the question. At least they were in the
10 background document. I'm not sure if it's that way in
11 the agenda now.

12 Okay. Issue 1. The HED CARC determined that
13 all three new studies, a rat and a mouse study with
14 malathion and a rat study with malaaxon, were adequate to
15 evaluate the carcinogenic potential of the test
16 substance. Although excessive toxicity was present at
17 the high dose or two high doses in all of the studies,
18 the next lower dose was either adequate based on marginal
19 evidence of toxicity or was less than one half of the
20 excessive toxic dose.

21 The first actual question relates to that. Does
22 the SAP agree that each of the three above-mentioned

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1 cancer studies were adequate to assess potential
2 carcinogenicity? If yes, why. If no, why not.

3 DR. THRALL: Dr. McConnell?

4 DR. MCCONNELL: Thank you, Madam Chairman. What
5 I would like to do here, at your pleasure, of course, is
6 to look just at the rats. Let us discuss that and then
7 go to the mice.

8 DR. THRALL: Very good.

9 DR. MCCONNELL: All right. Second, is I have a
10 request of the agency to put up that slide that shows the
11 cholinesterase levels at the different doses.

12 FEMALE SPEAKER: What slide number is that?

13 DR. COPLEY: Is it the one for the rat?

14 DR. MCCONNELL: Yes, in the rat.

15 DR. COPLEY: That would be Slide 15, I think.

16 DR. MCCONNELL: The experimental design -- and
17 I'm going to stick just to the design at this point and
18 not necessarily consider the results until the end of my
19 presentation.

20 These rats were fed the malathion 97 percent
21 pure in their diet at levels of 0, 100/50, 500, 6,000 and
22 12,000, and that calibrates to 229, 359 and 739 in the

1 male, and 335, 415 and 868 milligram per kilogram in the
2 females. The study was done for two years in Fischer 344
3 rats.

4 With regard to the design, I think that it was a
5 marginally well designed study in the sense that I would
6 have preferred to see a dose in between 500 and 6,000.
7 Now part of the reasoning for that is because of the
8 results we saw. And as usual in these kind of things,
9 hindsight is 20/20. Therefore, I think that the -- and I
10 think the pathology assessment was adequate and I don't
11 have any trouble with the pathology review. And
12 therefore I think that the data as presented to us is
13 probably adequate for us to make a decision.

14 Therefore, I would say that because there was a
15 response in the liver in the rats, and for other reasons,
16 that we can say that the -- I agree with the agency that
17 the top two doses, 6,000 and 12,000 ppm, were excessive,
18 and that the findings at 500 is where I'm having problems
19 in whether that is adequate or not.

20 Now the thing that helps me in this a little bit
21 is that at 500 there was some cholinesterase inhibition.
22 Not a great deal, but some. And at least we know that

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1 the malathion is having an effect at that level.
2 However, in females -- and this is the part I couldn't
3 remember and couldn't find in my data whether there was
4 cholinesterase inhibition or not.

5 The mortality of 47 percent in the male, if that
6 is truly greater than 33 percent in a statistical sense,
7 would also suggest that these animals are adequately
8 challenged to the material. However, we didn't see
9 either one of those -- at least according to what was
10 presented to us and what's on the screen right now --
11 same effects in the female.

12 So I'm a little more concerned about the saying
13 that this was a completely adequate study in female rats,
14 although the findings certainly were there at 6,000 and
15 12,000 and we didn't see anything at 500. So I guess we
16 don't know where the true MTD would be, but it's
17 somewhere between 500 and 6,000.

18 And with that I think I'll wait and see if there
19 are other comments by my colleagues.

20 FEMALE SPEAKER: May I ask Gene a question? Are
21 you saying that you think that 6,000 in the females is
22 excessive?

1 DR. MCCONNELL: Yeah, I do, by the way.

2 FEMALE SPEAKER: Oh, you do think that's
3 excessive?

4 DR. MCCONNELL: Yeah.

5 FEMALE SPEAKER: Okay.

6 DR. THRALL: Okay. Other Panel members? Dr.
7 Williams?

8 DR. WILLIAMS: Are we doing these one study at a
9 time now?

10 DR. MCCONNELL: Yes.

11 DR. WILLIAMS: Oh, okay.

12 DR. MCCONNELL: Just the rats.

13 DR. WILLIAMS: But just the rat malathion?

14 DR. MCCONNELL: Right.

15 DR. WILLIAMS: Okay. Well, I thought this study
16 was adequate for evaluation. It achieved -- it exceeded
17 a maximally tolerated dose. And there was adequate
18 survival in lower dose groups to make an evaluation.

19 So I concluded that this is adequate for
20 evaluation -- and I emphasis this -- of technical grade
21 malathion.

22 DR. THRALL: All right. Does anyone else have

1 any comments regarding the rat malathion study? Dr.
2 Boorman?

3 DR. BOORMAN: I would be more inclined to
4 support the EPA position where they accepted the 6,000 as
5 the high dose for the female rats.

