NATIONAL TOXICOLOGY PROGRAM

PUBLIC MEETING OF THE REPORT ON CARCINOGENS

October 21, 1999

DR. GOLDSTEIN: Let me introduce Dr. Kenneth Olden, Director of NIEHS.

DR. OLDEN: Good morning. I've been trying to convince the Department of Health and Human Services and the Environmental Protection Agency that they should buy a plane, and it would save the government a lot of money. This morning there were so many of us on the flight and it was late.

But let me say, first of all, thank you for taking the time to come here for a second time, and let me apologize for the fact that most of us were unable to get here three or four weeks ago. And I'm especially grateful to Bernie Goldstein because I called him after he had traveled halfway across the US -- he was out in the Midwest someplace -- to get here, and I reached him in the hotel after he had arrived telling him that we were going to be unable to get here, and we had to cancel this event.

So I really appreciate the fact that you've come here again to express your views about the

Report on Carcinogens. It is important to us and I know it's important to you. So we regret the conditions and certainly appreciate your understanding and your patience.

Now, let me just spend a few minutes to say that during my tenure as Director of the National Toxicology Program and the NIEHS, I spent an awful lot of time during the first year and a half to two years having conversations with various groups that are interested in the products of the National Toxicology Program.

For example, we visited universities and industry. We taught the university and industry scientists. We talked to heads of environmental groups, various industry groups, labor groups, leaders at various government agencies, for example, the Environmental Protection Agency, the FDA, NIOSH, CDC, ATSDR, NCI, Consumer Products Safety Commission.

We talked to an awful lot of people. We talked to members of Congress. And, actually, we had focus groups and town meetings around the country, and the purpose was to talk to you to find out what an agency like the NTP and all of its responsibilities should be doing for you, the

American people.

I also convened a round table in 1993 where we brought together all the various groups mentioned above -- industry, government, environmental groups, academia -- to talk about partnerships between NTP and the various groups.

I think it's fair to say that we've actually reached out to the American people to hear your concerns about the activities of the National Toxicology Program.

Now, based on what I heard during those first year, year and a half, we convened two panels. The panels were composed, roughly, of 40 people per panel, and one was to take a look at the National Toxicology Program. The second panel was to take a look at the Report on Carcinogens.

Now, many of the persons in attendance here today were also parts -- members of those -- either one or both of those panels. Now, the respective panels deliberated for more than a year. They wrote a set of recommendations, and I can say that the NTP and the Secretary of the department accepted all the recommendations made by these two review panels.

Now, the recommendations will be reviewed

shortly. The changes that we've made over the years in the Report on Carcinogens will be reviewed by Dr. Bill Jameson.

Now, let me make it clear. I think we have a good process. Also, I am satisfied that we have followed the process in the preparation of the 8th and 9th Report on Carcinogens. However, the fact that we have a good process and that we follow the process does not mean that the process cannot be improved. And that is why we're here today. We're here to get your advice and your input.

Now, many of you have written to me. As a matter of fact, maybe most of you have written to me, and I can say that you've offered many good suggestions. We will discuss -- we've already had internal discussions about many of your suggestions, and since we've gone through this process now twice for the 8th and the 9th, we have had internal discussions among the NTP Executive Committee and the NTP staff about ways that we realize and we believe that we can improve the process.

Now, I anticipate that I will hear -- we will hear many good suggestions offered over the next

two days. Maybe they'll be extensions of the good ones that you've already offered.

In closing, let me say that I am 100 percent committed to sending the Secretary an outstanding product, and that is the Report on Carcinogens. I think everything that we have done over the past eight years indicates exactly that. I want to send the Secretary a report that is based on the best science that is available at the time, a report that is based on rigorous external peer review.

I thank you for your input into the process, and I thank you for your support over the years, and I look forward to a productive discussion over the next two days. Thank you very much.

DR. GOLDSTEIN: Thanks, Ken.

Our next speaker is Bill Jameson from NTP.

DR. JAMESON: I would also like to welcome everybody to this meeting today and tomorrow, taking the time to come here and share your input with us about the Report on Carcinogens.

I'd just like to emphasize that we are here today to receive public comment on the criteria and the process for reviewing the nominations for the

Report on Carcinogens. That's the purpose of our meeting.

I'm Bill Jameson. I'm Head of the Report on Carcinogens Group at NIEHS and responsible for the coordination of reviews and the actual preparation of the report.

This slide just shows that the RoC was nominated as part of the 1978 Public Health Service Act, which requires that the Secretary of Health and Human Services to publish an annual report which contains either a list of substances which are either known to be human carcinogens or may reasonably be anticipated to be human carcinogens and to which a significant number of persons residing in the United States are exposed.

This legislation was amended in 1993 to make it a biennial report. So after the law was amended in '93, it clearly states that this report must be published every two years.

The latest report to be published was the 8th Edition, which was published in 1998. We are in the final stages of completion of the 9th Report, which will be submitted to the Secretary very shortly. Reviews of the 10th Report will begin this year, and we are working with a 2001 publication

date for the 10th Report.

The first set of nominations for the 10th Report will be reviewed in an open public meeting by the Board of Scientific Counselors Subcommittee, which is scheduled for December 16 and 17.

This slide shows the current criteria for listing in the Report. I realize this is a difficult slide to read, but you have copies as part of your handout that are available where you signed in.

There are two categories for listing: Known to be human carcinogens and reasonably anticipated to be human carcinogens. The descriptive bottom paragraph that follows pertains to both listing categories of the criteria. This paragraph became part of the criteria as a result of the public review of the criteria, which was performed in '94 and '95, which Dr. Olden alluded to earlier, and emphasizes that "conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment with consideration given to all relevant information." This revision to the criteria was one of the main reasons why the process for reviewing the nominations was revised to include external peer reviews in a public forum.

As you see, the criteria have two categories. The first is known to be human carcinogens, where agents, substances, mixtures, or exposure circumstances for which there is sufficient evidence of carcinogenicity from human studies are listed. Human studies are not limited to human cancer epidemiology studies, but also include consideration of relevant information from human metabolism, pharmacokinetic, or genetic toxicology studies which relate to the mechanism of action for cancer formation in humans.

The second category is reasonably anticipated to be human carcinogens, where agents are listed for which there is either limited evidence of carcinogenicity from the human studies or there is sufficient evidence of carcinogenicity from studies in experimental animals, which could include increases in malignant and/or a combination of malignant and benign tumors in multiple species or tissue sites, by multiple routes of exposure or unusual incidence, site, or tumor type, or age of onset, or there may be sufficient structure activity or mechanistic data, which indicates that it should be listed as a reasonably anticipated human carcinogen.

Again, to emphasize, the conclusions regarding either known or reasonably anticipated human carcinogens are based on scientific judgment with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance.

This slide gives an overview of the review process for the Report, and I will go through this in detail. A one-page outline and a four-page detailed description of the process is contained in the handouts that were available to you when you signed in.

We start here with the nominations. They are routinely solicited by publication of requests for nominations in the Federal Register and other appropriate publications. The nominations come from the public as well as State and Federal agencies, industry, labor, academia, and are also generated by review by the NTP of the current literature to identify substances that may meet the criteria for inclusion in the report.

Once a nomination is initially identified, there is an announcement published in the appropriate publications that solicits public comment on the nomination.

The original nomination, with data provided and/or supplemented by a limited literature search, and all public comments received in response to the announcement of our -- the intent of reviewing a particular nomination, our initial review by the NIEHS/NTP Review Group, which is referred to as RG1, to determine if the preliminary information available is sufficient to merit further consideration.

If the RG1 determines there is insufficient information in the original nomination available to warrant consideration by the NTP, the nomination will not be considered further and will be returned to the nominator, who will be invited to resubmit the nomination with additional justifications.

A notice of this action will be published, and the NTP Board of Scientific Counselors and the NTP Executive Committee are notified of this action.

If it is determined that a nomination merits formal consideration, that it contains sufficient relevant information to go forward, we initiate our own independent search of the literature and

prepare a draft background document, which contains all of the relevant information and addresses issues that have been identified in the public comments that we receive in response to the Federal Register announcement concerning a particular nomination.

I must emphasize that the data concerning the human and experimental animal studies that we include in the background document must come from publicly available, peer-reviewed sources.

The formal review of the nomination, again referring to the RG1, is described in detail in the handout. The original nomination and all public comments received in response to a nomination are formally reviewed by the RG1. The RG1 reviews all relevant information available for each nomination and makes its recommendation to the Director of NTP for those nominations determined to contain sufficient information for making a decision for listing or delisting in the report.

Nominations reviewed by the RG1 for which it is determined that sufficient information to make a recommendation for listing or delisting could not be obtained will not proceed further in the review process. The other RoC review groups, as well as

NTP Executive Committee, will be informed of this action.

The original nominator will be notified of the RG1 action and be invited to resubmit the nomination with additional justification for review for either listing or delisting in the report. All nominated agents, substances, or mixtures reviewed by the RG1 that are not selected for listing or delisting in the report will be included in subsequent editions of the Report on Carcinogens with the reasons why they were not considered further.

Once the nomination has completed the RG1 review, it goes forward to the Interagency Working Group for the Report on Carcinogens, which we'll refer to as the RG2. This is a committee made up of representatives from the NTP Executive Committee and includes the NCI, NIEHS, the FDA/NCTR, NIOSH, NCEH, ATSDR, CPSC, EPA, and OSHA. Again, the handout that you have describes in detail the RG2 review.

After the RG2's consideration of all the relevant information and the public comments, it makes its recommendation to the Director of NTP concerning the listing or delisting of the nominated

substance.

Following the RG2 review, the background documents that are listed there is finalized and an announcement is published announcing the meeting of the Board of Scientific Counselors and the public availability of the background documents as well as solicit public comment. So at this point, again, we actively solicit public comment on the nomination and also make the background document that we had prepared concerning the nomination available for public distribution and comment.

So the notice also invites interested parties to submit written or present oral comments at the Board Subcommittee meeting -- during the public meetings that are held.

Since the establishment of the new review procedures for the Report on Carcinogens back in '96, this announcement was published four weeks prior to the Board Subcommittee meeting with a deadline for submission of comments of the day before the meeting, and this particular process has caused some concern as it is felt that it does not allow enough time for consideration of the comments by the Board Subcommittee.

This is an issue that has been a topic of

many discussions by NTP staff, as Dr. Olden alluded to earlier, and I'm sure will be discussed here today. The NTP is considering several options concerning this issue and following the input received today will make changes in the process to address that concern.

The NTP Board of Scientific Counselors, the Report on Carcinogens Subcommittee, meets in an open public meeting to review the nominations and receive public comments concerning individual nominations.

Again, details of the Subcommittee review are contained in the handout. I won't take the time to go through them now. Upon completion of its review, the Board Subcommittee makes its recommendations to the Director of the National Toxicology Program concerning the listing or delisting of material in the report.

Again, following the Board Subcommittee meeting, we actively solicit public comments on the final recommendations that were made by the three scientific review groups.

There is an announcement published that contains all recommendations of the three scientific review groups and solicits final public comments

and input on the nomination. Following receipt of the final public comments, the recommendations of the RG1, the RG2, and the Board Subcommittee and all public comments that have been received in response to the various announcements concerning review of the nominations are submitted to the Director of the National -- are reviewed by the NTP Executive Committee.

The NTP Executive Committee, made up of the agencies that I pointed out earlier, reviews the public comments and the recommendations concerning the nominations and will make -- or, actually, they provide their agency's opinion of the recommendation of the nominations to the Director of NTP.

Then all of the recommendations that have been made by the various groups, the RG1, the RG2, the Board Subcommittee and the Executive Committee, plus all the public comments that are received in response to our announcement, go forward to the Director of the National Toxicology Program, who reviews all of this information and ultimately makes his final recommendation to the Secretary of Health and Human Services for what should be listed or delisted in the report by

submitting the final draft of the Report on Carcinogens.

The Secretary of Health and Human Services has the final authority for what is contained in the final version of the Report on Carcinogens. Upon review of the final draft submitted by the NTP and approval of the report, the Secretary forwards the report to Congress, and a notice is published announcing the availability of the final report, and this announcement also identifies all newly listed or delisted agents, substances, mixtures, or exposure circumstances in that edition of the Report on Carcinogens.

So this is a rather extensive two-year process to put together the final draft of the report, which the NTP, as delegated by the Secretary, submits to the Secretary for approval.

So that concludes my presentation. I tried to make it short because of the time constraints, and I'll be available if there are any comments or questions.

DR. GOLDSTEIN: Thanks, Dr. Jameson.

Dr. George Lucier is head of the Environmental Toxicology Program for NIEHS/NTP.

DR. LUCIER: Thank you, Bernie.

One of the recommendations that we've heard, really, on multiple occasions from you is that we should hold these meetings in Washington, our external peer review meetings. And based on the level and diversity of the participation that we have at this meeting, that seems like it might be a good idea.

Given the lateness of our start and the fact that you're here to present to us your ideas and not here just to listen to us, I'll make my comments very, very brief. Let me just say two things. One is, as Dr. Olden said, we've worked very hard to develop the process for the Report on Carcinogens that's open and transparent and one that brings into it all the best and relevant science that's available to determine whether or not a substance should be listed as a known or reasonably anticipated to be a human carcinogen.

The second point is that, as Dr. Jameson said, we have a number of review groups that look at this. He just went through the details of the process. We have an internal group at the NIEHS affectionately called RG1. We have RG2, which is the Interagency Working Group, and you recall the

agencies that are involved in that.

We have an external peer review made up of individuals primarily outside the Federal Government, external peer review which is a new step that we added beginning with the 8th Report on Carcinogens and have an NTP Executive Committee that provides a policy oversight to the National Toxicology Program made up of agency heads that are designates.

We have many representatives of those support groups here today, I think a total of 15, and we thank them for coming, but they, like Bill Jameson, Ken Olden, John Bucher, and myself, are here to listen to your ideas about how the process might be improved in determining how we go about listing substances in the Report on Carcinogens.

I want to especially thank two of our board members, Clay Frederick and Lynn Goldman, who will be assisting Dr. Goldstein in attempting to focus the questions after each set of presentations. So thank you very much. This has been an extremely arduous task. And many thanks to Dr. Goldstein for his agreeing to take on this very difficult task. Thank you very much, Bernie.

DR. GOLDSTEIN: Thanks, George.

Well, I agreed to do this only after having gotten lots of reassurances from NTP and NIEHS that, in fact, people were willing to listen and willing to make changes. I think that that's crucial.

We really want to try, if we possibly can, to focus on the changing issue: What can be done with the process, if anything, that will change it in the right direction? I think we'd all agree, as Ken has told us, that any process can be improved. Certainly something as complex as determining carcinogenicity and where to put chemicals on -- where we have a continuum of evidence, but, yet, we have to draw lines through that continuum and put chemicals into a box and whether we call it known or reasonably anticipated or A, B, C, or D or, as some of our laws have it, we define the difference between the probable and the possible carcinogens.

It's a difficult situation because, inherently, you're putting a line through a continuum, and wherever you put that line, there will be some chemical that is just above or just below that line, and reasonable scientists will differ as to that. So the process, inherently, is a difficult one. It inherently can be improved and it inherently can be

made worse. Our goal is to focus on how to improve it.

Many of the comments that I've seen in the written documents have to do with individual compounds. Now, each of the presenters will have ten minutes. You can do with that ten minutes what you'd like. I would urge you, however, not to deal with the issues of the individual compounds, whether or not they should have been interpreted (inaudible), or any of the usual kind of things that have to do with individual interpretation, that simply isn't part of what we're discussing. It really will be a loss of time, and we need to focus on what the issue is here.

I'm actually going to demand that NTP folks, when they have a chance to respond, not to respond to these issues about the specific compounds. It will just be taking away from the time that we should be putting to talking about the process and giving ideas in discussing the process.

We're in the discussion section, and this is a different approach. The usual thing is to just march people up, say your peace. We'll transcribe it, and, eventually, something will happen. We're going to try to help focus the discussion on

individual points that seem to be themes that are emerging. For that, Clay Frederick of Rohm and Haas Company and Lynn Goldman of Johns Hopkins, recently of EPA, who are members of the Board of Scientific Counselors, will be helping us focus that discussion, trying to pick through the themes.

We're going to ask people to, at that time, try to stick to those topics, and we're going to try to ask those of you who haven't spoken before to get a little bit of a preference in terms of making comments. And I'll try to cut people's time so we don't have any further speeches to be made but really try to keep our focus.

It's an experiment. We don't know how well it will work, but it is an attempt to try to get at what is really the meat of this meeting and what seems to be the request by people who have asked for the meeting.

Let me emphasize that it should be ten minutes and ten minutes only for the presentation. That includes setup time. If any of you have videos that you want to show or whatever, and it's going to take you five minutes to set up, that's part of your ten minutes. We will have folks here. They're available to show the overheads, to show

slides. Please do get to them beforehand so that we can really move this along.

Let me ask, as a personal favor, that when you make your presentations, please avoid abbreviations and jargon as much as possible. It really will help. We've got a diverse audience here. If you want to make a point, to try to get to everyone, I think it's important that we speak a language that we all can understand.

The discussion time is really going to be our time. I mean, it's really an attempt to get everybody -- to bring to a head where the differences are while being, I hope, polite to everyone. And, again, during that time I'm going to ask the NTP folks please not to be defensive. This is not an attempt to attack NTP. If it is, it's not the point, and we missed the point if we're trying to do that.

And, similarly, the NTP staff here, who have worked very hard on this, inevitably, it's human to be defensive about what they've done. That's not the point here. There's no question. Everybody is agreed that we could do a better job if we just knew how to do it and could get the ideas and discuss them well.

We have some information that's available. Lots of people have submitted written testimony. There will, of course, be the transcript of this. I'm told that that will be available to anyone who wants it. That includes some of the material that was submitted in anticipation of the presentation in September by some people who could not be here at this meeting, so that, again, will be available to everyone.

George, do you know what time period that will be done?

DR. LUCIER: Bill says it's probably at least a month before we have the transcript, but, certainly, the materials they received today will be available very soon, as soon as we can compile and copy them, but the transcript in about four to six weeks, I'd say.

DR. GOLDSTEIN: Did everybody hear that? The transcript in about four to six weeks, copies of the material soon. There is room up front for -- I see some people stuck in the back corner there, so there are some seats here. I think the fact that the room is overflowing just testifies to the importance the people see of this.

We're going to go through, as I say, ten

minutes flat. I'm going to do my best to be evenhanded. I will make one exception. The first speaker, Dr. David Guston, is from Rutgers. David, you can have as much time as you want.

DR. GUSTON: My name is David Guston. I'm an Assistant Professor of Public Policy at Rutgers University. And for the past year, I've been engaged in research sponsored by the National Science Foundation on understanding how scientific and political considerations are combined in various decision-making arenas.

And before I go on, just let me say that my opinions here are my own and in no way reflect the representatives of Rutgers or NSF.