6 DR. THRALL: So that you do not think that the
7 6,000 is excessive, then?

8 DR. BOORMAN: Right.

9 DR. THRALL: Okay.

10 DR. BOORMAN: I mean I think that that's
11 probably a debatable point. But as Gene said, it's
12 probably somewhere between 500 and 6,000. But it's
13 probably not unreasonable to accept the 6,000 for the
14 female rats.

15 DR. THRALL: Okay. Dr. Gaylor?

16 DR. GAYLOR: I agree with Gene. It would be
17 nice looking backwards to have a 3,000 or something in
18 that order -- 2 to 4,000 part per million.

19 In a way I think this question is a little bit
20 out of order. It is kind of hard to answer whether this
21 is adequate if we later on say the two top doses are of
22 no value. Then the question is, is 500 adequate. It was

1 clearly stated by EPA that this did not reach a MTD. And
2 then I would have to conclude this is not an adequate
3 study.

4 If we feel like we can work and use the data at
5 6,000 and 12,000 parts per million and that helps us,
6 even though we're calling that excessive, it may be
7 excessive for cholinesterase, but is that really
8 excessive as far as tumor production is concerned.

9 So we've got to have that discussion. And I
10 think until we have that, I don't know how we can answer
11 whether these are adequate studies.

12 MALE SPEAKER: I agree with that.

13 MALE SPEAKER: I agree.

14 MALE SPEAKER: I agree.

15 DR. GAYLOR: Maybe we can kind of revisit or
16 maybe this question will get answered as we go through
17 the rest of the questions. Maybe we can't really answer
18 that right now.

19 DR. BOORMAN: Can I pose one question
20 surrounding that, if we get to that discussion early on?
21 One thing I'm a little unclear of is -- if we agree, for
22 instance, that the two highest concentrations are

1 excessive and it comes down to the issue of is that 500
2 ppm adequate, I'm a little unsure in my own mind where
3 500 ppm stands on the saturation of metabolism.

4 So in other words, in this discussion we're
5 probably going to come down -- coming up with that
6 clearly concentrates that clearly saturate metabolism
7 lead to adverse hepatic effects. And what I was
8 wondering is, where does 500 stand in the saturation of
9 metabolism? Because if in fact a concentration of 500
10 saturates metabolism, then we might come up with a
11 conclusion that in fact that is your highest relevant
12 concentration for the bioassay.

13 DR. THRALL: Does anyone from Kemy Nova have the
14 answer to that on the tip of their tongue? Okay. Maybe
15 tomorrow?

16 DR. GAYLOR: I would like to add something to
17 what Dr. Boorman talked about. And that is that we
18 haven't discussed the -- we, as a panel, the results of
19 these studies. But in my view, the liver tumor in female
20 rats was statistically significant at 12,000 when you
21 combine the adenomas and carcinomas, but was not at
22 6,000.

1 So even though in my opinion the 6,000 ppm was
2 excessive, if there were no neoplasms at 6,000, then this
3 would suggest to me that certainly there wouldn't be any
4 at 4,000 or 2,000 or whatever that level is. So probably
5 it is adequate in that sense in determining whether this
6 material is or is not carcinogenic.

7 With regard to the males -- and this is less
8 important because the rat tumor issue is not apparent in
9 the rat. So from that standpoint, I guess -- and I would
10 like to hear this flushed out a little bit more by some
11 of the other people on the Panel -- it's probably
12 adequate to answer the question if this material is
13 carcinogenic in rats. Although the design could be
14 better.

15 DR. THRALL: Dr. Needleman?

16 DR. NEEDLEMAN: I think -- following up on what
17 Dr. Gaylor said -- there are two major issues that have
18 to be discussed before you can say whether a study is
19 adequate. And the first is, the post hoc exclusion of
20 two dosing groups on the basis of, quote, excessive. The
21 validity of that has to be gone through very carefully.

22 And the second is the PWG. The re-diagnosis of

1 a substantial number of tumors has to be looked at
2 carefully. And I think before we address that as
3 thoroughly as we can, we cannot come to a decision about
4 whether a given study is adequate or not.

5 DR. THRALL: Dr. Boorman, did you have a
6 comment?

7 DR. BOORMAN: I was only cranking up my
8 colleagues.

9 DR. THRALL: Oh.

10 MALE SPEAKER: Well, why don't we discuss those
11 two issues?

12 DR. NEEDLEMAN: Well, could I throw one more on
13 the table that might be very easy to dispense with and
14 one that has been bothering me. We have had -- there
15 were earlier studies that were done, five carcinogenicity
16 studies, and they haven't been talked about. They've
17 been dismissed. And they essentially may be a neutral or
18 a zero contribution to the weight of evidence.

19 Is that something that everyone is comfortable
20 with? If not, then that may also need to be dealt with
21 before we go too much forward. I really don't know.

22 DR. THRALL: De. Dementi?

1 DR. DEMENTI: Can we participate in this, just
2 as you all participate?

3 MALE SPEAKER: It doesn't matter to me.

4 DR. DEMENTI: Considering the male rat, when you
5 consider the mortality was 100 percent in the high dose
6 group and 74 percent in the next group, can you really
7 conclude that male rats have been properly tested such
8 that you can conclude it's negative for males? I mean,
9 that's my concern.

10 You know, you don't have a definitive negative
11 study, and then you drop down to 500 ppm, which is not an
12 adequate dose, in my opinion. And then I'm concerned if
13 whether the F344 rat is indeed -- the male rat is
14 adequate to be tested at sufficiently higher doses to
15 evaluate for carcinogenicity.

16 DR. GAYLOR: Well, I did kind of put into this
17 some of the previous studies. The NTP study at 2,000 and
18 4,000 in the Fischer rat was equivocal for the liver.
19 And that kind of -- it was involved in my thinking on
20 this. You know, I don't recall at what point the animals
21 were dying in that 6,000 ppm group.

22 MALE SPEAKER: On the male rats?

1 DR. GAYLOR: Male rats. Seventy four percent --

2 MALE SPEAKER: They were dying at 79 weeks -- 79
3 to 106 weeks.

4 DR. GAYLOR: Seventy nine to 106? So that -- I
5 think you probably would have had a tumor -- liver tumor
6 response if one would have been there at that late point.
7 I mean, we're up close to 18 months plus.

8 DR. DEMENTI: Well, I seem to recall the NCI
9 study had mortality problems in males.

10 DR. GAYLOR: Had no mortality. But it was at
11 2,000 and 4,000, wasn't it not? I can find out.

12 DR. DEMENTI: Well, I'm saying that there were
13 mortality problems. It was like almost 100 percent
14 mortality at the time.

15 DR. THRALL: Am I getting the sense that the
16 Panel feels that we cannot discuss -- we cannot respond
17 to question number one until we respond to some of the
18 other issues?

19 MALE SPEAKER: I don't know. It seems like it.

20 DR. THRALL: Okay. Well, why don't we go ahead
21 and discuss those issues? Dr. Needleman?

22 DR. NEEDLEMAN: I think that any post hoc

1 revision of a study -- going back and looking at a study
2 after you've got the results -- and then excluding
3 samples is done under great peril. You have to be very
4 careful that you're on solid ground. And the exclusion
5 on the basis of excessive, defined as the level of an
6 enzyme when the outcome of interest is cancer, I don't
7 think that's dependable.

8 DR. THRALL: But it wasn't just the level of the
9 enzyme, right?

10 DR. NEEDLEMAN: Right.

11 DR. THRALL: It's other things like mortality.

12 MALE SPEAKER: Well, are you talking at the
13 6,000 and 12,000?

14 DR. NEEDLEMAN: Yeah, right.

15 MALE SPEAKER: Well, I'm saying the 6,000 and
16 12,000 -- I would maintain that there is significant
17 toxicity there. I mean if one looks at something like
18 just the liver to brain rate ratios, there are tremendous
19 differences between the first three groups and groups
20 four and five.

21 DR. NEEDLEMAN: Is that not part of the
22 carcinogenic process at those doses? I mean, how do you

1 separate that out? Now to me to say that because the
2 ACAG was the major strut of that argument in defense is
3 like saying, I'm not going to marry you because you're
4 shoes are too big.

5 DR. GAYLOR: No. Herb, it wasn't for me the
6 major -- in fact, I didn't even consider it in
7 considering whether it was an excessive dose -- the ACAG.

8 DR. NEEDLEMAN: Well, why were they excluded by
9 CARC II?

10 DR. GAYLOR: Because they were dying from the
11 material.

12 MALE SPEAKER: Yeah, it was systemic toxicity.

13 DR. GAYLOR: And they weren't gaining weight.
14 Classical reasoning for interpreting whether a MTD has
15 been exceeded or not. This met the classic definition.

16 DR. NEEDLEMAN: Because the rodents were sick at
17 that dose?

18 DR. GAYLOR: Yeah. And dying.

19 DR. NEEDLEMAN: And that excludes the
20 carcinogenic mechanism?

21 DR. GAYLOR: No, it doesn't necessarily exclude
22 it, but it puts it in a light where you try to explain

1 it. And typically it does -- it certainly taints an
2 observation. And in a case like this, it probably
3 suggests that those doses were excessive to the point
4 that these animals were not normal by any reasonable
5 definition.

6 DR. NEEDLEMAN: Well, I'm going to go back and
7 read CARC II, because I don't think that was the
8 expression. That was only a part of it. The major strut
9 of the exclusion argument, I believe, was that the ACAG
10 levels were down in blood and brain, and in brain there
11 were only 20 or 30 percent.

12 DR. COPLEY: If I may make a comment? We never
13 said we excluded those. We actually concluded that there
14 was a carcinogenic effect at those levels.