The National Toxicology Program and its Report on Carcinogens have been part of that study, which, unfortunately, is far from completed. I would, however, like to present some preliminary findings that may be relevant to some of the discussions about the review procedures and listing criteria for the report.

What led me first to investigate NTP in detail was the apparently unique combination of technical subject matter with explicit voting rules in order to come to a policy-relevant conclusion.

Although there are no actual surveys of such mechanisms, the predominant mode of decision making in scientific advisory boards seems to be consensus, meaning that the group continues to deliberate until no explicit dissent is encountered.

A small study by the California Environmental Dialogue, for example, found that scientific advisory panels normally begin with charges to seek consensus, and where consensus cannot be reached, panels prefer to describe areas of disagreement rather than to offer minority reports. The National Academy Complex, for example, works in this way.

Consensus decision making is notoriously difficult to study, but votes are a gold mine of empirical data to a political scientist like myself. Table 1, if you would, please, shows the votes by nominated substance and panel for the 9th Report. You don't have to worry about reading that.

If you can flip to Table 2 now, what's notable in this data is the level of consensus - here meaning consensus as an outcome rather than a process -- that's demonstrated. This consensus-as-outcome can be measured in different ways. First, I looked at the overall agreement within each

advisory panel across all substances. Table 2 shows the percentage of 'aye' votes -- that is, votes in favor of the proposal on the table -- cast in each panel over all the substances reviewed, which is uniformly high.

A second way to look at the level of consensus is to examine the agreement within each of the three panels. Votes can be categorized as: Unanimous, meaning no one present voted against the outcome preferred by the rest; strict consensus -- unanimous means all present voted for the same outcome; strict consensus, meaning that no one present voted against the outcome preferred by the rest, but may have abstained; supermajority, meaning that two-thirds of those present voted for the same outcome; or simple majority, meaning that more than one-half of those voting voted for the same outcome.

Of the 73 total votes, 35 were unanimous, an additional 6 were strict consensus, 22 were supermajorities, and only 10 were simple majorities.

A third way to look at the level of consensus is to look across the three panels for the 24 substances. As Table 3 shows, three of the substances were subject to all-unanimous

conclusions and three more to unanimous or strict consensus conclusions. So for six of those 24 substances, no one in any of the panels dissented, but perhaps some may have abstained.

A supermajority or more held in all panels for 10 substances, and a majority held for an additional four substances. For only four substances was there any divergence, that is, a majority or better of one panel voting in opposition to the majority of another panel.

This level of consensus in itself seems to me an important achievement. One might compare it, for example, to findings by sociologists of the seemingly surprising disagreements among reviewers of research proposals to the National Science Foundation or to general expectations of disagreement within a highly politicized system, perhaps comparing things that might go on with the Report on Carcinogens to toxic torts, things that are adjudicated in the courtroom.

My research intends to explore the reasons behind this apparently high level of consensus, particularly probing the hypothesis that the consensus is a product of relatively strict procedures and criteria and that divergence is at

least, in part, attributable to the characteristics of the panelists and departures from the applications of the criteria.

Preliminary analysis suggests that the sectoral affiliation of members of the Report on Carcinogens Subcommittee has an important role. I'm not sure if you can actually make out the colors from a distance here, but what Table 4 does is it takes each member of the Report on Carcinogens Subcommittee for the 9th Report and assigns to that person a three-dimensional coordinate.

Where the vertical axis is the number of times that a member voted the same as the majority group, that it's as protective as the majority of the substance was, where this axis is the number of times the member voted in a less protective way than the majority, this axis is in a more projective way, and I've color-coded these individuals by their sector of origin, university, labor, industry, and government.

And I'm not sure if you can make it out, but the sort of pinkish lines and boxes are the university members, and they're somewhat clustered around the as protective. The governing members of the committee are, basically, on all corners.

There is one who's, if you will, the least protective, one who's even on with the majority, and one who's someplace over here, I think -- I can't see the colors very well from the slide -- who is somewhat more protective than the majority.

And the industry representatives, to the extent that they deviate from the majority, are uniformly less protective, the labor representative uniformly more protective than the majority.

For those of you who picked up a copy of my remarks, you will note that there is a Table 5 in there. Please disregard Table 5 because there is an error of aggregation there. I'm sorry about that.

One might think, for example, that because of its more diverse public membership, the Report on Carcinogens Subcommittee might be subject to greater internal disagreement than the other two committees.

There is, at best, slight evidence to support this contention. For example, it had lower overall levels of agreement, as Table 2 showed earlier, but as shown on Table 3, it agreed unanimously more than either RG1 or RG2 did.

The choice of using a voting rule rather than a consensus rule may contribute to the

appearance of consensus. More than half of the individual panel votes were unanimous or strict consensus, and, therefore, one may judge their conclusions to be independent or relatively so of the mechanism of coming to a conclusion, but almost half the panel votes were super- or simple majorities, and, therefore, they may have reached their conclusions only under conditions of voting, and they may be very sensitive to the kinds of procedures and criteria that are under discussion here.

There are other ways that the procedures and criteria influence the level of apparent consensus. The current review process has only a limited number of bins - known human carcinogen, reasonably anticipated to be a human carcinogen, or not listed - into which to sort nominated substances.

These three bins may assist a convergence of opinion, for example, by directing panel members who have concerns about a substance to label it reasonably anticipated to be a human carcinogen because there is no other label other than delisting, which they may interpret as meaning implicitly safe. This came out of discussions between myself and

Dr. (inaudible) before this that the reasonably anticipated to be a human carcinogen bin is relatively large.

And an additional factor is that it may differ in size depending on which side of it you're looking at. It may seem relatively large when considered on the side of the alternative of delisting a substance. It may seem a different size when looking at it from the side of the alternative of being listed as a known human carcinogen.

There is -- adding bins, for example, presumptive evidence of human carcinogenic activity or laboratory animal carcinogen presumed not to be a human carcinogen, which was suggested in the '95 review procedures, might spread the votes more thinly and reduce the apparent consensus.

So, basically, the take-home point here is, to some extent, the choice of procedures and criteria is related to the degree of consensus. And if this consensus is valued, and I think it should be because there are too many other arenas in science and policy that promote adversarial relations, there is little reason to tamper with current arrangements, and any proposed changes should clear a very high hurdle.

Nevertheless, consensus is not an absolute value, and the full information and the expression of uncertainty deserve attention as well. As Table 4 describes, the current process does express some of the uncertainty inherent in the deliberations -- expressing it through votes that are either more or less protective than the majority opinion.

Allowing some more concrete expression of minority opinion other than simply casting dissenting votes might be productive because without damaging consensus formation, it could, first, help clarify how the procedures and criteria are applied by individuals in specific circumstances; (2), publicly commit individuals to neutral analyses, potentially inhibiting the influence of economic or other biases; (3), provide additional guidance to future research on substances that might reduce existing uncertainty or resolve existing conflicts; and (4) provide a more coherent representation of the conclusion of the scientific review by providing more information about the range of beliefs of the panel members.

I would thus endorse what NTP, in describing some suggestions already received, has characterized as a Comment Response Document or

a narrative justification - that would address these four rationales - to accompany decisions.

Thank you.

DR. GOLDSTEIN: Thank you, Dr. Guston. Our next speaker is Thomas Starr of the American Forest & Paper Association.

DR. STARR: My name is Thomas Starr. I'm an independent consultant for the practice of risk assessment issues. I'm here today on behalf of the American Forest & Paper Association. The views I'm presenting are my own.

In spite of the admonition not to address individual chemicals, I thought the comments I have to present are well-characterized by the experience the NTP has had with the consideration of Dioxin for listing.

It has a fairly long history in consideration for listing in the Report on Carcinogens. It was first listed in the 2nd Annual Report in 1981 as reasonably anticipated to be a human carcinogen.

Then in 1997 it was nominated internally for upgraded listing as known to be a human carcinogen by an RG1 vote of 10 to 0 and an RG2 vote of 8 to 0. Both voted to upgrade.

In the end of September of 1997, the TCDD

Background Document was issued, and a month later, on Halloween, the Report on Carcinogens Subcommittee voted 4 to 3 for an upgrade to known to be a human carcinogen status. It was actually a 3-3 tie broken by the Chair.

After that decision created a great deal of concern in interested parties, letters were written to Dr. Olden protesting that the process was defective and inadequate in consideration of Dioxin. Dr. Olden determined somewhat later on that the Report on Carcinogens Subcommittee Review may not have been adequate and called for a second review of by that Subcommittee in April of 1998.

In December of last year, the Subcommittee voted 7 to 5 against upgrading the Dioxin listing. The NTP Executive Committee vote has been taken. We don't know that. The final recommendation has not yet been made to Mr. (inaudible).

What specific problems are there in the process that the Dioxin example illustrates? First of all, the Background Document is inadequate. There are significant factual errors in it. Just one example, the Dioxin Background Document stated that the IARC Working Group identified a causal association with all cancer mortality among the

most highly exposed subgroups, but IARC concluded that the human evidence was limited; that is, "chance, bias, or confounding could not be ruled out with reasonable confidence." In fact, the Background Document, which I have here, is 99 percent the IARC document, and only two pages are devoted to the human evidence that the NTP put together.

So there's a problem in even interpreting what other groups have done in the Background Document. The problem with the Background Document further is that no modifications are even allowed after public release even though they might be well justified.

The defective Background Document needs to be improved, and I would recommend early release of it by RG2 for review by the public and selected outside experts with subject matter specialties, modification by RG2 as appropriate, including their recommendation of whether or not to go forward.

The Report on Carcinogens Subcommittee meeting, there are too many issues, too little time, too little relevant expertise. There's insufficient opportunity to explore the complex issues in depth,

both in preparation for and during the meeting.

The Background Document was issued just 30 days prior to the meeting. Public comments were obtained right up to the beginning of the meeting. There was no real opportunity for the Subcommittee members to review carefully all of that material.

There was insufficient opportunity for public comment, just five minutes per individual, and it was limited to one spokesperson per organization. Unscheduled comments were not permitted even though there were microphones in the audience presumably to take unscheduled comments.

There was insufficient expertise in epidemiology, which is the critical subject area of Dioxin. In the first vote, there were no epidemiologists present when the vote was taken. In the second vote, there was just one.

So the recommendation here would be to limit the number of substances considered in a two-day meeting to four, so you would have a morning and afternoon -- a morning or an afternoon for each of the substances for consideration.

Also recommending enlistment of multiple

outside epidemiologic experts. When Dioxin was concerned in terms of the causal question, "Is there a causal association between exposure and human cancer?" when EPA was undertaking its reassessment back in 1993, they employed eight outside epidemiologists for a full day. When IARC deliberated on this question in 1997, they employed ten epidemiologists for a full week, yet we had votes from either no or one epidemiologist present in the RoCS meeting.

There's no explanation of votes given. No rationale is provided for votes by the deciding groups, so you cannot determine the reasoning behind these votes. This is especially important when votes are inconsistent, as they have been for Dioxin, between and/or within groups, indicating that reasonable doubts exist about classification.

So the recommendation here would be that written explanations be provided for decisions by RG1, RG2, and the Report on Carcinogens Subcommittee as well as the Executive Committee, including minority reports when votes are split. Finally, transcripts should be taken of all group meetings so that a full record is available to the public.

Finally, I want to address a clarification that Dr. Jameson did not reference that appeared in the Federal Register in April of 1999, clarification of the criteria for known to be a human carcinogen listing. The clarification as it is worded is much too vague and open-ended. There is an and/or clause. Specifically, this can include traditional cancer epidemiology studies, data for clinical studies, and/or data derived from the study of (inaudible) substance in question and useful for evaluating one of the relevant cancer mechanisms operating in people. This and/or clause will permit listing as known to be a human carcinogen without any direct evidence of carcinogenicity in humans.

What I recommend is that NTP follow the advice it has received from two eminent epidemiologists, Greenberg from the Medical University of South Carolina and Richard Monson from Harvard University, in a June 1, '99, letter in response to this (inaudible).

They state: "A scientific judgment that there is a known relationship of cause and effect in humans should rely solely on the fact of exposure and the fact of disease in humans."

"Sufficient evidence of carcinogenicity for

humans should derive from human epidemiology studies alone."

Thank you very much.

DR. GOLDSTEIN: Thank you, Dr. Starr.

Our next speaker is Jim Tozzi, representing the Multinational Business Service.

MR. TOZZI: I try not to leave too much of a record of what I say.

Good morning. I'm privileged to be here. Mr. Chairman, distinguished members of the panel, I'm Jim Tozzi with Multinational Business Services, and I would like to compliment NTP for having this meeting because Washington history is not replete with agencies opening up their proceedings.

I also think they should be complimented for their commitment to not only have the meeting, but to review in some detail the comments people make today. And there's going to be speakers more knowledgeable on some of the technical processes than I, both those preceding me and those that follow.

So I'm not going to make any particular points of those, but I want to make just one point – most of my points are very easy, sometimes too

simple -- is that I think if you want to capitalize on this process that you're having today, it's important that you make one change in the procedures, and let me go on to what I mean with that.

I'm most appreciative of what the Chair said, that you're going to have a discussion after the comments on these because I think that ventilates them when they're warm.

Now, what is the only comment I want to make today in all of this process? I mean, it's an exceptional program. I think the only point I want to make is sort of a question. That question is: Why is the rush? What is the rush to publish the 9th Report? You may say, Well, that sounds sort of (inaudible). Let me explain a little more on that.

First of all, you're way ahead of schedule. You get an "A" on that. Some agencies (inaudible) around 22 years. Of course, I used to be in business, but -- so the first question is: Why not sit back and take time on this? Because your last report was in May of '98. If you add two years to that, and I don't want to add to the technical complexity of this topic, but you would have -- it would be in the year May 2000.

So the first question is: Why this rush to

have the report done now? Seems to be a question in my mind because (inaudible). Then you may say, Well, let's look a little further. What was the record of the agency in issuing reports in the past? Well, the last report was in 1998.

Well, let's go back from there. Now, it's a relationship (inaudible). So the report prior to that should have been in 1996. Was it in 1996? No. Was it in 1995? No. Was it in 1994? You win. Four years. You may say, "Tozzi, you don't know much about mathematics. That's just a point estimate. You have to look at the whole data set."

Well, let's take 1991. That was -- 1994 was the last report. Go back two years. It would be 1992. Was that report written in 1992? No. It was in 1991. That was three years. Then they did make it two years in 1989, but from 1989, back two years is 1987. Did they make 1987? No. Did they make 1986? No. 1985.

So what you see is, over a 15-year period, only once did you make a two-year report. Most was three to four years. So why the rush? It's not clear given the kind of scientific evidence you're going to hear today. What is this rush to publish the report ahead of time?

Now, I'm not criticizing the agency for taking four years because some of these are very difficult issues. I applaud you. What I don't understand is: Why the rush to publish?

Now, let me give you what I -- and this is, most certainly, not specific, Mr. Chairman, to any commodity on that list. These recommendations are in keeping with what the Chair has said are very generic. One, don't rush. And, second -- let me give you the idea.

First, I think we should prepare a transcript of this meeting, which Dr. Lucier said you're going to have available in four to six weeks. Second, I think you should analyze the comments from this meeting and make them available to the public, which I think the NTP staff is going to do anyway or they wouldn't be able to benefit.

Now, here's where a little extra works comes in. Third, I think you should give the public an opportunity to comment on the agency's responses to these proposed actions. Fourth, I think you should assemble all this and put them out for public comment, and then based on that record, you all make the determination of what you want to do in the 9th annual report.

Now, what I'm recommending differs a little bit from what was in the NTP announcement. How is it different? The NTP announcement says that all these views are to be given in respect to the 10th Report. My view is: Why waste a good thing? Why not capitalize it now on the 9th Report? Why wait two to three years to do it?

Mr. Chairman, I have four minutes left?

DR. GOLDSTEIN: Four minutes and four seconds left.

MR. TOZZI: Thank you, sir.

So let me give you my views, a question: What is the downside of taking slower (inaudible)? What is the downside of ventilating these issues?

Well, I see a downside of not doing it. One of the downsides are that there are many unsettled issues here, and the resolution of which will have a big impact only not on particular products in 9th Report but what gets in the 10th Report and how they're addressed.

I don't think these issues are going to go away. You don't play to a packed audience like this because there's no interest in this issue. And to what extent are these going to go away ought to be addressed in a formal way. I think they're not

going to go away.

Second, to those people that -- I'm hearing repeatedly that this is just a hazard identification and not a regulatory report. Let me just speak to that. This report in draft form is used at the local level by governments to ban products, and I'll be glad to give you the localities. And they're acting on the draft report, not even the final report. They don't care that that little sign says Draft. (Inaudible.)

So it has a big impact at the local government. Forget inside the Beltway. It's outside the Beltway where post people live, and that's where it counts.

And, third, I think what you said in the 9th Report are going to be precedential, and to have these kind of precedences established without this ventilation of issues I think is sort of sad.

So, in summary, I think Dr. Olden set it on the right track. He said this morning: You want a sound science report. And my only comment is: The objective is to do it right. Don't do it fast.

Thank you.

DR. GOLDSTEIN: Thank you, Mr. Tozzi.

Our next speaker is Stuart Cagen of the Shell Chemical Company.

MR. CAGEN: Thank you.

I'm Stuart Cagen with Shell Chemicals. I'm going to be speaking today commenting on the RoC process, several items, that the process right now has always had the best of intentions. However, the intentions have not been actualized. There's some additional difficulties beyond that. I'll recommend quickly some process improvements and recommend some implications for today.

As has been stated already several times, NTP, of course, has the best of intentions, especially, as Dr. Olden has pointed out since he came on board, that there should be a correct and defendable list of decisions by NTP that is comprehensive and is an open discussion of current science and has consistent application of sound criteria.

However, many of these intentions were not actualized. Has there been comprehensive and open discussion of current science? Many times the quality of the background document was a poor reflection of science or out of date, and the process itself had a limited ability to respond to or

even hear public scientific review and comments.

In that regard, there's a limited response of the NTP process to the scientific comments, little evidence that comments are reviewed or considered. There's no documentation of why they were accepted or rejected.

The peer review system does not have adequate time or structure for scientific interchange. Many times the review is not -- those involved are not experts in those particular chemicals, and there's very much a time-compressed process for that expertise to be brought forward, and, as I mentioned, there's little time for scientific interchange with the peer review body.

Some additional difficulties: I think when something is called known, that it has a special, additional hurdle on it. When is known known needs to be a little bit better defined. And many times, as Dr. Jameson mentioned, there's exposure criteria. I'm not sure whether that's consistently applied.

Some suggestions on process improvements: Invite the public and other experts in early in the process. The process should allow for modification of background documents when new

information is presented. Allow time for expert review and scientific interchange. Document reasons for accepting or rejecting the science arguments. And more attention to criteria. Clarify criteria for listing and make sure they are consistently applied.