15 DR. NEEDLEMAN: Yeah. But they were --

16 DR. COPLEY: But we never said that these
17 weren't tumors, and we never said they weren't due to
18 treatment.

19 DR. NEEDLEMAN: Right.

20 DR. COPLEY: So I'm not sure what you're saying
21 we're excluding.

22 MALE SPEAKER: You excluded it from risk

1 assessment.

2 DR. NEEDLEMAN: In deciding whether they were
3 carcinogenic or not, you dismissed those two groups from
4 your consideration.

5 DR. COPLEY: We concluded they were
6 carcinogenic. But if you're talking about malathion as
7 in total, we didn't look at any one individual study.
8 That's where the weight of the evidence comes in. And I
9 think you should look at the individual studies first
10 before you make a conclusion that really has to do with
11 the entire weight of the evidence that pertains to all of
12 the studies together and the whole database.

13 MALE SPEAKER: But for the purposes of the rat
14 study, can we talk about whether we think as a Panel the
15 maximum tolerated dose has been exceeded at 6,000 and
16 12,000, because isn't that the issue at hand? And I mean
17 that was done on a basis of systemic toxicity, not on a
18 basis of depression of the cetyl cholinesterase levels.

19 MALE SPEAKER: Right.

20 DR. GAYLOR: It was for me. I mentioned the
21 cholinesterase levels at 500 just to show that the
22 animals were getting an exposure that did cause some

1 effect.

2 MALE SPEAKER: Yeah. I mean the one aspect of
3 the MTD is that it produces -- the animals are dying from
4 toxicity other than that relating to the development of
5 tumors. And that's clearly the case here in both males
6 and females. There is excess mortality due to the
7 toxicity of the compound, so it has exceeded a MTD.

8 DR. ROBERTS: Can I ask Dr. Copley a quick
9 question? If I understand you correctly then, the agency
10 has used these, quote, excessive doses to make a
11 qualitative decision, but would not necessarily use those
12 to make a quantitative decision in terms of establishing
13 dose response relationships.

14 Would that be a fair statement?

15 DR. COPLEY: That's one of the statements that
16 is actually in the guidelines that I read to you.

17 DR. ROBERTS: Okay. So in other words, to make
18 a decision about whether or not in a qualitative sense
19 it's a carcinogen it was used by the agency.

20 DR. COPLEY: Right.

21 DR. ROBERTS: But the agency wouldn't recommend
22 because of an altered physiologic state that these

1 represent dose response information that would be
2 valuable.

3 DR. COPLEY: When you look at this study
4 individually, we concluded that although the incidence of
5 the liver tumors were observed only at excessive toxic
6 doses, it provided evidence of carcinogenicity. When you
7 look at that study.

8 DR. GAYLOR: In the female?

9 DR. COPLEY: In the male also. I'm sorry. In
10 the female. I'm thinking the mouse.

11 DR. GAYLOR: I'm only talking about the liver,
12 too, by the way.

13 DR. COPLEY: In the female, yes.

14 DR. GAYLOR: We need to get to the oral tumors.

15 DR. COPLEY: No. When I said the male, I was
16 thinking of the mouse. In the female.

17 And I just want to make one comment on
18 mortality. For the female, it was 31 percent for the
19 controls, 26 percent and 25 percent for the next two low
20 doses. At 6,000 it was only 38 percent, which is not a
21 whole lot higher than the controls, and it jumped up to
22 64 percent at 12,000 parts per million.

1 And that's one of the reasons why we didn't
2 consider 6,000 to be excessive, because at 500 parts per
3 million, the mortality was 47 percent, and we didn't
4 consider that one to be excessive, either.

5 DR. THRALL: Yes, Dr. Dementi?

6 DR. DEMENTI: Back to that NCI study --

7 MR. LEWIS: Dr. Dementi, into the microphone,
8 please. Thank you.

9 DR. DEMENTI: In the 1978 NCI study in the F344
10 rat for malathion, survival was 16 percent at 4,000 ppm.
11 No, I'm sorry. Survival was zero at 4,000 ppm. It was
12 28 percent at 2,000 and 54 percent in the control. In
13 other words, survival was a problem in the NCI study.
14 Even at 4,000 or 2,000 in males, we are not out of the
15 woods with mortality.

16 MALE SPEAKER: Can I just remind you that is a
17 different test material than this test material?

18 DR. DEMENTI: Oh, yeah, that was American
19 Cyanamid. You're right.

20 DR. THRALL: All right. Gene, do you want to
21 address the other studies as potential carcinogenic?

22 DR. MCCONNELL: Well, I think we ought to

1 continue on the rat.

2 DR. THRALL: Okay.

3 DR. MCCONNELL: But I'm at your pleasure. Are
4 we at a point where we can talk about the oral and nasal
5 tumors?

6 DR. THRALL: Certainly.

7 MALE SPEAKER: Well, what are we doing here?
8 Are we deciding whether the studies are adequate, or are
9 we evaluating the studies?

10 DR. THRALL: Well, there was some discussion
11 that we could not determine whether these studies were
12 adequate to assess the carcinogenicity until we had some
13 further discussions. And I think that's sort of where we
14 were.

15 DR. GAYLOR: And I think we've had that
16 discussion.

17 DR. THRALL: So are we happy with that?

18 DR. GAYLOR: And I probably will bend towards my
19 colleague. I guess I would have to agree, after thinking
20 more about it, that while I was equivocal on the females,
21 I probably -- or males -- I think they are probably
22 adequate.

1 But, again, I would like to hear other people.
2 This is just me. We didn't --

3 MALE SPEAKER: Could I get EPA -- you had
4 indicated that in the males the 47 percent mortality was
5 -- you really didn't consider that to be significant at
6 500?

7 DR. COPLEY: I'm not saying it's not
8 significant. What I'm saying is it's not evidence of
9 excessive toxicity. It is toxicity, but we -- that's one
10 of the things that you --

11 MALE SPEAKER: Well, I guess the question would
12 be, in absence of the other two concentrations, would
13 that 500 milligrams per kilogram be an acceptable MTD for
14 a study?

15 DR. COPLEY: It probably would be an acceptable
16 high dose.

17 DE. DEMENTI: And I disagree. For females?

18 MALE SPEAKER: Who's disagreeing?

19 DR. COPLEY: We're talking about males.

20 MALE SPEAKER: Well, for males or females.
21 Females had even less mortality. It was 38 percent or
22 something like that.

1 MALE SPEAKER: That's more of a concern to me
2 than the excessive toxicity. It sounds like we can
3 identify many parameters that would contribute to that.
4 But I'm more concerned that we've got what's left, an
5 adequate MTD to call it adequate or negative.

6 Oh, you say it is. By EPA standards?

7 DR. COPLEY: I would agree with Dr. McConnell
8 that we're talking about marginal adequacy, because we're
9 only dealing with two doses at this point. But if we saw
10 that type of effect at the high dose, we would not
11 consider that to be an unacceptable high dose of the
12 study.

13 DR. GAYLOR: Well, I disagree.

14 MALE SPEAKER: Well -- okay. I mean, my take --
15 we're talking about males, now, is that right? Okay. So
16 the way I would look at this is that 12,000 exceeded the
17 MTD, 6,000 was a MTD, and I would evaluate that dose. I
18 wouldn't evaluate 12,000.

19 MALE SPEAKER: In males?

20 MALE SPEAKER: Males.

21 DR. GAYLOR: But --

22 DR. DEMENTI: There was 74 percent mortality.

1 MALE SPEAKER: Yeah, but it occurred quite late.
2 You only had --

3 DR. BOORMAN: I think that -- excuse me. Gary
4 Boorman here. I think that you've also got to look at
5 the survival. And we had NTP studies where people have
6 argued about the survival, and then you find out that
7 most of the mortalities are in the last two or three
8 weeks. And essentially the animals are at risk.

9 And certainly if --

10 DR. THRALL: Gary, do you want to bring that
11 microphone closer to you?

12 DR. BOORMAN: If you look on page 32 of one of
13 the many handouts that we have --

14 MALE SPEAKER: Any particular one?

15 DR. BOORMAN: Yeah. I don't care which one. At
16 500 parts per million, you had just only 300 -- you only
17 had three unscheduled deaths up to 78 weeks of age as
18 opposed to in the highest dose you had, you know, almost
19 20. And so there is quite a difference, and you had a
20 lot of animals that were at risk at least for 18 months.
21 Now the other thing that you might have to look at is
22 time to first tumor to see how many animals were at risk

1 for each tumor type.

2 But there was fairly reasonable survival in this
3 6,000, at least through the first 18 months, and we would
4 need a more detailed analysis to find out whether it was
5 19, 20 or 21 months when they died.

6 MALE SPEAKER: So you're saying 20 animals died
7 before 18 months in the 6,000 part per million group?

8 DR. BOORMAN: No. Three.

9 MALE SPEAKER: Three in the 6,000?

10 DR. BOORMAN: Three unscheduled. And this is on
11 page 32 of this document two.

12 MALE SPEAKER: And then about 20 in the high
13 dose?

14 DR. BOORMAN: Right.

15 DR. MCCONNELL: I think that's a strong argument
16 in my experience.

17 MR. ROWLAND: Well, what about body weight?

18 DR. THRALL: Mr. Rowland?

19 MR. ROWLAND: In addition to the mortality and
20 the cholinesterase inhibition, at the 12,000 in males the
21 body weight gain decrease was 32 percent, and at the
22 6,000 it was 13 percent.

1 MALE SPEAKER: Thirteen?

2 MALE SPEAKER: One three.

3 MR. ROWLAND: And in the female at 12,000 the
4 decrease was 15 percent, and at 6,000 it was four.

5 DR. MCCONNELL: So I think it's fair to say
6 that, you know, these animals certainly were challenged
7 by this material, and for a majority of them -- or a vast
8 majority of them for greater than 18 months. And I don't
9 think it's unreasonable to believe that if a carcinogenic
10 effect were to occur in the liver, that it probably would
11 have been seen in those males at that 6,000 ppm.
12 Possibly not at the higher dose, because they didn't
13 survive quite as well.