A little bit more detail. This can be manifested in the fact that the RG1 prepares a draft document, makes its listing recommendation with the rationale. RG2 at that time invites comments on the background document from the public and experts and sponsors the workshop. RG2 then would revise the background document and listing recommendation, as necessary, and provide rationale for its recommendation.

RG2 then forwards the revised document and recommendation to the Board of Scientific Counselors well in advance of the subcommittee meeting. The board then conducts a review meeting with adequate time to consider complex scientific issues and engages in meaningful scientific interchange with the public presenters.

The report then goes to the NTP Director, including a recommendation on the listing proposal with explanation of how the recommendation fits in

with the criteria as well as explanations of how major scientific issues were resolved. And the Director, in consultation with the NTP Executive Committee, formulates a listing recommendation and forwards the report to the Secretary of HHS.

Path forward, I definitely agree. There needs to be process improvements, and they should be considered in a formal manner. Suggest a blue ribbon panel with experts on the outside.

And with all due respect to Dr. Goldstein's discussion about whether we should discuss chemicals on the 9th Report, I think many of the specific examples are very relevant to how the process has some problems and can be improved and, in particular, several compounds on the 9th list -- chloroprene, isoprene, (inaudible), nickel, ethylene oxide, and Dioxin, which you're going to hear or have already heard some discussion of today -- are very relevant to these particular comments and problems. And, in fact, what is the rush? I think those, in particular, should be reconsidered with the new and improved process.

Thank you.

DR. GOLDSTEIN: Thank you, Dr. Cagen.

Our next speaker is Philip Leber, who is speaking on behalf of Jim McGraw from the International Institute of Synthetic Rubber Producers.

MR. LEBER: Thank you very much, Mr. Chairman.

Mr. Jim McGraw, who is the officer in the International Institute for Synthetic Rubber Producers, had prepared a presentation for September and was not able to give it, so he asked me to do so. I'm from the Good Year Chemical Company and President of the Isoprene Toxicology Committee within that organization, so he asked me if I would make these presentations.

According to the Chair's request, I'm trying to speak as generically as I can, but I think it's illustrative to give some specific examples to lend credence to the generic points to be made.

First of all, the first point I'd like to make is that the people at IISRP and industry groups have a very vested interest in these chemicals. We consider ourselves major stakeholders from not only economic perspectives but also from health, safety, and environmental. And I was pleased, also, to hear Dr. Olden use the term partnership as it

relates to the overall process.

We certainly have sponsored a significant amount of research with several of the monomers used in these rubber products. We all have MSPS's and some substantial product literature that deals with health and safety. Nobody, I don't think, has more experience in terms of the uses and the potentials and, subsequently, the potential exposure scenarios that may occur related to these products.

Finally, we do have a specific toxicology committee to address -- keep up with the literature and try to provide comments when the opportunity avails itself.

So I'm going to use isoprene as sort of my prototype here of a situation that needs comment. Back in '97, the NTP had a bioassay report which indicated that there were three major tumor types induced in rats and that they indicated that with all of these tumors, there was an increase in the benign variety.

However, the NTP went from the benign increase to, quote, clear evidence based on these incidences. It was acknowledged that both testicular and kidney tumors were all benign, but then it indicated that the mammary tumors were,

quote, neoplasms, and when you look at the table within the report, it says, quote, benign or malignant increases. Finally, the report indicated that 3,700 people were potentially exposed to isoprene in occupational settings.

Now, with regards to the evidence on cancer, the text nowhere -- if you read the text only, nowhere did it mention that all the increases in tumors were of the benign variety. This is important because the criteria for clear evidence, one of them is there is an increase in malignant tumors and then a second criteria is an increase in the combination of benign and malignant tumors, and there was a third, but nowhere is there an increase in benign tumors only as a criteria, and, nevertheless, the clear evidence was assigned.

Okay. On the third point, significant exposed populations, and when I saw the figure 3,700 people, worker population, exposed, I thought, now, this is going to be an easy one, a noncontentious issue. We can work this out with NTP.

So we did a survey of all our member companies in the industry, and there was only 325 people who were employed in these environments,

either monomer or polymer environments.

So since we didn't know the definition of what a significant number of exposure meant, we went further and said: Maybe 325 people are being exposed to very high levels. That then becomes a significant number.

So we went further and we looked at the workplace areas and found that 91 percent of all the air exposures, PWA's, were less than one part per million. 99 percent were less than 10 parts per million, very low occupational exposure.

Then, finally, it was mentioned in the document that most exposures were related to residual monomer isoprene coming out, leaching out, migrating from the polymers. So we went to one of the final steps, and we looked at the monomer residues in these polymers, and all of the polymers that we looked at had less than 40 parts per billion levels of monomer remaining.

So the point is that there just is virtually no opportunity for consumer or other worker exposure coming from these polymer residues. And, overall, I would interpret that, anyhow, to probably conclude that there is not a significant number of exposed folks in the United States.

To summarize, the reports' texts are selective in their discussion of the tox data allegedly supporting the clear evidence. And when you use terms like benign or malignant, if you look deeper into the report and look at the tables, the benign numbers and the benign or malignant numbers are the same, meaning there is no increase in malignant tumors, but when you read that kind of text, you're led to believe something else. The second point, exposure data demonstrates that there is no significant exposure to isoprene in the US, so the criterion were not met.

So, very broadly, I think the situation was this. We offered NTP written comments and these data on the worker exposure, and there was no changes in the draft background document. We then gave public comment at the Board of Scientific Counselors orally, and what happened was, and this is typical, you get an opportunity to speak for five minutes. You sit down. There's no questions. Nobody from the Board of Scientific Counselors says, "NTP, are these new numbers correct or is there a misunderstanding?" There's no dialogue. There's no attempt to resolve differences.

And so what happens, no discussion.

Somebody makes a motion: "Let's vote on this report as it now stands." People vote and end of discussion, and this is how errors are incorporated and are retained in these types of reports.

And I just might -- I'm very willing to be called wrong. I get a lot of that from my kids, so I'm somewhat used to it. I don't mind being told that, "Leber, your 325 numbers there can be updated. We've got recent information," and I say "Okay. Let's talk," but there is no opportunity. And if there's one message I think that we would like to get across this week, today and tomorrow, is that we give information. We put a lot of effort into our comments, but there is no evidence that the comments are considered.

Thank you.

DR. GOLDSTEIN: Thank you, Mr. Leber.

Our next speaker is Dr. Emanuel Rubin from Thomas Jefferson University.

DR. RUBIN: Thank you, Mr. Chairman, members of the panel. I'm Emanuel Rubin. I'm Chairman of the Department of Pathology, Anatomy & Cell Biology at Jefferson Medical College at Thomas Jefferson University in

Philadelphia. I've had a long-standing interest in the adverse effects of environmental agents, and I've been well funded by the NIH for over 30 years.

I previously provided written and oral testimony to NTP at the request of the Beverage Alcohol Industry in which I contested NTP's proposed listing of alcoholic beverage consumption as a known human carcinogen.

With regard to my oral presentation, I was disappointed that after vigorous and even fractious discussion, the Board of Scientific Counselors Report on Carcinogens Subcommittee voted to recommend this proposed listing. It is not my purpose to discuss the specific errors underlying this decision but, rather, to register my concern about the process or lack thereof by which NTP reached its decision.

Specifically, I wish to bring to your attention three items: The scope of the review, the decision-making process, and the need for more transparent and public deliberations.

Let me go through the history a little. In November 1998, I sent a letter to Dr. Larry Hart in which I requested a number of items. I asked for

the selection criteria for literature citations since only less than 20 percent of the 800 studies identified by NTP were cited in its background document.

I also requested information relating to the criteria used by NTP for determining the causal effect in this particular instance. Finally, I requested abstracts of the papers identified by NTP. None of my requests were honored, and this critical information has yet to be released to the public.

Thus, the overall criteria for review employed by NTP remain obscure. Moreover, other than the discussion by the board, the public had no opportunity to hear the deliberations of NTP's various subcommittees. This lack of transparency does not inspire confidence in decisions made by the NTP.

Now, in March 1998, I filed comments with Dr. Jameson of the NTP Report on Carcinogens Program. In these communications, I emphasized a number of items: The negative eugenicity studies of alcohol, the failure to produce cancer by administering ethanol to experimental animals, the enormous differences between moderate alcohol consumption and the various maladies associated

with alcohol abuse, and the importance of using commonly accepted causation criteria, also known as the Hill criteria, in evaluating the epidemiologic evidence in this case. There was no adequate response either to my written or to my oral comments.

Now, neither the review panels nor the Board of Scientific Counselors gave adequate consideration even to the most important causation criteria, which include strengthen (inaudible), consistency, biological plausibility, dose response, and exclusion of confounding factors.

For example, despite the fact that the preamble to the Report on Carcinogens states that dose response should be considered when evaluating potential carcinogens, there is no evidence that any attention was paid to this matter.

This omission is particularly relevant to the issue of alcoholic beverages in which a high dose actually defines a serious disease complex, namely chronic alcoholism. This disorder introduces a wide variety of potential confoundings. For example, nutrition, metabolic changes, drug ingestion, bacterial and viral infections, and concurrent disease of many organs.

Let me just give you one example. The NTP report actually accepts the original IARC report on the supposed carcinogenicity of alcoholic beverages, which they accept alcohol as a carcinogen for the liver. All of those studies were done without controlling for the most important liver carcinogens in the world, namely Hepatitis B and Hepatitis C.

Since the IARC report, it has been demonstrated that there's probably 10 times the incidence of Hepatitis C in alcoholics as in the general population. So, clearly, this type of listing is totally questionable, and far, far more studies would have to be done to attribute any cancer of the liver to alcohol rather than to Hepatitis B and Hepatitis C.

Now, in December 1998, I testified orally before the Board of Scientific Counselors Report on Carcinogen Subcommittee and I supplied additional written comments. With respect to my oral testimony, the time allotted for my presentation regarding alcoholic beverages which are consumed in moderation by over 100 million Americans was no different from the time accorded exotic industrial chemicals.

The time constraints further precluded an informed discussion of a topic that has the potential for a significant negative impact on public health. Moderate alcohol consumption has been demonstrated to be beneficial in terms of protection against coronary artery disease, stroke, and osteoporosis, and overall mortality of social drinkers is lower than that of abstainers.

Thus, think of the consequences. An erroneous listing of alcoholic beverages as a known human carcinogen is not simply an academic matter but may have serious, albeit unintended, consequences for public health.

Given the flaws in its review of alcoholic beverage consumption, NTP should withhold the decision on this nomination and should consider some of the following recommendations:

One, NTP should adopt rigorous criteria for review of epidemiologic evidence and should disseminate this information to the public. Two, the information upon which NTP relies together with records of internal deliberations should be available to the public.

Three, NTP should publicly respond to written and oral comments as part of the

decision-making process. Four, the time allotted for oral presentations and public discussion by the committee should be proportional to the importance of the topic and sufficient to facilitate scientific interchange.

Thank you for the opportunity of addressing this committee. I hope that my comments will be helpful in improving the decision-making process of NTP.

DR. GOLDSTEIN: Thank you, Dr. Rubin.

Our next speaker is Dr. Peter Infante from the Occupational Safety and Health Administration.

DR. INFANTE: Thank you very much.

The NTP Report on Carcinogens is of vital importance to citizens of the US as well as governmental research and regulatory agencies. It is the only governmental program in the US specifically designed to inform the public about the occupational and environmental causes of cancer.

OSHA specifically relies on the evaluations of the NTP Report on Carcinogens. Under our Hazard Communication Standard, the listing of a substance or process in the Report is one tool

that's available to assist manufacturers in hazard determination.

The Hazard Communication Standard contains specific requirements that relate to the information that must be provided to workers through warning labels and material safety data sheets. These warnings have the potential to inform millions of workers about hazardous exposures of which they might not otherwise be aware.

This information can result in more effective control of the work practices to reduce exposure to carcinogens on the job, particularly in exposure situations where adequate workplace standards have not yet been promulgated. My recommendation, in general, is that more substances known to be carcinogenic in humans or experimental animals be added to the report.

An evaluation that leads to informing workers about cancer hazards on the job is also an environmental justice issue. The majority of substances or exposure situations known to cause cancer in humans have been identified by studying blue-collar workers.

This legacy of identifying cancer-causing substances by studying blue-collar workers simply is

a reflection of the relatively high exposure levels to carcinogens that these workers disproportionately experience.

Now responses to issues raised in the NIEHS press release that announced the September 15th meeting. Industry representatives have asked that their experts be involved earlier in the process and have repeated opportunities to comment and critique the data upon which decisions are made.

As is the case with IARC, scientists representing those with economic interests in the outcome of the cancer evaluations should not be permitted to participate in the evaluations. The NTP is a governmental scientific program that bears the responsibility to make decisions on carcinogenicity based on scientific data.

The current NTP review process allows for all perspectives to be presented and considered. In the interest of public health and the environment, these evaluations cannot be encumbered with views that are determined by economic rather than scientific considerations.

Also, reviews of chemicals by others, whether they represent industry or government, should not be placed before the NTP. The NTP has

the obligation to review the data, not the opinions of others, when it comes to evaluating chemicals for carcinogenicity. This is also the policy of IARC.

Now, should the NTP expand its database for evaluation of studies to include unpublished reports? Very emphatically, no. Unpublished reports are not peer reviewed, and they should not be included in these important cancer evaluation. Furthermore, published reports that are not peer reviewed should not be considered in the NTP evaluations.

Regarding where these meetings should be held, I suggest that NTP do a pilot by holding a few meetings in the DC area, and the agency can then decide which place affords more greater range in public participation.

Other issues for NTP to consider: It's my understanding that the NTP is considering a transfer of the Report on Carcinogens to the National Academy of Sciences. This would be a grave mistake. The NTP has a delegated responsibility to complete these Reports. It is demonstrated that it has the expertise and ability to produce the Report and has invaluable experience in doing so. No

other organization in the United States has demonstrated this experience.

The staff of scientists at the NTP has contributed to this success, and the removal of the process from the NTP would impair the quality of the Report because of diminished NTP staff participation.

NTP has developed a very good review process. The National Academy does not have an established standing committee that could develop the Report in the manner in which the NTP has accomplished its goal.

Furthermore, it may be difficult to determine the affiliation of committee members that the NAS would select to participate on the review committees. This could result in conflict-of-interest situations that would not be apparent to the public. Thus, it is of paramount importance that the program be maintained in the scientific environment of the NTP.

The carcinogenicity portion of the summaries for the substances listed in the Report on Carcinogens is usually two short paragraphs. Often these summaries are the only part that is read by the public. For this reason, I recommend

that the cancer evaluation portion of the summaries be expanded to perhaps three to four times the current length so that the reader will have enough information to understand the basis for the NTP cancer designation.

This expanded summary, however, should focus only on the categorization of the substance, as is currently done, and should not include information on cancer potency or risk management issues.

I also recommend that the major studies that are relied upon for the evaluation of the carcinogenicity be maintained in the docket at the NTP in North Carolina and be made available to public members who may request these studies.

In its Reports on Carcinogens, the NTP has not listed a number of substances or agents found in the occupational setting or the environment that IARC has already classified as human carcinogens and for which workers are at an elevated risk of exposure and the subsequent development of cancer. I recommend that the NTP place the listing of these substances on a fast track so that workers and the general population will be informed of these cancer hazards.

In addition, IARC has listed 13 industrial processes or industrial exposure circumstances as known human carcinogens. NTP has placed these 13 industrial processes in an Appendix to the 8th Report and simply states that IARC cites these as known human carcinogens.

If IARC can list these substances as known human carcinogens, then why is it that the NTP can only place them in an appendix and state that IARC has listed them? If the NTP chooses not to list these exposure circumstances, it needs to provide the basis for their not being listed. In the interest of public health, they should be listed.

If these exposure circumstances have changed such that they are no longer carcinogenic, a petition to NTP can be made to delist them. In the interim, I recommend that all 13 of these exposure circumstances be removed from the Appendix of the 8th Report and be added to the list of known human carcinogens.

In addition to these 13 industrial processes, there are several mixtures that NTP has not listed as known human carcinogens that IARC has classified as Category 1, known human carcinogens. And I recommend that these mixtures

also be listed, and I nominate them for listing. For example, wood dust. There are over 600,000 workers exposed to wood dust in the United States, and it would be beneficial to these workers to have wood dust listed as a human carcinogen.

In the listing criteria for carcinogens on .Page 2 of the 8th Report, it states that evidence of carcinogenicity in laboratory animals can be downgraded if, quote, there are compelling data indicating that the agent acts through mechanisms which do not operate in humans.

NTP needs to establish criteria for downgrading evidence of carcinogenicity. Hypotheses related to downgrading need to be tested to determine the merit of arguments being used for downgrading evidence. It is not scientifically objective or defensible for the NTP to downgrade on the basis of uncontested hypotheses.

Furthermore, the NTP needs to state explicitly that it will also use mechanistic information to upgrade a substance. IARC has used mechanistic information to upgrade substances to known human carcinogens when epidemiologic studies of cancer mortality provided limited evidence of carcinogenicity to humans.

Therefore, I recommend that the listing criteria be more scientifically balanced and state that the evidence of carcinogenicity can be upgraded if there are compelling data indicating that the agent acts through mechanisms which are thought to be similar to those that operate in humans.

Thank you.

DR. GOLDSTEIN: Our next speaker is Adriana Oller of the Nickel Producers Environmental Research Association.

DR. OLLER: My name is Adriana Oller, and I'm here representing NiPERA, which is the Research Association for the Nickel Producers (inaudible).

I would like to thank NTP for organizing this meeting and giving me an opportunity to illustrate some of the cause of the problems with the RoC listing process as they apply to nickel compounds.

In 1998, NTP announced that nickel metal and all nickel compounds were considered for listing as known human carcinogens in the 9th RoC. Now, this meant an upgrade for a few nickel compounds, but it was the first-time listing for the

majority of nickel compounds, which are in the hundreds. The NTP Notices never distinguished between these two groups.

The RoC Background Document was prepared on all nickel compounds and public comments submitted had indicated that the analysis should be made for the different groups of nickel compounds. This document became available for commenting November of '98, and to put it politely, again, the scientific quality left much to be desired, and I'll be happy to give you examples of errors in the document, data sets that were not considered and biased analysis. Unfortunately, as mentioned before, the reviews done by the groups 1 and 2 have already been made on this document that it was not a (inaudible) document.

During a period of three weeks, the nickel industry prepared lengthy and detailed comments on this document and submitted them to NTP, and the comments pointed out errors and deficiencies in the document and also offered scientifically supportable carcinogenicity assessments for the various nickel species.

These comments were made available to the Board of Scientific Counselors Subcommittee the

following week, which was Thanksgiving week, allowing them very little time to review these comments in preparation for their December meeting.