14 Would the rest of the pathologists and others
15 agree with that statement?

16 MALE SPEAKER: Yeah.

17 DR. BOORMAN: Well -- and also I take into
18 account the fact that 26 percent of the animals survived
19 to the end of the study.

20 DR. MCCONNELL: And still there was no evidence.
21 Right.

22 DR. BOORMAN: Yeah, nothing.

1 DR. MCCONNELL: Does anybody on the Panel take
2 exception to that?

3 DR. GAYLOR: Well, I have a problem with the
4 males being an adequate study. The females I think
5 probably okay.

6 DR. THRALL: Dr. Gaylor, could you speak up?

7 DR. GAYLOR: I think the 6,000 part per million
8 dose in the females seems to be acceptable at a MTD or
9 thereabouts.

10 But in the male rat, they have no survivors to
11 the end of the study. They had --

12 DR. BOORMAN: No, that's not right.

13 DR. GAYLOR: We had 26 percent in the 6,000 part
14 per million group surviving to the end of the study. And
15 it would be nice if we had survival curves like NTP
16 publishes. Then we could look at these and it would be a
17 lot easier. I mean, we've got one table here that shows
18 18 month survivorship. Well, 71 -- well, it shows 98
19 percent survivorship in the 6,000 part per million group.
20 That's pretty good at 18 months, right?

21 MALE SPEAKER: Yeah.

22 DR. GAYLOR: That's in the male rat at 6,000

1 parts per million. So it looks like at the 6,000 parts
2 per million group in male rats was adequate. There were
3 enough animals at risk.

4 DR. THRALL: So the Panel thinks that the rat
5 study was adequate to determine carcinogenicity for the
6 liver.

7 DR. GAYLOR: For the liver.

8 DR. THRALL: All right.

9 MALE SPEAKER: Well, and for any other organ.

10 MALE SPEAKER: Yeah.

11 DR. GAYLOR: Well, we're not saying whether it
12 was positive or negative, but it was adequate to
13 determine whether there was a carcinogenic effect. And
14 then we'll have to discuss the different tumor types
15 subsequent to that. I think we're trying to get some
16 direction to this in that sense.

17 DR. THRALL: Okay.

18 DR. GAYLOR: Now I think the females -- I think
19 there is a consensus that that was an adequate study,
20 correct? All right?

21 DR. THRALL: All right.

22 DR. GAYLOR: So do you want to move -- in terms

1 of adequacy, do we want to move to the mice?

2 DR. THRALL: Let's move to the mice.

3 DR. GAYLOR: All right. Well, one other thing
4 we ought to say about adequacy. And that is that we have
5 significant body weight depression, and it's well known
6 that there is a decrease in tumor incidence with a
7 decrease in body weight for several tissue sizes,
8 particularly the hormonal type tumors.

9 So with the large body weight depression that we
10 have in the rats, 10 percent in the males at 6,000 parts
11 per million and 15 percent at 12,000 parts per million,
12 we may have severely decreased our ability to see certain
13 types of tumors that are related to body weight. And
14 it's just speculation. I don't have any evidence one way
15 or the other.

16 MALE SPEAKER: Well, that's one of those
17 circular kinds of arguments that one can never design an
18 ideal study, then. If you design a study where they have
19 adequate weight --

20 DR. GAYLOR: No, you can't design it. But the
21 data analysis can take into account the reduction in body
22 weight and make an adjustment for that, or look at the

1 power of these studies in terms of that reduced body
2 weight. And that would help us answer whether these are
3 adequate or not.

4 DR. WILLIAMS: David, can I ask you a question
5 about that?

6 DR. GAYLOR: Yeah.

7 DR. WILLIAMS: Gary Williams here. What you're
8 saying is certainly true with choleretic restriction.
9 But has it ever been demonstrated that a chemical
10 mediated toxicity impaired the ability to detect a
11 tumorigenic response?

12 DR. GAYLOR: Well, yeah, if you kill all the
13 animals, obviously.

14 DR. WILLIAMS: Well, yeah. But you were talking
15 about body weight.

16 DR. GAYLOR: Body weight?

17 DR. WILLIAMS: Yes.

18 DR. GAYLOR: Yeah. And you can go back and look
19 in some of the NTP studies where there is a significant
20 decrease in body weight due to what ever reason. The
21 animal didn't eat or was toxic. And Sealkoff has
22 published a paper in '95, I believe it is, that shows

1 relationships between body weight and tumor incidence for
2 a number of tumor sites.

3 And a 10 percent decrease, for example, in body
4 weight -- I would have to look at their paper. But a 10
5 percent decrease in body weight -- and I'm thinking of
6 mice right now. It could have as much as -- it could
7 reduce the tumor incidence in liver tumors, for example,
8 in mice by an incidence change of 20 percent. It can be
9 quite high.

10 And you know, that's another part of the
11 analysis. We've got liver tumors, anyway. We don't have
12 to go through that adjustment here. But the question is,
13 well, possibly there were some other tumors that might
14 have been missed. I don't know.

15 DR. WILLIAMS: I mean, what you've have to see
16 is the chemical inducing tumors at a dose that doesn't
17 effect body weight gain. And then when you get into a
18 higher dose where there is a reduction in body weight
19 gain, then the incidence of tumors drops off.

20 DR. GAYLOR: Well, we've got a lot of examples
21 in these data where at the high doses we have a decrease
22 in tumors.

1 DR. WILLIAMS: Yeah. But we don't have tumors
2 at the lower doses.

3 DR. GAYLOR: But we have some -- we have some
4 examples that I want to talk about tomorrow where at mid
5 doses we have maybe an increase in tumor incidence and
6 then we don't have it at the higher dose. And that may
7 be due to survival. It may be due to body weight. I
8 think we need to discuss some of this tomorrow.

9 MALE SPEAKER: Can I ask a clarification? I
10 hate to sub-divide questions to make more work. But are
11 we judging -- we're judging the acceptability of the
12 study to make a qualitative determination of
13 carcinogenicity, or are we judging the acceptability for
14 determining a dose response relationship? And it makes a
15 difference, again, on how we use those high doses.

16 DR. THRALL: Dr. Copley?

17 DR. COPLEY: Yeah. It's a matter of if the
18 study had no tumors in it whatsoever, and we had these
19 doses with these effects, would we consider this an
20 acceptable study?

21 MALE SPEAKER: Yes.

22 MALE SPEAKER: Absolutely.

1 DR. COPLEY: That's essentially what the
2 question is. And then you can go from there to decide if
3 the tumors are treatment related or spontaneous or
4 whatever. But if the study is not acceptable, you're
5 already starting from a problem.

6 DR. NEEDLEMAN: I want to raise a question about
7 that.

8 DR. THRALL: Dr. Needleman?

9 DR. NEEDLEMAN: Are we including in the
10 definition of acceptability the PWG re-read?

11 DR. COPLEY: The PWG re-read has to do with the
12 tumors. It doesn't have to do with the general toxicity.
13 It's whether the doses are considered acceptable.

14 DR. NEEDLEMAN: I understand that. So
15 appalachian of acceptability ignores PWG?

16 DR. COPLEY: It is not looking at the
17 carcinogenic effect.

18 DR. NEEDLEMAN: Okay.

19 DR. COPLEY: If you have a study, however, that
20 has no toxicity at all, we would normally say it's not an
21 acceptable study. But if you actually had tumors at that
22 high dose, we would say we accept it anyway.

1 DR. NEEDLEMAN: Okay. I understand.

2 DR. COPLEY: But the PWG -- the cancer values do
3 not play into initially whether a study is considered
4 acceptable or not.

5 DR. NEEDLEMAN: Okay.

6 DR. COPLEY: Unless it's positive.

7 DR. NEEDLEMAN: Well, that's a matter for later
8 discussion. All right.

9 DR. THRALL: So I think the consensus of the
10 Panel is that the rat studies are acceptable.

11 Now can we move on to the mouse?

12 MALE SPEAKER: Sure.

13 DR. GAYLOR: All right. The mouse study, of
14 course, was at higher dose levels of 8,000 and 16,000.
15 And let me change my page here.

16 DR. THRALL: Page 18 in the handout that you got
17 a couple of days ago, if you're looking there. I mean
18 page eight. I'm sorry.

19 DR. GAYLOR: And this study was with B6C3F1
20 mice, males and females, 65 in each group. And I thought
21 the number of animals was adequate. Again, this was in
22 the diet. Stability and so forth was tested and it

1 appeared to be stable for two weeks. And they changed
2 the feed every week. So I felt that in that regard it
3 was an adequate study.

4 The choice of doses, again, has the same
5 problems that the previous study had. Ideally there is a
6 big gap between 800 and 8,000, although it was explained
7 to us the rationale for choosing those doses. Whether I
8 agree with it or not is a different issue. But at least
9 it was explained.

10 As I see it, I can go several -- do several
11 approaches to this. But I think it's going to come down
12 to the bottom line in terms of the adequacy of the
13 design. It's going to be the duration of the study, the
14 18 month versus a 24 month. Now the EPA guidelines call
15 for 18 months. We understand that.

16 But I imagine that was done way back when -- and
17 most of your studies are in CD-1, and 18 months was
18 certainly adequate for a CD-1 mouse, because they have a
19 shorter life span. But with this strain of mouse, which
20 you have a pretty good survival to two years, it would
21 have been more ideal to have a two year study.