At the Subcommittee meeting, the nickel industry presenter was allowed just five minutes to explain what was wrong with the Background Document. This is to summarize 20 pages of single-spaced comments and appendices and to summarize the very extensive human, animal, and mechanistic database for each group of nickel compounds.

The five-minute limit for presentation was particularly frustrating since it was clear that the Subcommittee members had not had a chance to review and be aware of the issues that were raised in those comments. During the brief discussion that followed, industry scientists were not allowed to address any of the questions raised by the Subcommittee members.

And, again, I can give you examples of some of the issues that were raised but were answered incorrectly or dismissed without discussion. It was also clear that the Subcommittee members did not know that metallic nickel was no

longer considered for an upgrade because it had been removed earlier in the year from consideration or that soluble nickel compounds had never been listed before, and, therefore, this was the first time they were going to be included in the list.

The change for metallic nickel was clarified at the Subcommittee meeting, but the first-time listing for soluble compounds was never mentioned. And, indeed, in press reports that I've written, it's mentioned -- it's written that nickel compounds were just considered for upgrade.

So just to summarize the points (inaudible), the confusing listing in the Federal Registry and then to the BSC members as to how different nickel compounds were considered. It was a poor quality of the draft Background Document, which can definitely benefit experts, part of the process of writing this document and be involved early on in the process and the fact that it was never revised to respond to comments or correct errors.

There was a lack of timely and meaningful opportunity for public comment, the lack of NTP response to public comment, and the token public participation at the meeting, which five minutes is not a substitute for the lack of consideration of the

comments.

The fact that there was limited knowledge of nickel-related epidemiology and toxicology by the presenters and the BSC members, who, as I mentioned before, are asked to do too much in too little time. The superficial, confused, and hurried discussions at the meeting where independent peer review is supposed to occur and, finally, the failure of the different groups that make recommendations to explain the scientific basis for these listings and how they fit the criteria that NTP is supposed to apply.

And these are all things that I think were mentioned for other compounds and, you know, definitely can be corrected easily. And I think the nickel industry has worked together with other groups in making recommendations for improvements, and some of them have been presented already by Stuart Cagen and further were presented by Phil Leber, and we'll be glad to work with NTP on this.

Finally, the next slide and last slide, I would like to illustrate how the procedural differences can affect results. I would like to compare two carcinogenicity assessments that were

conducted in parallel. One was the one conducted by NTP on all nickel compounds, and the other one, which was conducted for soluble nickel compounds, was sponsored by US EPA, Health Canada, and nickel industry.

This assessment was done by TERA, which is Toxicology Excellence for Risk Assessment, an independent group, and they were conducted at the same time and looking at the same database.

The first big difference is that while the document prepared by NTP, as I said, had certain deficiencies and superficial data presentation, the document prepared by TERA had exhausted data and analysis. Both asked for public comment, but while NTP did not respond to these comments, nor did they incorporate the comments into the document, TERA responded in writing to the main comments raised by regulatory agencies as well as industry and incorporated those comments into the document.

Both had peer review meetings, and as you can see, they were almost at the same time. However, while NTP took less than two hours for all nickel compounds, the TERA independent review meeting took two days just for soluble nickel

compounds.

Public participation in NTP was limited to five minutes presentation only. In the TERA peer review panel, presentations by industry representatives were allowed and participation was sought for their expertise during the discussions.

The conclusions, then, could not be more different. NTP concluded all nickel compounds should be listed as known human carcinogens. TERA concluded that carcinogenicity of soluble nickel compound by inhalation and oral routes of exposure cannot be determined, and this was based on the fact that even though epidemiological data demonstrated an association with exposures to soluble nickel compounds, this was in the presence of other nickel compounds, more insoluble, clear carcinogenic compounds, and this association was not supported by all the negative animal, inhalation, and foreign studies and the mechanistic data. So based on the conclusions that TERA reached for soluble nickel compounds, this group of compounds would not have fit the criteria for listing in the 9th list.

So I think that NTP now being aware of the problems with the process as they relate to those

compounds, we hope that this carcinogenicity assessment will be reconsidered under an improved process.

Thank you very much.

DR. GOLDSTEIN: Thank you, Dr. Oller.

Our next speaker is Peter Lurie of the Public Citizens Health Risk Group.

MR. LURIE: Good morning. Let me offer a small correction. That's Public Citizens Health Research Group. We're in the business of minimizing risk, so I just wanted to correct that.

I want to start off with two historical notes. First is a very nice, I believe, bit from the New York Times reprinted (inaudible) talking about the unfortunate death of Dr. David Rall. And he, as all of you know, was former Head of NTP and was a tireless advocate for reducing consumer exposure to environmental and occupational chemicals, someone who understood the importance of animal carcinogenicity data.

I think there would be no greater tribute to the work that he did and his legacy for this report to continue to come out in an expeditious fashion, as clearly written as it often is, publicly available

and so forth for the reasons that I will go on to outline.

The second historical note is that in preparing for my talk here, I took the occasion to review some of the documents related to the 1995 reconsideration of the listing criteria for the annual report -- or biennial report.

And I also compare it to the recent letter from industry complaining about the problems they see in the process for arriving at a listing in the review of carcinogens, and what struck me was how numbingly competitive the arguments offered in the recent letter were to those same ones offered in 1995.

We heard again in this recent letter complaints about the criteria. For listing, that is. Much of that has been reiterated again in people's comments today and no doubt will be over and over again for the next couple of days.

We've heard about the importance of risk assessment. We've heard about the importance of considering mechanisms of action again, as Dr. Infante pointed out in a kind of one-sided direction for the purpose of downgrading, but usually not for the purpose of upgrading.

We heard about the problems back in 1995 of introducing non-peer-reviewed data, and we saw the same sorts of delaying tactics that are now being recommended by the industry. How ironic this is, complaints about process from industries that are usually complaining about red tape, arguments for transparency from industries that are usually invoking trade secret exceptions to prevent consumers from getting important information about drugs and toxic chemicals. How unusual this is.

And as to the question of why the rush put forward by Mr. Tozzi, well, (A), it's important, but there's a simpler reason. It's the law. That's why the rush. Every two years there has to be data to be presented to show -- in fact, by and large, the agency has not been consistent with the law. Very often it's taken three years, not two. Why the rush? Because it's the law. In addition, as I pointed out, this is very useful information to consumers.

One of the reasons that the reports do not come out at the frequency required by law is because, as no one has so far pointed out, very often the report gets tied up in lawsuits from the industry. First, there was dichlorobenzene. After

that, it was fibrous gloss, and now we're talking about Dioxin.

These are some of the reasons that the report keeps getting held up, and that's the reason for the agency, I think, to get ahead of the (inaudible), and so far have, and maybe we'll see the report on time this time. And, again, as I've mentioned, questioning of animal evidence was a feature of the 1995 arguments and we're hearing it all again.

Why is this report so necessary? Well, as has been pointed out, it's the basis for regulation. It's the basis for regulation by FDA, by OSHA, by EPA, by the Agriculture Department, Consumer Product Safety Commission. That's why it's needed. Much of your objections -- let's be honest about this -- is about the industry's efforts to avoid regulation. That's what the objection is.

The second reason that the report is so important is because many consumers, I believe, labor under the misconception that, as the expression goes in the popular culture, "Everything gives you cancer," but nothing can be further from the truth. Actually, it's a very limited number of compounds that cause cancer, limited enough to

end up in a rather small book, as the report turns out to be. That, I think, is reassuring to the public, and so I think that that's sort of another reason why it's such an important report.

There is substantial opportunity for public input. As was pointed out by Dr. Jameson, there are at least three opportunities for public input. One can write a letter whenever one wants to. I think the least of the problems faced by the NTP has been the lack of opportunity for industry to provide input. In fact, what has mostly happened is that there's so much opportunity that it's led to delays or particular lawsuits, and, as a result, often the report has not been timely.

Now, Dr. Goldstein started off by asking the speakers here not to speak to specific chemical compounds, but, in fact, most of the industry has been unable to resist this. Instead, we've got a plethora of comments that amount to retrying decisions that the industry is unhappy with. We've heard about isoprene, Dioxin, alcoholic beverages, nickel, and there will be more to come in the next couple of days.

The fact is that these are complaints about outcome that are masqueraded as complaints about

process. Sure there's some changes needed in the process. The idea of moving the meetings to DC is a good idea, especially for those of us on the Red Line, but the fact of the matter is that, by and large, the process is sound. The strength of industry's opposition is the best evidence for the usefulness of this report.

Thank you.

DR. GOLDSTEIN: Thank you, Mr. Lurie.

The next speaker is Ellen Silbergeld. I don't see her in the audience. I think that perhaps she isn't here yet. We're a little early. I think that perhaps the best way to deal with this is to try to keep the schedule so that people who were expecting to hear others or to be at certain points would be able to keep to this schedule and know where others are speaking.

So what I'm going to suggest we do is that we take our 20-minute break now, reconvene at 11:30 rather an 11:45. If Dr. Silbergeld is here by then, we'll start with her. If not, we'll just move ahead. So until 11:30.

(**WHEREUPON**, a break was taken from 11:10 a.m. to 11:30 a.m.)

DR. GOLDSTEIN: Dr. Silbergeld, unfortunately, couldn't be here. She has her written comments, which will be part of the record.

I said this morning we're going to try a little experiment here. We're trying to focus in on some of the comments. Again, I would hope that we could, by this, help illuminate some of the issues.

We're asking the NTP folks to be listening. Obviously, I think we're all familiar enough with governmental processes that we're not asking for an immediate response from NTP, yes or no, right now on whatever idea they've heard. This is more to put some breadth and some depth into some of these ideas.

Let me start by first asking the NTP folks, George Lucier, Bill, if there's anything you want to say in terms of clarification.

DR. LUCIER: I'm glad to be part of the experiment, Bernie. As I will throughout the course of this meeting, I'll make my comments relatively brief, and just issues of clarification is what I'll deal with.

One of the things that came up this morning was the composition of the Board of

Scientific Counselors and the external review group and sort of the breadth of expertise on those boards.

The intent, and I think it's pretty well balanced at this time, is to have people who are knowledgeable about animal cancer studies, have people that are knowledgeable about mechanistic studies, (inaudible) chromosomal changes and so forth, and have people who are traditional epidemiologists on the board as well. Right now I think there are 12 people on the board, and it's pretty well divided up into those categories.

I should also point out that some of the board members would have a history affiliation that they formerly are dealing as an independent scientist for their activities on the Board of Scientific Counselors, not as a representative of any particular industry. So everyone functions as an independent scientist on the Board of Scientific Counselors.

The composition of the review groups, RG1 and RG 2, also involve people in those three major categories: Mechanistic expertise, animal toxicology expertise, and epidemiologic expertise.

Thank you. Anything else you think I

should --

DR. GOLDSTEIN: Well, I've got, actually, a question that I think maybe -- I should point this out. I really haven't been part of this process except way back when sitting with the EPA part of it about 15 years ago, so I'm not really that familiar with it. I've been listening to it.

One of the things that I thought I heard some of the commenters say was that the Board of Scientific Counselors, in their voting, votes to accept the background document. There's been a fair amount of criticism of the background document not always getting its facts right.

There are certainly EPA processes, other government processes, the Clean Air Scientific Advisory Committee, which I served on, where we really feel, as part of the process, that we've got to make sure that EPA gets its document correct.

Let me ask you whether or not the board is being asked to vote up or down on the recommendation in the document or on the entire document itself. And, obviously, the key point is that a board member could sit and listen to a comment and say, "I agree with the comment. They got that wrong in the document, but I still think

that the overall position is correct in terms of where this is as a carcinogen."

DR. LUCIER: The vote is on the level of carcinogenicity, either known or reasonably anticipated to be a human carcinogen, or vote to delist in some circumstances, if that's the consideration under action. It's not a vote to accept the background document. We've clearly had cases where different review groups have voted differently on the same background document, so that's not the case.

So it's a vote on whether or not a substance or mixture should be listed as known or reasonably anticipated to be a carcinogen or delisted, not on the report itself.

DR. GOLDSTEIN: Let me then move this to –

DR. FREDERICK: Let me say something on that specific point. Speaking as a member of the board, my votes -- and I think my votes are probably representative of other members. My votes on the issue at hand, which is exactly what George said, it's a recommendation to Ken Olden, who actually is the ultimate decision maker on the list that goes in to Dr. (inaudible), it's a

recommendation on what to do on the motion at hand. It is definitely not an endorsement of the booklet, per se. Happens to be a background document.

The actual votes that are taken are informed by the booklet from NTP, who have had the different -- I'll have to say that I've dealt personally. They vary sometimes. But it's informed by that booklet, by external information that's submitted in the course of the year prior to the meeting, all written stuff, and I read every page that's submitted, as well as the verbal comments, as well as other peer-viewed scientific information that happens to be in my purview as a professional.

So it's a fully informed document or decision with regard to the body of information at hand. It's a scientific recommendation -- that's all -- on the issue of whether we should upgrade or not, and I think we could get hung up about this, that, or another phrase in one of these documents. That is not the point. It's a scientific evaluation on the overall body of information.

DR. GOLDSTEIN: That doesn't mean that NTP couldn't change this around completely and go over to an EPA process?

Frank, do you want to speak specifically to that comment?

DR. MIRER: Yes. Absolutely. We are, as reviewers --

DR. GOLDSTEIN: Let me say that Dr. Mirer is a member of the BSC.

DR. MIRER: Yeah. As reviewers, we're asked to critique the document itself, and if you want to make a recommendation, we provide a rationale -- for the primary and second review, provide a rationale for their recommendation. I'd like to believe it was taken into account. There's a lot of -- five to ten pages of commentary in some of my reviews.

So we do critique the document, and we do -- or, at least, I read the material that is sent out by the participants. There's no rule that they have to give us the night before, and some seem to get it to us two or three months before the actual review occurs. At least, I take it into account in doing my review, but we do critique the document.

DR. GOLDSTEIN: Thanks.

Before we get into comment time, we've asked Dr. Goldman and Dr. Frederick to look for themes and think of where they may be some issues

that we could particularly highlight during this discussion section. So, Lynn?

DR. GOLDMAN: Yeah. I've heard a few things, and one that I think is probably a good starting point is, actually, the issues of the process, of the peer review by the Board of Scientific Counselors.

I'm a new member of the board, and, actually, in my earlier life was part of the Executive Committee for the NTP and, in fact, chaired it during the time when these processes for peer review were put in place. And I guess, you know, no good deed goes unpunished. Now I have to participate in this process.

But the -- I think that -- and there's been a lot of email traffic among board members about some of these same issues, and one thing I'm encouraged by is some of the themes that are pulled forward that are some things that board members are concerned about, frankly, some of them are kind of going the opposite direction, but I think that they're issues that really need to be talked through here very carefully.

And one has to do with, really, how information is brought forward to the board and

discussed at the peer review meetings. There is a tremendous volume, and what Dr. Frederick said, I think that's shared by all the members, and that is that there's a tremendous volume of information that's provided in advance that because of the earlier comment processes gives a very good flavor for the views of scientists coming at the issues from different perspectives, not just the NTP and the other government scientists but, also, those who have commented from industry and elsewhere. And the members do read all of that material.

And hearing the discussion this morning, I almost wish that there were tests so that people could feel some faith or trust that that material has actually been read by the principal reviewers because those who are assigned with those reviewing responsibilities, from what I can see, take those responsibilities very seriously and feel that it's a very difficult and serious task being involved in that.

And there is frustration, though, and I think I've heard it here, too, and I think NIEHS is already trying to take steps to fix this with -- when there are last-minute materials that want to be provided, that perhaps, you know, there's new

information or maybe people feel they just want to say it again to make sure that they've been heard, and there certainly is a lot of that in this process, that that will come sometimes just within a matter of a couple of days of a meeting.

And even if it's something that is a reiteration, you have to read it to make sure that that's what it is, and that's a lot of last-minute effort. And so -- and I think that that's already -- there's already a decision on the part of NIEHS and the NTP to change that process so that there isn't the possibility of getting a barrage of last-minute material to wade through, and that's a good thing.

And I think then what has happened sometimes in some of these public meetings is that, you know, you see people just throwing their hands up in frustration about having this huge pile of material to read on an airplane or something and -- but, you know, I think people do agree that rarely has there been anything truly new in that and that that could have been done in advance and that that would probably be a better process.

The other thing is that the nature of the oral interactions that happen in those meetings and if -- you know, that in these formal oral

presentations that are given that are often, really, a reiteration of the materials that were provided in advance of the earlier comments and so are issues that have already been in much more detail because reading is a much more efficient way to get information than listening and so in much more detail have been heard.

In sake of fairness, to make sure people are heard, that's a good thing, but on the other hand, some of the members of the board sometimes feel that then there's not very much time to actually have scientific exchange and discussion because time is spent going -- you know, listening -- actually listening, and that's not maybe the best engagement of the brains of the people around the table, and that kind of -- so something, maybe, is lost in that.

And I guess the other thing that I've heard, and Dr. Frederick might want to, you know, enlarge on this a little bit, is that sometimes members of the Subcommittee would like to see more back-and-forth exchange between the scientists who are coming in with points and the scientists from the NTP, but on the other hand, they don't want to get into kind of a, you know, debate of free-for-all.

So how do you engage those meetings so that there can be some exchange without it being just a matter of, say, one party being on attack and the other one on the defensive, which isn't necessarily the way good science really happens. And so these are not easy issues at all, but, you know, those are some issues that could be involved in terms of improving the process.

The second issue that I've heard very clearly and I think at some point would be worth talking about is, really, a whole suite of concerns related to dose and whether the exposures in the population should have any bearing on listing, whether dose-related effects should have any bearing on the classification, and there are a number of people who made comments kind of around that issue.

Another one having to do with the process of using data other than direct human studies for making that determination of whether a substance is a human carcinogen or sometimes referred to as upgrading or downgrading the classification based on that. And, you know, the view of the BSC is that the data can be used to drive a classification decision in one direction or the other, either to

upgrade or to downgrade.

And there were comments this morning that -- you know, in both directions, one comment that, you know, they're only used to downgrade, but I think there's plenty of evidence that they've been used to upgrade, both ways, and, second, that they should only be used to downgrade.

And I think that a sense by the BSC is that if you're going to bring in those considerations, that the science can point in either direction and that you have to let the chips fall where they may in terms of the science.

And then a final issue that I picked up and, really, because of one of my inherent biases, which is just the need for better epidemiological input into the process when there are a lot of human studies involved. And I recognize that that's an issue that the NTP is trying to address by bringing more epidemiologists into the process early on and by bringing people into the peer-review process, but it does seem to be an issue that was raised a lot this morning.

DR. GOLDSTEIN: Thank you.

DR. FREDERICK: Yes. I'd just like to pick up on some points from the presentations

this morning, and I'd like to go through those in sequence, if I could, and then we can discuss those if they look like they bear more discussion.

On David Guston's presentation, there are two points I want to make. One is the Board of Scientific Counselors does not strive for consensus in any aspect. The individual members of the board both are conscious on the issue at hand and reflect their professional judgment. And it's my feeling that there's actually no -- as opposed to committee situations where you're moving for a consensus decision, I don't feel like that's the dynamic of the committee at all.

The second thing is there were a lot of unanimous votes there, but it's biased by exactly the point that David noted. There's a fairly low threshold for listing materials as probable human carcinogens, and most of the unanimous votes are in that area.

In the area where you're moving to known human carcinogen with regard to delisting votes, there are many more mixed votes in that area, and I think a reanalysis of the data on that basis would provide a different perspective that's probably more reflective of the dynamics of the voting in that

particular group.

The second issue from Dr. Starr's presentation is that these votes are advisory, and the real message on a mixed vote -- in the case of Dioxin, we voted twice, and there happened to be mixed votes in both cases. And it turns out I voted both sides of that issue. I hadn't really noticed until Tom put the slide up there. I was on the losing side both times.

But the point isn't exactly what the vote was. The point is that it was a mixed vote. And the recommendation to Ken is there is a mixed scientific opinion on this specific issue from this body of people, and the fact that I voted both sides of it says that, you know, I've been swayed. I've been kind of on the borderline. I am trying to vote exactly what the science is, and I've been swayed by the body of information, which has changed somewhat.

It doesn't matter what I believed when. The point is, in trying to vote exactly what the science is and the message to the agency, to Ken Olden, is that there's a mixed scientific opinion on this, and I think that's reflective of the consensus (inaudible).

If we move to Dr. Leber's talks, he feels

frustrated for the lack of dialogue, but this is a straight scientific evaluation. It's up or down on the science, and dialogue doesn't really do any good for that.

Quite honestly, the written information that's submitted covers the points. In dialoguing on it, it doesn't move anywhere. It doesn't make any difference if 3,000 people are exposed or 300 people are exposed. The law that drives this process says there's a significant number of people, and we aren't going to quibble over the exact number. That goes in the risk assessment arena. This is a hazard identification process.

The concern is: Is there a substantive -- enough of a level of concern based on the body of science, basically, to look at the degree of the concern, but that's handled somewhere else. It's just with regard to the hazardous identification issue.

The issue on benign or malignant, that sort of thing, and how the group gets into the nuances of the science discussion, which we don't want to get into other than to say that, we look at the whole body of information, including all the mechanistic information, to try to reach the best

decision and recommendation for society.

Moving to Dr. Rubin's talk, Dr. Rubin's talk was very interesting because it's a very good example of something we've run into a couple of times where an individual comes in as an advocate for an industry or a group and, in fact, the message is not exactly what was intended. We discussed this when Dr. Rubin gave his original talk at the meeting, so I'll reiterate this.

In his published papers, he's shown and argued quite conclusively that excessive alcohol consumption causes (inaudible) -esophagus and is directly responsible for esophageal cancer. And he says that very clearly in his written documents, A to B to C, and there's direct correlation between excess alcohol consumption and esophageal cancer. And, you know, those documents were submitted to us, and I confirmed it verbally with him at the meeting.

And it doesn't matter what the mechanism is. If you have linkage of exposure and the ultimate effects there, that's sufficient for the needs that we have on the table. And to a certain extent, his publications were part of the reason my vote went the way it did, and we gave explicit advice to

NTP staff to say that moderate alcohol consumption had not been shown to correlate with excess cancer risk, and we want the list to reflect that. It is only excessive, and that's the way the study showed it, and we wanted that reflected in the documentation.

So that was the advice we gave, and that was my perception of the advice we gave, and it was very strong, very direct and reflective of the science and reflective of where we were on the issue.

If we now move to Dr. Infante's comments, even as Lynn said, we use mechanistic data and the full body of information to upgrade and downgrade equally. It's an overall package of information. We're trying to get the right answer with regard to the body of science.

And Dr. Oller's presentation with regard to nickel, it's illustrative of a very good problem that you run into when you serve as an advocate for an industry. Part of the package that was submitted to us invoked Dr. Max Costa's work, who's Head of the Environmental Toxicology Program at NYU, a very distinguished scientist in metal toxicology.

And as we read and evaluated that

information as well as all the other information, then you may come to a different position than what might be presented at this particular meeting.

I would point, for example, to a recent publication of Dr. Costa's, and he starts out -- the first sentence of this publication says: Nickel compounds have been well established as human carcinogens. Well, that creates a problem with an (inaudible) industrial presentation. And then he goes on to talk about the difference in potency between insoluble and soluble forms.

So it reflects the fact that by looking at the overall body of information and all of the published papers of the people cited in this body, then you may come to a different conclusion than what might be presented in one of these meetings.

So I think I've brought up enough issues to fuel a lot of fire for discussion.

DR. GOLDSTEIN: Let me do it this way. Unfortunately, some of Clay's issues and some of your issues are issues which, again, get us to specific chemicals. I've just been sitting here doodling some things about the BSC, which I think is perhaps the first place we ought to try to focus on.

I'd like to -- again, I apologize if I've got this wrong. I've left out -- I'd like to get us to focus on the recommendations part. What we've heard, we've heard denied. It's unimportant as to whether it's right or wrong so much as: What are the recommendations to deal with this perceived issue?

We've heard that the BSC is hurried. It's hurried in terms of the members. Maybe it is. Maybe it isn't. We've heard there's too much material, too little time. It's hurried in terms of the public. You only got five minutes to make a presentation and sure that what happens there is really transparent. Is there enough information? Is there not enough information as to what the decisions were made on?

And some people are concerned that it's not iterative enough. You make the presentation to the public. You don't find out -- there is no specific response. It's not an EPA kind of record where every public comment gets a written response to it. It's done in a completely different way.

These are the kind of differences of opinions that we've heard. We've heard some people say, you know, "There's no need for all of

this iteration or written record. Let's just go forward. This is something that's been built on a couple of previous approaches, and this is just, yet, a final approach."

So I'd like comments on what is clearly a difference of opinion here from folks, hopefully restricted to that. I know people will want to go beyond these, but just to start with.

And, please, when you do make a comment, please tell us who you are and who you work for. We're trying to record this, so we'd appreciate it.

DR. BACAU: I'm Dr. Bacau (phonetic), and I'm representing (inaudible). And the reason -- one of the things that you have on the list that probably -- it's the impression that the audience had that by the time that public meeting occurs, every one of those members has already made his mind up or her mind. This is the distinct feeling I received when I listen to the deliberations in the BSC meeting.

Every one -- on every compound -- wasn't limited to one compound. On every compound I listened, I felt that all this was -- the message I got, it was a show, that we -- they gave an opportunity to the public to come, give a five-

minute presentation, then the members already had made up their mind way before that, maybe unjustified. It might not be the true feeling, but this is the message I received. I don't know how many people who were in that meeting received the same message.

I feel that one of the recommendations we can make is that these meetings should be held not once, but twice, because I think if we have one meeting where the public can make this five-minute presentation or ten-minute or whatever the number of minutes is, and then the Board of Scientific Counselors sit down, address those issues and so on and then have another meeting where we can listen to some of the issues that were brought and their reaction to it, I think that will convey a better feeling in the sense that, "Yeah. I had an opportunity to make a comment. Somebody heard me, and this is their answer to my comment." I know it might create a major problem for the timing, but I think that's the best recommendation.

DR. GOLDSTEIN: There's a comment over here.

MR. KELLY: I'm Bill Kelly with Federal Focus, which is not a newsletter. It's a

research organization. I've been an observer at the last two RoC Subcommittee meetings, and I was very interested in Dr. Lucier's comment and Dr. Frederick's comment, also, that the Subcommittee is not voting on the background documents, which -- and those background documents are the only written record. We have this up here as one of the issues. I think it's an important issue.

I mean, when the recommendation goes to the Subcommittee, there's a certain rationale stated, and it's stated only in that one document. And, certainly, as an observer, I was surprised today to hear that because I had the distinct impression that, basically, the Subcommittee was voting on the rationale stated in the background document.

And I was also surprised to hear from Dr. Frederick that they had a kind of -- what would you call it? -- a change to suggest with regard to alcoholic beverages, but that -- I don't think it showed up in the subsequent record like in the Federal Register notices where they record the various votes. You just see the numbers.

So something is not actually changed in the background document in the Subcommittee

meeting, give the impression it's been approved, and then that's not the end of the process. That document goes forward at least through three more steps: The Executive Subcommittee, then to Dr. Olden, and then to the Secretary. And, finally, it's my understanding it gets, basically, printed in that form in the final report.

So if the Subcommittee does have something in there that it feels is wrong or that needs to be qualified or changed, a record needs to be made on that, and it needs to be passed up the line to the Executive Committee and to Dr. Olden and to the Secretary because it's certainly not -- I appreciated the clarification, but it certainly wasn't a clarification that was needed. I have to admit that even after the clarification, I'm still a bit fuzzy on it.

You know, that document goes forward. It states a certain rationale, and if everybody is voting in favor of it or so many votes against it or there's a significant split on it, you don't know what it is that people are descending from or what they're disagreeing with. The document just goes forward unchanged.

That goes to this whole issue of, you

know: Is there an adequate written record of what people have actually thought about the scientific evidence here?

DR. FREDERICK: Let me clarify the recommendation. The recommendation is what goes in the final report that's published for the public to see, and we, as a body, recommend to the NTP staff what the final publication -- assuming that Dr. Olden took the recommendation of the Board of Scientific Counselors, that the text that actually goes out to the public in the listing would reflect the scientific evaluation of the board, that moderate consumption of alcohol -- I just use that by example. It doesn't make any difference, but moderate did not carry a risk. It was only excessive carried a risk. That's sort of the gist of the --

DR. GOLDSTEIN: We have a comment as to what actually goes forward.

DR. BUCHER: I'm John Bucher of NTP. I'd like to clarify exactly what the background document is and what we consider the entire body of information that's used here.

The background document is comprised of two parts, generally. There's the information on

which the whole listing is -- the recommendation for listing is based and then there's a summary statement that appears in front of that background document that is what we intend would be going into the report itself.

So the background documents are a living document in that they are changed in response to comments of RG1 and RG2, and they go to the Board of Scientific Counselors Peer Review Subcommittee. The background document is not changed beyond that because we want to have a record, a solid record, of what the information was that was presented to the board for them to reach a decision at that point.

All of the information that we receive as comments is considered part of that background information and it's added to the background documents. So when all of the information goes forward to the further steps, we say background document plus all the comments that have been received.

So make sure that you understand that. There will be changes to the wording of the summary statements based on the conclusions at each stage of the review, and what appears in the

final book may differ slightly or substantially from what appeared in the Board of Scientific Counselors Review Panel.

DR. GOLDSTEIN: Just to be clear, when this gets to Secretary Shavel (phonetic), you're saying it's got the original background document that is seen -- word for word is seen by the Board of Scientific Counselors, plus it's got all of the comments that have been received, and they all go to Secretary Shavel that way?

DR. BUCHER: The actual document that is submitted to Secretary Shavel is only the final Report on Carcinogens. All the information that Dr. Olden uses to make a decision about listing is the entire file of information that has been collected from the very beginning in consideration of that -- of the information.

DR. GOLDSTEIN: So all of the information, including the public comments, go as far as Director Olden?

DR. BUCHER: Yes.

DR. GOLDSTEIN: And at that point, there may be changes in the summary statement?

DR. BUCHER: Yes.

DR. GOLDSTEIN: And there may also be changes in the summary statement at the level of the Secretary's Office?

DR. BUCHER: I would -- that's possible, but I'm not sure that that's happened.

DR. GOLDSTEIN: Thanks, Doctor.

Dr. Oller?

DR. OLLER: I would like to make a couple of quick comments. One is, again, I want to reiterate I think it's very important that the background document be a high-quality document, and I think when the reviewers of the Board of Scientific counselors, which is where the peer review occurs, when they get this document, this may be the first time they become familiar with the literature in a particular compound. And, therefore, what the document is saying and what recommendations have been made up to that point will be the basis for the decision that they're going to make.

Now, then a few days before the meeting, they get comments, comments that may disagree with what's in the document. How can they judge who is right and who is wrong unless NTP takes the time to answer to the comments that I submitted

and said, "We disagree with your comments because of this and this and this reason," or, "We -- okay. We agree with part of your comments," and that may not have been clear in the document. That has to be done. Otherwise, I cannot see how the Board of Scientific Counselors can really take these comments and understand the issues that are raised.

I also would like to point out that as an industry scientist, we have recommended that the listing of certain nickel compounds be upgraded to known human carcinogens. So we're not here just saying everything has to be downgraded. It's just that we think that there are differences in the behavior of these compounds that are supported by the data, and there are some of them which are clearly carcinogenic and others that are not.

Furthermore, you may not be aware that Dr. Costa and I have written papers together, and he agrees with the concept that soluble nickel compounds are not carcinogenic.

Thank you.

DR. GOLDSTEIN: I should have made the point that that's Dr. Adriana Oller of the Nickel Producers Environmental Research

Association.

DR. FREDERICK: Bernie, let me respond. I don't want to talk about the specifics of nickel, but I just want to -- with regard to particular scientists and how we can be affected by a number of inputs, but the real point is I think you're taking far too narrow a view of our role.

Each of the members of this committee are scientists in the absolute sense of the word, and we don't -- if you think we just look at the input that comes in one document from NTP, you're sorely, sorely mistaken. And if industry waits until the last minute to submit their comments, they're making a really big mistake.

Those comments should be going in a year ahead of time. They should be sending in a package that would be a part of what comes to us, and then you only tailor that at the last minute if you've got, you know, something that you want to change with regard to some specific points. Then those come out three weeks ahead of time or whatever it might be.

But the point is, waiting until the last minute to get your comments in is not an effective way to present information for scientists to

evaluate. This is a scientific exercise. You get the fullest body of information on the table.

MR. LEBER: Philip Leber, Good Year. I agree implicitly with what Clay is saying, and I think hidden in that message was comments and so forth have to -- and input have to be made much, much earlier in the process.

But as it currently stands, Clay, we see a draft document weeks -- one to two weeks before the hearing. We can give comments, but we don't know what we're commenting on. We just unload our database as -- on isoprene or whatever. What's going to happen with it? We have no clue at that point, so there's no comments to be given earlier.

Secondly, on the issue of -- oh, the background documents and just tweaking at the last minute, I have one here that says: Chemical X is a reasonably anticipated human carcinogen based on evidence of benign and malignant tumor information in multiple organ sites and multiple species. For Chemical X, that is a false statement.

And that comment was made in writing. On the day of the Board of Scientific Counselors' meeting, it was not acknowledged that this was a false statement, and, therefore, board members were

voting on the assumption that this is a multi-species, multi-organ carcinogen, and that's not true, but what they're voting on is not that point but that it's reasonably anticipated. Now, if you take away that information or you correct it, is it still reasonably anticipated to be a human carcinogen? I have some serious doubts.

So, you know, that's why this iteration and the complaints of legal action and so forth occur, folks, because, you know, we give comments and we give input, but, you know, if it's being heard, there's no acknowledgment that it's being heard, and there's no attempt to correct the bona fide errors that are clearly in there.

DR. GOLDSTEIN: Let me pursue that with you a bit just so we have some clarification. There's two issues I think you're asking there when you're talking about the --

DR. FREDERICK: Phil, don't leave.

DR. GOLDSTEIN: We've got two issues. We've got process issues and we have, if you will, factual issues. Are you saying that, in fact, there are multiple tumors caused in multiple species, and because there is scientific debate and, in fact, the scientific debate was something that

you did not have a chance to present because the process was too slow or was it -- is it something that just there was an absolute misreading of everything?

If it's a question of just there's differences among the scientists and you think they're wrong and they think they're right, and the board got an opportunity to hear both sides of it, that's -- I mean, that's a little different from saying that the board didn't have an opportunity to hear that point.

DR. GOLDMAN: Well, (inaudible) debate, Bernie, because, I mean, we can't get away from the fact that there's a tremendous amount of hearing through reading that's going on in the process.

DR. GOLDSTEIN: Hearing because it was too hurried or that there wasn't enough time to put this data together. And then, of course, one issue I haven't heard yet or I did hear once, but it's buried in some of the writing we'll hear later is: Was this published or unpublished data?

So could you respond to that instance? Are you talking about a situation where you think they had enough time and they just disagreed with you

or they --

MR. LEBER: I'd be pleased to.

In this particular case, there is definitely multi-organ, multi- -- I'm sorry -- multi-organ malignant tumors in one species. In the second species there was only benign tumors. And the way this reads is you're supposed to believe that there's multi-organs, multi-species carcinogenic benign and malignant tumors. Now, in that second species there was only benign tumors. Okay?

This was commented on at the draft stage in writing. The Board of Scientific Counselors meeting, we did not hear anybody from NTP say, "We've got to make a change here on the basis of what we're going to be voting for reasonably anticipated to be a human carcinogen. There's an error there." That was not changed, so I repeated it verbally that day and got no comment there either. The vote was taken, reasonably anticipated.

DR. GOLDSTEIN: Let me pursue this. Is it conceivable that the scientific members of the panel voting up or down on the issue of the classification believed completely what you said, agreed with you completely, but still voted the classification the same way? They still think.

DR. FREDERICK: The answer is yes, Bernie.

DR. GOLDSTEIN: Is that the issue here? Try to get your focus on the issue.

MR. LEBER: That may be, but, Dr. Goldstein, I would assume that if you're presenting -- or NTP is presenting a statement, given the basis for why it is a reasonably anticipated, that there would be a correct statement for that basis.

DR. GOLDSTEIN: Here's a question of the record, not so much that the facts were not able to get to the board. Those are two different issues, important issues. I just wanted to get it clarified.

Dr. Mirer?

DR. MIRER: Frank Mirer again, from UAW, and also a member of the Report Review Committee and past member of the Report Review Committee and present member of the Report on Carcinogens Subcommittee.

First of all, let's go to the background document. I would say about 80 percent, 85 percent of the content of the background document typically is the IARC review of the material, which

is the most prestigious and complete document available. There's a veneer on top of it which reviews additional information that's developed since the IARC review and contains some of the other material required for the report.

We also receive what are perceived to be the key papers underlying the IARC review and subsequent to the IARC review, and we can request additional papers if we think they're relevant. So the BSC members have the complete record in front of us. There's no rule that says the new stuff has to come in the night before, and, typically, it comes in months before to our offices. Those of us who are involved in the material go through it.

The five-minute summary, in my view, the oral comments at the meeting, basically, truncate the discussion of the board members who are reviewing the material. The reasons why people take a position if you disagree with the critique, you have to state the reasons you disagree with the conclusion. I guess people who don't disagree don't usually write down reasons why they agree, but the record is completely there.

And I resent the notion that we're incompetent to review that material and render an

opinion on it. So I think we do critique. At least, I view my role as critiquing that report and suggesting changes in it. So I don't really accept the criticism.