22 I would say, using your terminology, if this

1 study had been negative at 18 months, I would have called
2 it inadequate. But it wasn't. I mean there was
3 significant tumor response in both the males and females
4 in the liver. So in that sense, you were able to show a
5 carcinogenic effect. And I don't think there is any
6 debate about whether it was or was not carcinogenic. It
7 certainly was.

8 So the issue for me was at the 100 and 800 ppm
9 levels, which were not significant, whether they would
10 have been significant if the study had gone on to 24
11 months. And I think Dr. Dementi asked that same
12 question, right?

13 DR. DEMENTI: I mean, I didn't actually ask that
14 question, but certainly that would be the one question.
15 I'm asking the question a little bit different.

16 DR. GAYLOR: So I'm going to reserve my view on
17 this until I hear some -- my bottom line until I hear
18 some comment from other people.

19 DR. THRALL: Dr. Williams?

20 DR. WILLIAMS: Gary Williams. Well, I concluded
21 that the top two doses had achieved a MTD, both by body
22 weight gain reduction and of course these other,

1 particularly the brain cholinesterase effect. And I
2 think there is good survival, so we've got heavily
3 challenged animals to look at for 18 months. And this
4 answers your question from rats, whether 18 months is
5 enough to see a tumor, and it is.

6 So I think for me it's a good quality study. I
7 accept it.

8 DR. THRALL: Do other Panel members have
9 comments? Dr. Gaylor?

10 DR. GAYLOR: Well, obviously it was adequate to
11 see liver tumors. I guess the question is, was 18 months
12 in the mouse adequate to see other types of tumors that
13 might occur later than liver tumors. That would be one
14 question.

15 If we accept the high dose liver tumors, you
16 could say well, it doesn't really matter. But if we're
17 not going to accept the high dose liver tumors as being
18 relevant because the animals are excessively stressed,
19 then I guess we would have the same problem if we had
20 seen any tumor. We would argue it was due to stress and
21 not due to the chemical.

22 Well, we're going to discuss the relevance of

1 the tumors in subsequent questions, right? And by
2 relevance I mean in terms of classification of malathion
3 as likely or unlikely or whatever.

4 But at this point, I think we're restricting
5 this to whether the study was adequate to determine
6 whether there are carcinogenic effects. And I guess I
7 agree with Dr. Williams that we certainly saw
8 carcinogenic effects, so it's adequate from that
9 standpoint. Adequate to see liver tumors. I don't know
10 whether it's adequate to see other tumors.

11 I would like to hear some other people speak to
12 this. I don't want to hog the microphone.

13 MALE SPEAKER: Well, I think one thing we have
14 to accept here, and that is that if a study follows the
15 guidelines that have been in place at the time the study
16 was done, that you can't change the rules after the fact.
17 Now we've got an 18 month study. And we can lament that
18 we didn't see the last six months, but we can't disregard
19 it.

20 (END OF TAPE 4, SIDE A)

21 DR. THRALL: All right. So that covers
22 malathion. Do you want to address the third study, then,

1 the adequacy of the malaoxon?

2 DR. GAYLOR: I really hadn't focussed on the
3 malaoxon as much. I've got to find my notes around here
4 somewhere. I was going to do this tomorrow morning, by
5 the way.

6 DR. THRALL: We'll let Dr. Williams go ahead.

7 DR. GAYLOR: Yeah, if you don't mind.

8 DR. WILLIAMS: Okay, yeah. Gary Williams. Yes.
9 I concluded that this was also an adequate study. It
10 produced at the high dose toxicity and increased
11 mortality, about 50 percent in both genders, which then
12 leaves enough -- plenty enough mice -- or rats, that is,
13 for evaluation.

14 So I considered it an adequate study.

15 DR. THRALL: Does everyone on the Panel concur
16 with that or have any additional comments? All right.

17 DR. GAYLOR: Can you give us a minute or two?

18 DR. THRALL: Yes.

19 DR. GAYLOR: I want to look for my notes.

20 DR. THRALL: Dr. Gaylor?

21 DR. WILLIAMS: I mean, by the way, you know, the
22 CARC considered 1,000 adequate. But, I mean, I also

1 considered 2,000 to be adequate.

2 DR. THRALL: All right. No additional comments
3 then? So, Dr. Copley, have we sufficiently addressed
4 question number one?

5 DR. COPLEY: Yeah.

6 DR. THRALL: Okay. Then I think, unless anyone
7 else has anything further to add, that this is probably a
8 pretty good place to adjourn for today.

9 We will reconvene tomorrow morning at 8:30, and
10 we'll go directly into issue two at that point.

11 MR. LEWIS: I think the Panel today has asked
12 various parties that have presented here, such as the
13 agency and public commenters, for information. I think
14 everyone knows what is being required of them, based on
15 their remarks today.

16 Okay. Just again I want to thank the Panel
17 members for their service today. I look forward to
18 seeing everyone tomorrow at 8:30.

19 Thank you.

20 DR. THRALL: And if Dr. Frank Carter is in the
21 room, we've got two messages up here.

22 **(Whereupon, the meeting was adjourned.)**