DR. GOLDSTEIN: Let me raise a different issue about the BSC. And I should have -- Tom brought this up, Tom Starr: Is the composition right? I will point out that none of you, as far as I can hear, claim that the group is biased one way or the other. There is, at least in one of the written comments, some passing comment about academics, and I will not respond that one, but let me raise that issue.

Is there anyone who would like to comment on the composition of the BSC in any way? Again, having already heard something about the need for more epidemiological expertise from the point of view of Dr. Starr. Any other comments in that way?

MR. LEBER: At the tox forum, again, there was a comment made that, certainly, the Board of Scientific Counselors was – represented a political cross-section, and I think -- that was not an industry person, however, and then I think it does also represent the wide range of

expertise from statisticians, MDs, and so forth.

One of my concerns, though, is that so much of the data that is applied to carcinogenesis comes from bioassay data, and the bioassay field is sort of a unique, somewhat capsulated -- encapsulated realm within the field of toxicology.

You have a lot of issues, such as high historical incidences of certain tumors, testicular and so forth. You have a lot of chemistry that's involved in the generation of atmospheres and inhalation studies.

And many of the people who are represented on the boards are mechanistic people or they're people who don't have very much experience in the bioassay field. That's one of my biggest concerns. And epidemiology. I think you definitely need bolstering in that arena.

DR. GOLDSTEIN: Other comments?

Dr. Guston, please introduce yourself.

DR. GUSTON: Dave Guston from Rutgers. You heard about me before, and I put the little graph of the people's votes in the three-dimensional spaces.

When you aggregate those data, and I won't show you on the overhead because, like I

said, there is an error of aggregation there, but when you aggregate those data, it appears that the people with university affiliations are normally distributed around the majority opinion. The people with government affiliations seem to be similarly normally distributed around the majority opinion. Again, these are aggregating all of the individuals with those affiliations.

The people with industrial affiliations, and here I'm going to add the people with labor affiliations because that seems to be part of the idea, and even with the addition of the labor affiliation to the industrial affiliations, you get something that is shaded more than the university and government folks toward less protective.

Now, I'm not going to say that that makes the committee biased or not because you can't say where the meeting ought to be, necessarily, but it's based on where the majority is. That's the way these people with these substances ended up coming up.

I can't say for anything other than these substances, and I don't think that necessarily implies bias in the committee, but that's the aggregation.

DR. GOLDSTEIN: I can't wait for the word to get out about that.

DR. GOLDMAN: I just want to ask you a question, if you could come back up to the mike, because one of the things that I was wondering about in hearing your analysis and just speaking about the process, in a way, you could think of this process as kind of a quality control step, in a way, of -- which is coming off a conveyor belt and assembly line, except they're not all the same.

And some of these are very complex, difficult decisions, and some of them are much more straightforward, and I think, as Dr. Frederick pointed out, that, particularly, the ones where you're talking about listing something as a known human carcinogen or, conversely, when you're talking about a delisting decision, that those tend to be particularly controversial.

And I guess one thing I want to put to you is: Is there a way that you could look at, say, the type of decision, the type of product that's coming forward, and perhaps not -- should we be considering having a different process design for the reviews that are going to be more complex,

more difficult on priority, you know, like listing a known carcinogen?

DR. GUSTON: Yeah. That's part of the difficulty of presenting stuff in the middle of the research program, but I just had to take Dr. Frederick's suggestion seriously to decompose the data and to look at the decision based on which bin you're sorting. The idea -- just sort of offhand, the idea of a different process for a different bin strikes me as potentially problematic. I --

DR. GOLDMAN: Well, then you get into other issues like: Then do the people who have the less special cases feel they're not getting as much of a hearing or as much of a discussion? So, I mean, you could have an appearance of inequity, but –

DR. GUSTON: That might be a way to priority sort.

DR. GOLDSTEIN: Couple of comments? I would -- we've got about five minutes. Please come up and make your comment.

I would like -- I'm surprised we haven't heard anything about the written record issue among us. I'd appreciate comments on that. I think among all of the things that are up there,

that the idea of a written record that gets responded to is perhaps more central to changing a process than almost anything else that's there.

MR. KELLY: I thought that was the first thing I came up here to talk about.

DR. GOLDSTEIN: Okay.

MR. KELLY: Bill Kelly with Federal Focus. If the Subcommittee disagrees with something in the background document, in other words, it's voting to go along with the classification decision but on a different rationale, that should be documented, or if there's a mistake that could be significant in the background document, that should be documented. That's the written record.

DR. GOLDSTEIN: What about the issue, though, of all of the comments that come from the public should be responded to in writing and become part of the record? Which is what I think I heard some people suggest. That makes that -- that's obviously a much more of an iterative process. It gets people to respond to the record.

DR. FREDERICK: That's not, from my perspective, the whole philosophy of this process in the sense of going through the regulatory process of an EPA risk assessment or

something like that. That has a whole different protocol associated with it, using the scientific advisory opinion of a group of scientists who have looked at a big body of information. Not all of it is going to be consistent, generally, but you're trying to get out the signal from the noise with regard to what the scientific issue is, to make a health recommendation for the public.

People look at that body of information and they provide their opinions by way of a vote, and I think that's -- that's it. That's the punch line. And I think getting into a long iterative-type process as you're going through, you know, like, an air pollutant standard or something like that, that totally misses the point of this.

DR. GOLDSTEIN: I think that's a key issue that was raised by a number of speakers, and I'm offering the opportunity for people to talk about it now. We can talk about it later as well.

MR. KELLY: What I would -- that's not what I really got up here to address, but I would say if you're going to handle that, it should at least be handled in a separate section of the background document. At that point, the agency already has a set of comments from the industry on

its original listing proposal even though it didn't have a rationale at that point.

I think, at a minimum, the background document should set aside a brief section where it addresses the principal comments and what the -- how the agency -- what the agency's responses are that are relevant to what's going in the background document.

DR. GOLDSTEIN: You had something else to say?

MR. KELLY: That had to do with composition, which was the next subject, composition of the Subcommittee. And that's something nobody's mentioned, is that sometimes, on some of these substances, we're dealing with a huge and complex database, and I don't think anybody needs to impugn or denigrate the scientific expertise of the members on the Subcommittee, but I find it difficult to believe that members of the RoC Subcommittee in a couple of days or a couple of hours -- I'm not sure what -- can get completely up to speed on some of these huge databases.

And, for example, in the case of nickel compounds, I heard a dispute developing here over just what was said by a couple of experts in the

field. Shouldn't we have -- when we're dealing with very complex issues, call in some of the people who have special expertise on those substances?

As the process works now, the people who come in and comment always have a vested interest, and so they're tainted with a color. This person represents industry. This person represents a public interest group or whatever, and that, I think, taints the consideration to some degree.

There's an EPA model, and I know it complicates the situation, which Dr. Frederick doesn't like to hear, perhaps, and that's of calling in a subgroup of consultants who are experts in that particular field or on that particular substance to offer their views without being associated with a particular industry or a particular company, and that's actually the IARC model, which NTP relies on to a great extent in their deliberations.

IARC will go out of its way to pick people who are experts with regard to that particular substance to develop the IARC views on that, but NTP does not do that. It's a very generalist approach, and I think the process suffers as a result. And it may just be that Congress has given the agency an impossible task here, and maybe that

needs to be addressed, too.

DR. GOLDSTEIN: Thank you.

Again, we've got some -- I'm happy to have had some very specific recommendations, and, obviously, we won't mention them all, but subgroups, two meetings, whatever that had come out for NTP to be considering.

DR. GOLDMAN: Bernie, just to add to that idea, actually, what NTP often does is not set up a new subgroup but, rather, bring in specific consultants to add to, say, the science advisory board, a standing advisory committee. There will be ad hoc consultants brought in to participate in reviews where you need that, you know, area of specialized knowledge and it isn't present already on the advisory committee, which is a little different than setting up a whole new committee. It's more like adding to the discussion.

DR. FREDERICK: There's an underlying philosophical problem here that I think kind of permeates this that I'd like to get at. I work for industry, and I think I understand how industry works in terms of the culture, and I've been a part of this board for a while, and I think I understand the culture of this group.

Industry likes to comment on documents. They like to have a target, something to work off of. And I think industry has been frustrated because they haven't had this document early in the process to comment off of, to work on.

And it's a rare day -- well, I'd say it's atypical for industry early in this process, a year ahead of time, when these notices go out, to send in a really good comprehensive package of an industry position. That's what the -- if industry, in general, understood this process, that's what they could and should do. That is atypical.

Independent of whatever is going on at NTP in terms of the development of their document, industry presents their position. And then only later, when you actually get this document, then you respond to it, but that's just not the way the culture works. The culture is you get the document, whatever is being developed in government, and then you respond to it. You attack it. You deal with weaknesses and errors and all that sort of thing.

I think that fundamental cultural difference is the primary problem, if I can say there's a problem here, from my perspective, and I think

there are a variety of ways of addressing that, but I think that's the principal source of concern.

DR. GOLDSTEIN: My target right now is lunch. We'll have an opportunity for discussion later. I'm sure a lot of the speakers will bring up much the same points, and we can go back over these. There are other areas, such as mechanistic research, that were raised before.

So we'll start again at 1:20 sharp. Let me thank you all for your participation.

(**WHEREUPON**, a lunch recess was taken from 12:30 p.m. to 1:20 p.m.)

DR. GOLDSTEIN: Our first speaker this afternoon is Susan Nathanson of the Y-ME National Breast Cancer Organization. Again, for those of you who hadn't heard before, we're going to try to stick to the ten-minute time period for each of the presentations, and, again, we ask the presenters to try to stick to the process rather than to the individual chemical. Thank you.

MS. NATHANSON: I want to thank the Chairman and the panel for allowing me to speak. My name is Susan Nathanson, and I'm the Executive Director of the Y-ME National Breast Cancer Organization, and I appreciate the

opportunity to share our concerns with you regarding the classification of Tamoxifen in the Report on Carcinogens.

Briefly, the Y-ME National Breast Cancer Organization is a patient advocacy group that was formed 21 years ago by two women with breast cancer to educate and support other women and their families in our communities who also are dealing with breast cancer.

Basically, our mission is to try to decrease the impact of breast cancer and create an increased breast cancer awareness and through information and the interpretation of science that's available and evidence to provide a mechanism for women to be empowered to ask their health care providers the right questions and determine what is best for themselves in partnership with those providers and do that so that, essentially, no one faces breast cancer alone.

We achieve this mission in several ways. We educate, inform, and support women diagnosed with breast cancer through the provision of two 24-hour, seven-day-a-week hotlines, which at the moment receive well over 31,000 calls a year, plus a web site that gets, in mid year this year, over

half a million hits and over 2,500 direct questions about various treatments and diagnoses with regard to breast cancer. We do that both in Spanish and in English.

We have support groups around the country in over 25 chapters in the United States, and we do it through annual and biannual educational conferences on numerous topics. Last April, in particular, we had a conference on breast cancer in African-American women.

We also provide workshops to raise awareness about breast cancer in topics such as early detection of breast cancer through breast self-exam, age-appropriate mammography, and clinical breast exams. We also have a national bimonthly newsletter that carries critical up-to-date information to over 15,000 individuals on recent findings on breast cancer diagnosis and treatment.

I am here today to urge the NTP to consider listing the pharmaceutical product Tamoxifen in a different manner than with other human carcinogens. We are not here to dispute that Tamoxifen is associated with an increased risk in endometrial cancer in women taking this drug, and we realize that this is a serious side effect.

On the other hand, we have 25 years of information collected about the use of Tamoxifen for the treatment of breast cancer that indicates that for women taking this drug for treatment, the benefits outweigh the potential risks of endometrial cancer.

Y-ME believes that women should know the risks and benefits they incur by taking any drugs. Many of the drugs that they take are cardiotoxic, and some of them lead to other malignancies as well, but these are the treatments that are available today for breast cancer.

We feel strongly that these risks and benefits need to be communicated in a responsive and responsible manner, and we try very hard to make sure that the women understand the science behind the -- the scientific evidence behind the risks and benefits that we tell them about.

The fact that the FDA has fully evaluated this product and approved its use for the treatment of breast cancer we feel should be taken into account, along with the fact that the risks and benefits are included in the product information.

Y-ME is here today because we are concerned that the release of this list with the

inclusion of Tamoxifen as a human carcinogen, a known human carcinogen, without a strong, balanced statement about both the benefits and the risks will frighten hundreds of thousands of women currently taking Tamoxifen for the treatment of breast cancer and could result in unnecessary confusion as well as women stopping the treatment they're involved in.

Therefore, we are asking that the NTP release the information about Tamoxifen so that both the benefits and the risks are included with an advisory to women who may be concerned about this listing to contact their physicians for details and advice.

We are especially concerned that the media will release this information in such a way as to sensationalize to list Tamoxifen as a human carcinogen without information about the full benefits as well as the risks associated with taking this drug.

As you know, people diagnosed with cancer of any type are fearful, not only for their lives but especially for their choices in the kind of treatment that they engage in. On the hotline, we try to give reasoned responses to questions regarding any

treatment, including the risks and benefits of all, but when a story is reported in the media, we hear about it from thousands of women. We can barely handle the calls that come in.

For example, when the media reported that there was fraud found in some of the results of the NSABP trial for Tamoxifen, even though those investigators were exonerated, thousands of women called our hotline because they were terrified by the possibility that they had made a mistake in the choice of treatment that they had taken.

The same thing occurred when the whole issue of silicone breast implants were reported and were listed as a cause of systemic and immune system disease. Women were unnecessarily frightened by all of that, and these were women who had -- many times had had silicone implants and went through the surgical procedure of having them removed where, in most cases, it might not have been necessary. And, again, women are really afraid of the fact that they are choosing the wrong treatment or choosing -- making the wrong decision with regard to how they live their lives following a diagnosis of breast cancer.

So, basically, we are here today to urge

public health officials to take great care in how this information is released and to consider listing this drug in a separate category to allow the NTP to better communicate the risks and benefits of the drug therapies involved.

DR. GOLDSTEIN: Thank you. For those of you who don't know, that organization is one of the most effective ones out there.

Our next speaker is William Kennedy from AstraZeneca.

MR. KENNEDY: Thank you, Mr. Chairman. First, a personal thanks to you in my own risk management. Your strict adherence to the program allowed me the opportunity to push away from the luncheon table, getting the benefits of nutrition and avoiding the risk of overindulgence. I wish more of these things that I went to I would have these things.

Good afternoon. My name is Bill Kennedy. I'm a Vice President in the Drug Regulatory Affairs Department at AstraZeneca. I'm pleased to have the opportunity to share my thoughts with you regarding the classification of pharmaceutical agents in the Report on Carcinogens.

I commend the committee for holding this

public meeting to discuss the procedures used to prepare the Report, and we appreciate NTP's thoughtfulness as you review the complex issues surrounding the inclusion of pharmaceutical therapies in the Report.

The Report on Carcinogens is an important function of the NTP and reflects Congress's honorable intention to protect the health of the American people by providing information about possible health risks. Our concern is that the report may have the unintentional result of confusing and potentially hurting the public.

All pharmaceuticals inherently have health benefits and risks that must be carefully and consistently communicated to consumers. Because the Report on Carcinogens does not contain this important benefit information, it has the significant potential, as Susan has already pointed out, to confuse rather than inform patients about their drug therapies.

It's our belief that this confusion will cause patients not to take important lifesaving medications that their doctors have prescribed for them. Our concern is heightened because the most serious life-threatening diseases are the cancers

that are treated with some of the medications that are included in the current report.

Every day real people affected by serious illnesses must make important decisions regarding their medical treatment. Patients deserve clear and comprehensive information about the medications that have been prescribed by their physicians.

We recommend that the NTP seriously consider the proposal that has been made by the FDA to establish a pharmaceutical category in the Report on Carcinogens. Currently, listings in the report do not distinguish between a pharmaceutical product that the FDA has fully evaluated and concluded that it confers a benefit to human health. They don't distinguish this from any other substance in the clinical -- in the carcinogenicity report.

A pharmaceutical category would list pharmaceutical agents separate from non-pharmaceutical agents and provide the public with the information about FDA approvals for drugs as well as potential side effects. Most importantly, such a category would list benefit and risk information together for comparison. Without a separate category for pharmaceuticals, patients and their doctors could become confused about the

magnitude of the risk versus the benefit from a medicine or treatment.

When the U.S. FDA approves a pharmaceutical, it evaluates its benefit and risk and decides if the availability of that medicine is in the best interest of the public health. A pharmaceutical category would acknowledge FDA's critical role and better serve the public by providing complete information about listed drugs. A pharmaceutical category would continue to serve the Congressional intent of the report but acknowledge that the U.S. FDA has determined that the benefits outweigh the risks.

This new category would be highly appropriate for therapies like Nolvadex, our brand of Tamoxifen, a breast cancer therapy that is also credited with reducing the incidence of breast cancer in women at high risk and reducing the incidence of recurrence and second breast cancers in survivors.

The incidence of endometrial cancer, pulmonary emboli, and deep vein thrombosis is very rare. While women must be monitored for possible side effects, the FDA and other world health organizations have determined that the benefits far

outweigh the risks of women who are at high risk of developing breast cancer, have breast cancer, or are breast cancer survivors.

We cannot ignore the risks in favor of the benefits; nor should we ignore the benefits in favor of the risks. To focus on one and not the other does a great disservice to the hundreds of thousands of women who are fighting breast cancer today.

We appreciate and respect NTP's mandate to inform the public about potential health risks, and in the case of pharmaceutical drugs, it must be done without frightening patients away from the medicine that can successfully treat their serious diseases. We at AstraZeneca call upon the NTP to enhance its mission by accepting the FDA recommendation to create a separate pharmaceutical category in the Report on Carcinogens.

Mr. Chairman, thank you.

DR. GOLDSTEIN: Thank you.

Our next speaker is Michael Bird of the Exxon Biomedical Sciences, Incorporated, and the Butadiene Work Group of the Olefins Panel of the Chemical Manufacturers Association.

MR. BIRD: My name is Michael

Bird, and I'm here today on behalf of the Chemical Manufacturers Olefins Panel, and this panel comprises the US producers and some of the users of butadiene. The panel's been involved in health research for butadiene for about 20 years (inaudible) with others in the generation of (inaudible).

Just by way of brief background, butadiene is listed in the 9th Report as a human carcinogen. Butadiene in combination with styrene makes up SBR rubber, which you find in the majority of the car tires, but it's also a product of auto emissions as well.

Now, some of what I have intended to say has been adequately covered, and I certainly don't want to numb my audience. Being Speaker No. 13 in the afternoon, I have some trepidation, but there are some points that I want to go over.

First of all, this all important key background document is, essentially, prepared in a closed process. Now, there's nothing intrinsically wrong about a closed process, but it doesn't include outside input and especially that from those who have been involved in the business of generating much of that data.

And what we found in the case of butadiene, and I'm going to illustrate some of my process comments with butadiene, is the fact that this particular background document didn't include some important studies, both epidemiologic and mechanistic, and, also, there are a number of factors there which we felt were given more weight than, perhaps, they should have been.

The net result is that RG1 and RG2 had at their disposal -- the only document they had for their review was this background document. The first opportunity for industry to view or input – and not only industry, by the way. A number of the academics involved in generating the data was given two or three weeks before the RoC Subcommittee review.

We also note that the document tends to advocate a particular position rather than presents the evidence, and I submit to you that other organizations tend to have a rather more balanced document and tend to only develop the position after they've had adequate discussion and assessment. I've given you a technical example there. I'm not going to get into that.

There's no mechanism to revise the

background document, as we've heard this morning, and it's fine to have public comment in parallel, but, boy, I'd like to see some integration and, also, some of that addressed.

Now, in the case of butadiene, again, Dr. Frederick, it would be nice to have one year. In fact, we had three months from the time of first notice in the Federal Register that butadiene was going to be upgraded to your meeting, and, in fact, we had three weeks prior to your meeting to review a 60-page background document. So more time, please.

And, again, we submitted, and others from academia, detailed comments to the RoC, and I submit to you that we really do need to have discussion and adequate deliberation of those comments. As Phil Leber said this morning (inaudible) in response to comments provided, I too have children, four of them. They often say, "Hey, it's not right," or "No" to me, too, but, boy, it's sure nice to hear from them because at least it means that they have heard me. I'm not sure that we have been heard.

I'm going to skip right way down. You've had more than enough of the first two bullets.

Need chemical-specific expertise on subcommittee. We've heard about epidemiology, but with butadiene a lot of the material was epidemiologically related. There are a lot of subtleties in that data. And we've heard reference today already about IARC, the SAB, the Science Advisory Board of the EPA. Both IARC and EPA-SAB reviewed butadiene within two or three months of the NTP RoC review. I'll get into that in a minute, at least the (inaudible) views. And they had extensive and different compositions on their review boards.

Dr. Goldstein, if I could be (inaudible) this afternoon just to make sure I have an audience. It's important to have epidemiologists, and you need more than one. Okay? They're good buddies and friends. I work with them real hard, but I recognize (inaudible) that you definitely need, because they can't agree on a cause of death, and that's why you need debate and adequate time for debate.

And when we get involved in some of the reviews by IARC and EPA, IARC for instance had a separate epidemiology subgroup of some ten epidemiologists, and they took several days to talk

about the butadiene epidemiology.

Now, I'm not suggesting -- Dr. Infante, you made the point. I'm not suggesting NTP mimics IARC or EPA-SAB, but I think it's important, with the reviews being so close, they should take note of why they are so different and examine why the difference in interpretations because, otherwise, it's a very confusing message to the public and to others involved.

One of the facts involved in the EPA-SAB and IARC reviews was the fact that the epidemiology data is derived from the SBR, styrene-butadiene, rubber process as opposed to the monomer industry, and all the leukemia we've seen with butadiene could be derived from that industry.

And there's a lot of discussion and a lot of developing data pointing to the fact that when they did (inaudible) work, that these can't be excluded. We also had further data in metabolism, and I hear -- NTP might stand up and say, "We've got to draw a line somewhere," but, on the other hand, we have very new, critical data in a time (inaudible). It's very important, I think, to be flexible and at least have some footnote in your report that this is a

variable. So I submit that, currently, the background document as it stands is outdated and doesn't represent the scientific data as we stand at the moment.

If we look at the reasons why IARC and EPA-SAB might be different from the NTP, at the bottom line we'll see two different conclusions. For IARC and EPA, it's probable, implying some doubt. For NTP, it's known, and that's a pretty certain category. I divided it on the left in two aspects, the evidence, or data, and, also, the process.

Well, as I've mentioned, there's a lot of human data available for butadiene, which is why you need those epidemiologists, plural, but both IARC and EPA said that the human data wasn't consistent. One of the things they recognized was that monomer workers don't have leukemia. The SBR workers do.

They also recognized that there wasn't sufficient human data. They classed it as limited because the data really derived from one study, albeit very large. That study is just now being revised. It's now out, as I speak, and I think we'll be finding that the conclusions are rather different.

Also, IARC and EPA found that there wasn't

enough mechanistic data or there was mechanistic data to suggest there wasn't a parallel between some of the rodent findings and the human studies.

Now, NTP came to different conclusions, which is fine, I guess, but the NTP review process was very hurried and, I submit, different address the similarities of the IARC and EPA decision; nor did they address some of the critical new data.

And as you can see, I'm being critical here perhaps as to process. The quality review document for the IARC and EPA was very high. With the NTP, it was variable. There were some portions which were excellent and there were some portions which weren't so good, particularly the epidemiology. Peer review process, extensive for IARC and EPA. The NTP, limited. As you can see, if you have problems with the evidence and the process, that's just one of the reasons I submit you come to a very different conclusion.

Recommendations. First of all, I submit that we obtain input to and revise the Draft Background Document prior to submitting it to the RoC Subcommittee, and I mean well prior, and let's have adequate time and input even along the RG1 and RG2 so that those committees know and have a

complete database to work with.

Also, let's have a realistic period. Let's give us more than three months to review this complex subject from start to finish. Let's have adequate discussion. So far in the last 12 years, we've had four international symposiums. There's going to be another one next year on butadiene, isoprene, and chloroprene. None of those issues are dead. There's much scientific debate. Certainly, I wouldn't want to put any of those chemicals into the known category.

Let's provide adequate rationale for recommendations at each stage of review, and I suggest that if there's new information, which there is with butadiene, that we reopen the debate. Let's not just put out a document (inaudible) which is out of date. So my suggestion would be to take butadiene and consider it for re-review.

I think I'm finished. Thank you very much.

DR. GOLDSTEIN: Thank you.

DR. FREDERICK: Bernie, quick clarification point from Bill. Typically, they do -- there's a year's notice on the upgrade or downgrade or whatever. Was this one an exception to that?

DR. JAMESON: It turns out for

this particular one, which was reviewed in 1997, the Federal Register announcement announcing the nominations we were going to review that year did not come out until late June of that year. So in this particular case, that's correct. That is an accurate statement.

DR. FREDERICK: Okay. I just wanted to be sure on that.

DR. GOLDSTEIN: Our next speaker is Lee Coogan of Sorptive Minerals Institute.

MR. COOGAN: Good afternoon. My name is Lee Coogan, and I'm the Executive Director of Sorptive Minerals Institute, or SMI, the national trade association representing the manufacturers and marketers of sorptive mineral-based products. These product are widely used as pet litters, filtration aids, and industrial floor absorbents. They're composed primarily of clay minerals with trace amounts of quartz. It is this occurrence of quartz as a minor component in these products that led to SMI's participation in the National Toxicology Program's Board of Scientific Counselors Subcommittee review process for the 9th Report on Carcinogens. These comments are based on that experience.

On October 26, 1998, the NTP announced that the Board of Scientific Counselors' Report on Carcinogens Subcommittee would be meeting on December 2nd and 3rd of 1998. The stated purpose of the meeting was the peer review of substances, mixtures, or exposure circumstances nominated for listing in or delisting from the 9th Report on Carcinogens and the provision of the opportunity for public input. While the stated purpose for the December meeting was clear, SMI believes that the NTP process failed to adequately address that purpose.

In order for an independent peer review to be full, fair, and effective, a review panel must consider all of the available scientific information, including those materials submitted by outside parties. Only after carefully reviewing and considering all the relative scientific information can the panel make a truly informed decision. SMI believes that the process used in the 9th RoC did not meet the requirements that ensure an informed decision on these issues for the following reasons.

Prior to the meeting of the Board of Scientific Counselors Subcommittee, the NTP published a notice in the Federal Register soliciting

comments and input from interested parties and promised, and I quote, "another independent peer review group that assesses whether the relevant information available is sufficient for listing in or delisting."

Given the date of the Federal Register announcement for the 9th RoC meeting and the time frame for submitting comments, a fair and effective peer review of all the submitted information was a virtual impossibility.

NTP requested that comments from outside interested parties be received by November 30th, 1998. This was only 39 hours prior to the start of the Subcommittee meeting. As a result, the members of the Subcommittee had little or no time to read the information that was submitted and give the information the kind of careful and critical assessment that is an essential part of a scientific peer review. This fact was confirmed when during the course of the proceeding at least one Subcommittee member commented that they had not had time to review all of the materials.

Additionally, presentations made by the NTP staff that had obviously been prepared well in advance of the meeting failed to address or even

acknowledge the issues raised in the written comments. SMI has done a great deal of research on crystalline silica over the past 13 years. This is what was submitted (indicating). Due to the timing of the NTP notice, the Subcommittee was given one working day to consider that material. It is not unreasonable to believe that careful consideration of this information may have had a substantial impact on the final Subcommittee recommendations.

In SMI's opinion, the peer review process used for the 9th RoC was inadequate and incomplete. The process failed to provide the Subcommittee members with enough time for careful and critical review of the comments received from outside interested parties.

It is particularly troublesome that despite their obvious failure to consider all of the available scientific information, the Subcommittee felt compelled to proceed with a vote to upgrade crystalline silica to a known human carcinogen.

Due to the significance of this activity, SMI urges NTP to build more time into their peer review process. All of the available scientific material must be carefully reviewed and considered and understood by all of the Subcommittee members

prior to the Subcommittee making its final recommendations.

Members of the Subcommittee should receive copies of the written documents a minimum of two weeks prior to the scheduled meeting date. This will allow the members a reasonable amount of time for a thorough evaluation of the materials presented. It will also enable them to discuss the material both among themselves and with the presenters during the Subcommittee meeting. Only by making these changes will the NTP process provide the kind of thorough, critical peer review mandated by the Department of Health and Human Services. Without these changes, the review process is, at best, misleading, and the conclusions reached by the Subcommittee will be based on incomplete and poorly understood information.

In addition to the submission of written comments, the review process invites interested parties to make oral presentations to the Subcommittee. Unlike the presentations made by the NTP staff members, who were under no time constraint, presentations by interested parties were limited to five minutes. As a result, years of research and pages of scientific information had to

be distilled into a five-minute talk. This brief time period is woefully inadequate to discuss complex scientific material.

In short, I've been given ten minutes today to tell you what I think is wrong with the NTP process. I was given five minutes to distill this (indicating).

SMI recognizes the necessity for time limits on the oral presentation phase of the review process. Nevertheless, the serious nature of the process warrants that presenters are allowed more than five minutes to present their material. If, as SMI believes, the purpose of the review process is to ensure that the members of the Subcommittee clearly, accurately, and completely understand all the information being presented, then additional time must be allowed for questions, answers, and discussion.

SMI recommends that the Subcommittee allow a minimum of ten minutes for each party to present their remarks followed by a minimum of five minutes for questions and discussion.

Upon the completion of the oral presentations, there is a discussion among the members of the Subcommittee. In the case of

crystalline silica, there was a lengthy debate focusing upon concerns raised by two of the Subcommittee members. During that discussion, additional questions were raised that fell outside the scientific expertise of the Subcommittee members. Three experts, who moments before had completed their oral presentations, attempted to answer these questions or provide clarifying information.

Their attempts to provide this information was silenced by the Chairperson. In so doing, he effectively indicated that participation in the discussion was limited to the members of the Subcommittee regardless of whether the information being discussed was correct or not.

Such an exclusive discussion at this crucial point in the process is unacceptable. It increases the probability that the final vote of one or more of the Subcommittee members will be influenced by inaccurate information. SMI believes that it is essential for the process to allow dialogue between Subcommittee members, NTP technical science staff, and others with technical expertise on the subject under discussion. The Chairperson of the Subcommittee must allow, within reasonable time

limits, such relevant dialogue.

In terms of the criteria used for listing -- and, Mr. Chairman, I'll have to be somewhat more specific here -- in the case of crystalline silica, the NTP nomination to reclassify was based on the recent IARC listing of October 1997. However, the NTP background document failed to accurately represent the IARC finding. An important statement in the IARC listing recognizing the differences in crystalline silica and its potential carcinogenicity was inexplicably omitted from the NTP nomination.

The IARC listing included the following statement, and I quote, "In making the overall evaluations, the Working Group noted that carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its polymorphs," end quote.

In the presentation on behalf of NTP, the presenter failed to mention this extremely important qualification. Instead, the presenter stated that, and I quote, "their (IARC's) conclusion was, 'Crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is

carcinogenic to humans (Group 1),'" closed quote.

Therefore, while using the IARC listing as the criterion for considering the classification of crystalline silica, the Subcommittee chose to ignore IARC's conclusion that all forms of respirable crystalline silica may not be carcinogenic.

While two members of the Subcommittee raised this issue after hearing the oral presentations, the majority of the panel chose to ignore this glaring omission. In the end, the Subcommittee went ahead with a vote to upgrade respirable crystalline silica to a known human carcinogen, without qualification. By so doing, the Subcommittee, unlike IARC, indicted all forms of crystalline silica, including that found in common soil and beach sand.

The stated criteria used by NTP for reclassifying crystalline silica was the 1997 IARC evaluation, yet the Subcommittee selectively ignored an extremely important qualification, that evaluation. If the criterion for listing is to be the IARC evaluation, then NTP is obligated to consider that evaluation in its entirety.

In collusion, for the reasons I've outlined above, SMI believes that the NTP process failed to

fulfill its stated purpose of performing a full, fair, and independent peer review on the nominations for the 9th RoC. It is SMI's hope that as a result of these public meetings, the NTP review process will be improved to allow for a more balanced and thorough evaluation of all the relevant scientific information.

Until those thanks can be implemented, however, SMI requests that all previous work on the 9th RoC be discarded and that the process begin anew under the improved procedures.

Mr. Chairman, thank you.

DR. GOLDSTEIN: Thank you, Mr. Coogan.

Our next speaker is William Kelly from Federal Focus, Incorporated.

MR. KELLY: Good afternoon. I'm Bill Kelly for Federal Focus. We're a nonprofit research foundation. We're not here on behalf of any particular industry. I want to speak on just one subject, and that's the -- what Congress expected from this document and whether what's being produced is what Congress originally expected.

I happened to be a part of the Aspen

Toxicology Forum in July, and this issue came up very briefly. I think Roger McClellan actually raised it, if I'm not mistaken.

And in the last few weeks, I've gone back and -- gone to the Library of Congress and taken a look at the Congressional background materials there. And I don't have any neat slides or overheads, but I did take the time to set out what we found in a written presentation that's on the table out there. And I'm not going to read that presentation, but I would encourage you all to pick up a copy of it because the attachment to it actually has the language of what we found.

And I'm careful to say in there that we're not sure we got everything because when I was there, I noticed that there were hearings materials, for example, in connection with the 1978 legislation. There was testimony in hearings presented by NCI and NIH. I took a quick look at that, and I did not see anything on this, but my experience with Congressional materials is that there's usually a lot more there than you get out of just the reports or the floor debate.

The primary -- what comes across as a whole when you look at the Congressional materials

indicating what their intent was is really an intent that this be a consumer-oriented document. This was intended to be not just a technical document for academics or something that would be done as an exercise for government agencies. It was intended to be something useful to the general public.

And the report and the debates talk, actually, about this document allowing people to make decisions about what they would avoid, what exposures they would avoid, what they might be, where they might go. In fact, as far as saying, you know, it should enable them to be able to know that they've had a significant exposure to something, they should go in for medical screening before they get cancer.

Now, in order to do that, you have to know what you're looking for and you have to know whether you have actually received a significant exposure to something. That's the conclusion you immediately draw from those sort of statements.

So it's surprising when you pick up a copy of the Reports on Carcinogens and right in the preamble you see a listing here -- a statement that a listing here is not intended to indicate that a

substance poses a risk for people in their daily lives.

Well, I think everybody here knows the difference between the terms hazard and risk, but I'll bet if you went out and asked the man on the street what the difference is between hazard and risk, they'd know that about as readily as they'd know who the 23rd President of the United States was. And I don't know that. Maybe somebody will tell me.

So the whole object of the report is to give useful information, and I don't -- I think somebody said it at Aspen. In fact, I think it was somebody from FDA. You could not write in big enough and bold enough issues across the front of the report that this is about hazard only, not about risk, and have people understand that.

You need to provide information that will really alert people in a user-friendly way to what it is that's the type of risk. You know, is this dangerous? You know, if they barbecue a piece of meat, is that dangerous, you know, if they eat it? If they go out in their car and if they drive on the road, is this dangerous?

Is this only really known to be dangerous

for chemical workers in a particular occupation or people who have been exposed in an industrial accident or, you know, miners who have worked at least 20 years under certain conditions? that sort of thing.

And when you look at the Congressional history materials, you see that Congress was actually very aware of this, and I was very surprised, given what's in the preamble to the reports about this being only a hazard document, not a risk document, that everything in the Congressional history materials talks about risk.

They talk about wanting information on magnitude of risk. They talk about wanting information on significance of exposures, on subpopulations that have unusual exposures. And I think it's quite clear from the context there that they're not talking about subpopulations that have some unusual genetic susceptibility. They're talking about -- and actually give examples, as I recall, like chemical factory workers or workers in the nuclear industry or people who eat fish out of a particular river that has been contaminated with something.

So they want information given to the public. Should I really be afraid of this? And if I

should, under what conditions should I really be afraid of it? And I think the agency really needs to confront this issue. I've never seen anything from the agency that's confronted this issue.

Granted, when you read the specific language of the legislation -- I mean, it certainly can be interpreted to allow the agency to do a report the way the agency has done, a simple list with just known or reasonably anticipated followed by a compendium of information, but I don't think there's enough information, either in the listings or in the -- what they call the profiles later on in the report, to really alert the public and give them the information they need.

I think the industry needs to take a really hard look at that, and they need to think about – and they need to respond to it, you know, in a public way and say, "We've looked at this. Here's what we think. We're going to keep doing it for these reasons," or, "We're going to change it for these reasons."

Although I don't want to get into specific substances, I would note that just this morning I've heard references to several substances where this type of thing was an issue. This thing is really

only a significant risk under certain circumstances or very high exposures or they didn't differentiate between this particular exposure circumstance and that particular exposure circumstance.

So I would encourage the agency to confront this issue, and I would encourage them to actually consult what we put together on the legislative history materials, and I would also encourage them, perhaps, to dig a little bit deeper and see if there's anything else there that needs to be compared with what we have dug up so far.

Thank you.

DR. GOLDSTEIN: Thank you, Mr. Kelly.

Our next speaker is Richard Carchman from Philip Morris.

MR. CARCHMAN: Thank you, Mr. Chairman, members of the committee, the audience. Good afternoon. My name is Richard Carchman. I'm here at the behest of Philip Morris, and I think this is a wonderful opportunity for people interested in this area to have time for the kind of participation that I was listening to this morning.

I, working for Philip Morris, submitted

scientific information to NTP regarding one of the materials that was on the list, and I thought that was a very important process, and I was involved in the December presentation at Research Triangle Park, and I thought, again, this was a very important aspect.

And I'm only here not to -- trying not to reiterate many of the things that I've heard already but to try to highlight some points with regard to the process that may not have been touched on, at least as I understood it. So, again, the purpose is for people like myself and the company that I represent to express their views about the process and evaluation criteria.

The fact that the NTP may initiate an independent search of the literature and prepare a draft background document, I've heard a lot of commentary in terms of this particular process. And the components of the draft background document, I don't think that I have any difficulty with it. I think it's the right kind of bullets to try to address in arriving at the conclusion based upon some consideration of these types of facts.

Now, with regard to the review steps, the primary and secondary reviewers examine the

nomination, the literature citations, and the document for completeness and accuracy. Now, the conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment. So it's not simply a regurgitation of what some study says or some body or other organization says, but it requires an assimilation of the relevant information.

Completeness and accuracy are clearly the foundation for scientific judgment, but integral to that is an ability to critically analyze the information once you have some assurance that it is both complete and accurate because when you have completeness and accuracy and critical analysis, it gives you the best opportunity to apply the best scientific judgment in arriving at a conclusion.

Now, I was somewhat bouyed listening to Dr. Frederick when he alluded to the fact, as I heard it, that he simply doesn't rely upon the background document, that he embraces materials that may not have been included, that may be more current. I said: That's good news.

Unfortunately, the potential downside to that is that the people out there like myself and others may not have access to that kind of

information, nor the process by which Dr. Frederick and/or his colleagues may have used in arriving and utilizing that particular information. With respect to human studies, we provided comments with regard to environmental tobacco smoke, and I won't really spend any time talking about that.

I'd like to use as examples within that report some data that was provided in the background document on animal carcinogenicity studies. As it was pointed out by one of the NTP scientists this morning, the background document contains a body of information. There's a summary on the first page that then is a distillation of the background document.

If you look at the ETS document from NTP, it speaks to the epidemiology and it speaks to one of the several kinds of animal studies that were referenced in this document, and that was the A/J mouse. Within the background document but not within the summary were two other studies that the background study referred to, some studies by Dr. Hans P. Witschi and from Finch and colleagues at Lovelace.

So you have the mouse skin painting, in summary, which is a particulate smoke condensate,

the Finch study, which is inhalation of mainstream smoke with tobacco-specific nitrosamine, NNK, and the Witschi study, which is a sidestream/mainstream inhalation study.

All three studies had important and vital scientific information in drawing a conclusion. The mouse skin used the smoke condensate. The Finch study used tobacco smoke. The mouse skin condensate was carcinogenic when applied the way it was done there.

In the Finch study, NNK was carcinogenic in that mouse model. Tobacco smoke didn't do anything. In fact, at high enough levels, there was a suppression of the NNK-induced lung carcinogenicity, but there was no real discussion of that. The Witschi study was fascinating because this is the first study to demonstrate, by inhalation, increase in lung tumorigenicity in animals with a tobacco smoke surrogate. So you have these three studies.

What was missing was a critical analysis of just what was going on because if you look at the Witschi studies, he was able to demonstrate that the gas phase of this tobacco smoke material was totally and wholly responsible for the increase in

lung tumorigenicity.

Juxtapose that with the mouse skin painting, which is tobacco smoke condensate, which is a totally different material. Though they're all true, true, in some sense, related, any reasonable and thorough scientific analysis would have pointed out some of the difficulties here.

So, indeed, if Witschi's work is somehow related to the human smoking experience, it turns on its head the last 50 years of tobacco smoke carcinogenicity. No comment at all on this critical analysis.

What was missing from the background document? A publication by Dr. Maronpot, an NIEHS scientist that reviewed the strain A mouse work, an A/J mouse, the model that Witschi used, and Witschi's a coauthor of the Maronpot paper. And they did this review for the NTP, and the conclusion is pretty clear that they think it's an unreliable test to use as a decision-point approach for carcinogen testing. It was not cited in the background report.

Within the Witschi study, the background report mischaracterizes the overt toxicity. It said there is no overt toxicity. In the exposure aspect

of Witschi's studies, the body weight gain depression was at or above 20 percent, which normally would have invalidated it in an NTP study.

Putting that aside, the exposure levels in Witschi's study were 1,000 to 10,000 times higher than anything reported in the EPA ETS Risk Assessment Document, and the A/J mouse -- the animals died from adenocarcinoma of the lung just sitting in the cage, i.e. no exposure. There is no discussion of this at all.

And as I said in the last bullet point, the attribution of increased lung tumorigenicity to the gas phase of smoke, in fact, Witschi measured benzo (a) pyrene and NNK, a tobacco-specific nitrosamine, and he basically found and concluded that these could not possibly be responsible for the increased lung tumorigenicity he was seeing.

Now, Dr. Steven Hecht, who was a participant in this committee and present at the December meeting and probably one of the world's experts on tobacco-specific nitrosamines recently published a review in JNCI, and this is a quote in reference to the Witschi work:

"It was concluded that the vapor phase of ETS is as tumorigenic as full ETS and the

responsible agents are not NNK or BaP." These studies require confirmation. That's my highlighting, not his.

Remarkable. Again, no discussion, no commentary. These things are included as if they're used in some sort of meaningful, supportive way. Any kind of critical analysis of this would raise some very interesting and important questions. That was not evident at all.

Recommendation - that for the background report, we need to make sure it's both complete and accurate. Somehow we need to have critical analysis, a response to the submitted information, which seems to fall into a vacuum, and then justification for the classification system. Since it's not simply based on the background document, what is it based on?

Thank you very much.

DR. GOLDSTEIN: The next speaker is Stephen Lester of the Center for Health, Environment, and Justice. And, again, I'll recommend to the speakers that we stick to general points, not the specific chemicals or specific studies.

MR. LESTER: Good afternoon. My

name is Steve Lester. I'm the Science Director of the Center for Health, Environment, and Justice. Our organization was founded in 1981 by Lois Gibbs, the woman who organized (inaudible) Niagara Falls. Since that time, we've worked with a large network of community-based groups of over 8,000 groups. Our primary works involves (inaudible). Before I begin, I'd like to thank the NTP for the opportunity to make these comments and for having this meeting here in the Washington, D.C., area.

Like others before me, I'm here today to talk about the listing and delisting procedures, but unlike many others this morning, I'm here to say that I think this is a good process. I think it's a scientifically grounded process, one that is fair, one that is open, and one that provides opportunities for comment. I don't think this process is broken and I don't think it needs any major changes.

The most important elements of this process is the need for impartiality and for transparency. The NTP needs to maintain an objective, science-based approach for considering and deciding on the carcinogenic status of a substance.

The NTP staff must operate independently

and use the best science available to review their chemicals, and they must report results of their evaluation in an open manner that includes providing the basis for their decisions, the information they used for making their decisions, and the process by which they went through to get there. It is our opinion that the current process currently embodies these basic elements and principles.

The American people, public interest community, government at the federal, state, and local levels all rely on the decisions made by NTP in deciding the carcinogenic status of a chemical. If this information is questionable or tainted by a relationship with a company or special interest, then the credibility of the agency and its work will be seriously damaged.

The NTP staff should examine all of the scientific data and relevant information in deciding whether a substance is a carcinogen. This review should be based on published scientific, peer-reviewed information. There is no place in this process for unpeer-reviewed information or unpublished information.

The NTP should explain their decision, list

the papers that were relied upon in making their decision, and provide the public with an opportunity to review and comment on this process. We believe the process, as it's currently structured, works and does not need to be changed.

We also believe it's important that the NTP staff not make themselves available to special interest groups who have a favorite chemical up for review. There should never be private meetings between NTP and consultants for private companies or industries or special interest organizations. There is no need for it and there's no place for it.

Staff at NTP are perfectly capable of deciding, based on the best scientific information, whether a chemical is capable of causing cancer in animals or humans. The decision should not be decided by the pressures applied by industry or pressure applied by special interest groups.

The situation that currently exists at EPA should be a lesson learned for NTP. Over the years, the EPA has bent over backwards to work with industry to allow special interest meetings and to allow opportunities for industry to meet with the staff. As a result, the agency has reached a point where they're afraid to make a decision without

first speaking with these special interests. I don't think this is in the best interest of the public. It is not how government is supposed to work, and it's certainly not how scientific decisions are supposed to be made.

The situation with Dioxin is a perfect example of this problem. In the Fall of 1944, EPA released a health assessment document on Dioxin. At that time, they were deluged and overwhelmed with information from industry and special interests about this report. Since that time, the agency has continued to receive comments and continued to work with all of these special interests. As a result, more than five years later, there is still no final reassessment on Dioxin.

The NTP will suffer the same fate if they are not careful. If industry and special interests are allowed routine access to the staff, the process of listing and delisting chemicals will come to a crawl or come to a complete stop.

Public interest groups like CHEJ do not have the staff or budgets, as many companies and special interest organizations do, to dedicate to lobbying the scientists at NTP as they try to decide whether a chemical is a carcinogen or not.

This decision should not depend on whether someone or some company gets to speak directly with the staff and present special data that only they have access to. The decision on whether to list or delist a chemical should depend on the peer-reviewed, publicly available literature and on the scientific integrity of the staff to examine this information and analyze it and make a decision. As we understand it, this is generally how decisions are now made at NTP, and we would suggest that NTP not change this process.

Although there are many aspects of the process that are working well, we have several recommendations. First, we'd like to see more scientists with public interest background and experience be part of the panels and the review committees that are part of this process.

We also suggest that the NTP consider involving community activists at some level in these reviews, including, in particular, in terms of priority setting and research recommendations. NTP should not lose touch with the people who are directly exposed to these chemicals.

Second, we'd like to see these meetings continue to be held in Washington or perhaps other

cities such as New York or Los Angeles or Chicago. NTP should consider having some (inaudible) meetings to see how well this might work. Our organization could not have been here if this meeting wasn't held in this area.

In closing, the NTP process for listing and delisting chemicals is a good process. It does not need any major changes. Most importantly, it needs to remain divorced from the influence and lobbying efforts of industry and special interest groups.

Thank you.

DR. GOLDSTEIN: Thank you, Mr. Lester.

Our next speaker is Jackie Warren. And, Ms. Warren, I'm sorry. I don't have your affiliation listed.

MS. WARREN: I'm a member of the public.

DR. GOLDSTEIN: A member of the public.

MS. WARREN: Thank you.

Ten years ago, I represented the Natural Resources Defense Council and the Environmental Defense Fund as Intervenor in support of NTP when

a group of the Synthetic Organic Chemical Manufacturers Association and other industry groups sought to enjoin the publication of the 5th Annual Report on Carcinogens, to stop it from being published. That case raised many of the same issues that are being raised here today. There were then and there still remain very serious questions of public health protection and debate in these issues.

And I'm here today just as a private citizen to ask that the NTP give very careful consideration to the adverse impact on the integrity of its scientific judgments that would necessarily follow from the adoption of many of the procedural changes that are being demanded by industry participants at earlier points in this process as well as here today, the kinds of demands that are either blatantly threatening future legal action or by implication doing the same thing.

The Soffa (phonetic) case was decided before NTP's criteria for listing were amended the last time around, three years ago. That process has been expanded and opened up since that time. Nevertheless, at that time, the judge in the Soffa case concluded that NTP's then process, which

provided multiple levels of review, which is the case now even more, and continuing opportunities for public input was completely consistent with their responsibilities under their statute, was appropriate, and declined to enjoin the publication of the report.

But here we are ten years later hearing many of the same kinds of complaints and the same sorts of arguments in suggesting that NTP's process must, in every way imaginable, become a carbon copy of the regulatory process that EPA and OSHA and other regulatory agencies go through in their risk management balancing under their administrative actions.

Now, Congress apparently did not disagree we the Soffa Court's decision back in 1989 because (inaudible) NTP's statutory mandates in 1993, they didn't say, "Your process is wrong. It's warped. It's fatally deficient." They said, "Publish your report every two years instead of every one year." That's all they said. You cannot draw a conclusion that the NTP's process is in some way failing this law when Congress so recently took a look at the process and didn't reach that conclusion.

Therefore, I think that when NTP listens to

what I view as a deja vu kind of attack on the agency's process that they should bear in mind that a process that wasn't as open as this one is passed judicial muster and, also, Congressional scrutiny within the last ten years and that they're under no legal obligation to provide the kind of line-by-line written response to everybody's comments, to provide ever-increasing earlier (inaudible) intervention in the process so that the particular special interests who want to protect their chemicals and keep them, at best, from being listed in the annual report will have even more opportunities to come forward and do that.

The purpose of the annual report is informational. If you look at the language of the legislation, you can see that what Congress had in mind was the provision of a source of objective, peer-reviewed information for the public, for government agencies, for health professionals.

The statute itself that was enacted in 1978 was intended to increase the number of environmental chemicals that were being tested for carcinogenicity. The agency that was given that responsibility is not simply another group of political appointees and career bureaucrats who

don't really know what they're talking about. Therefore, we need some outside, very well-informed scientists to tell them what they should do.

I mean, these are highly skilled technical professionals whose life's work is the testing of substances for carcinogenicity. When they sit down to look over the list of nominations, they're not the man in the street or the woman in the street. They're people who have a lifetime of carcinogenicity testing behind them to look at, and their conclusions with respect to the substances that they review, I believe, and the court agreed at that time, is entitled to its degree of deference, which we're not seeing in this room, I must say, and I didn't particularly see in the comments.

Now, what NTP regards as its particular role is the hazard identification step of risk assessment, but not the risk assessment itself. The Court specifically upheld the propriety of that role under the statute so that NTP is not required to do the quantification or to do the kind of balancing that says, yes, this may be a carcinogen, but let's look at every little aspect that might say it isn't, and, therefore, the benefits don't outweigh the

costs that might be imposed on a manufacturer if this would be regulated. Those kinds of arguments are absolutely appropriate at the regulatory agency's venue, but they are not appropriate in front of NTP.

I think that the extent of the intrusion of economically motivated pressures into NTP's process, which should be, really, a purely scientific process, has been a subtle but gradual shift of the burden of proof away from the chemicals and onto the public. The result of this is that many substances to which people are presently exposed continue not to be either listed or, therefore, regulated or the exposures continue. And that, to me, seems to be the antithesis of public health protection.

It may be that some statutes exist that say when NTP puts a substance on their list, informational requirements have to be taken under OSHA or (inaudible). Those are informational requirements, however, but the actual regulation requires that these regulatory agencies do a cost benefit analysis and take into account all of the kinds of factors that are not appropriate for deciding whether the hazard exists in the first

place.

And over the ten years, watching what's been happening here, it seems to me that NTP is really not resolving the (inaudible) uncertainties in favor of protecting public health anymore, that when a substance is reviewed and mechanistic information is brought forward and there's controversy among the scientists, why should that substance be delisted when there's a debate in the scientific community?

Seems to me that once they're on the list, once there was a consensus that a substance posed a threat of cancer to humans, there ought to be compelling evidence that it is not to be a human carcinogen and will not be rather than taking it off on the basis of unproved theories for which there isn't a consensus in the scientific community and then simply waiting until the human data come in 15 years from now showing that, in fact, it was a human carcinogen.

Many of the substances that are known human carcinogens were positively carcinogenic in animals before we had human data. All of the substances which we know are human carcinogens are also positive in animals. That's the reason for

the whole premise of the NTP's criteria, which is if the substance causes cancer in animals, it is likely to cause it in humans. And to err on the side of the chemical in the face of questionable and controversial information seems to me to be a retreat from the obligation and the mandate that NTP has had in the past.

In my testimony, I spoke to some specific substances, which I won't do here, but I will say that I feel really strongly that NTP should not further compromise the scientific objectivity of its process. Just to look at the list of speakers today indicates who is knocking on NTP's door regularly, has already been allowed into the process more than I personally think they have a right to be and want to be even further involved.

They already have multiple levels of public opportunity. They'll have another opportunity at the regulatory agency if and when the substance is regulated, but they certainly have already, in my opinion, adversely affected the perceived scientific objectivity of the NTP to some extent, and that is because of the adoption of criteria which are based on unproven theories and controversial approaches to interpretation of data.

That kind of involvement has already seriously compromised the public credibility of the National Academy of Sciences. Now, their review panels have conflicts of interest which are not public and which occasionally get out into the press, doing great damage to the objectivity of the National Academy of Sciences. I would not like to see this process (inaudible) at all, but I think that it's very important that NTP do everything it can to avoid that same kind of result.

I also think that the industries potentially affected by the proposals within the 9th Report have readily acknowledged in one of the ten signature letters that went to Dr. Olden that the potential marketplace impacts of these decision weigh heavily in the balance for them. Well, the potential public health impacts weigh heavily in the balance for all the rest of the people in this country who deserve to have these reports prepared and circulated around to them, the way Congress intended.

One of the speakers said, if you looked at the legislative history, if you look at what the statute says and what the last judicial review of the agency's mandate showed, NTP is doing its job

properly and it should continue to do so.

DR. GOLDSTEIN: Thank you.

Our next speaker is Carolyn Nunley of Consumers Union, Public Service Projects.

MS. NUNLEY: My name is Carolyn Nunley, and I'm with Consumers Union, an independent, nonprofit testing and consumer-protection organization and publisher of Consumer Reports Magazine.

In the 14 years that I've worked on toxics issues, I've conducted substantive research on the toxicity of commercial chemicals, how they're used, and the level of exposure that such use generates.

I'm continually struck by the lack of publicly available information on both use and exposure and toxicity. The Report on Carcinogens is one of the few readily available sources that offers a broad, independent view of the extent of knowledge that exists on potentially carcinogenic compounds.

A chemical's listing is not an end but a beginning, a place to start if you're looking for information on the risks associated with a chemical. The Report on Carcinogens flags those chemicals that may pose cancer risks so that agencies charged

with managing such risks and members of the public can map a course for whatever further action may or may not be warranted, be it further investigation, regulation, or other types of action.

I have three basic points to make in my comments today. One, the Report on Carcinogens in its current form works well and should not be significantly changed. Two, as its mission is to in form and educate rather than manage and regulate, the listing process ought not be encumbered by stakeholder involvement of the nature that is more appropriate for regulatory decisions.

While we are among the strongest advocates for openness and transparency, we believe that the process already allows for a tremendous amount of public participation in a manner that's both efficient and sufficient given the fact that risk management decisions are made elsewhere.

And, finally, because the Report on Carcinogens is such an important resource for the public, to subject it to the bias of parties that have a commercial interest in spin-doctoring chemical listings would, essentially, destroy one of the few

useful resources whose purpose is solely to inform the public.

With over six trillion pounds of some 77,000 chemicals in US commerce today, almost none of which have been adequately characterized as to their potential toxicity, it's critical that we haven an efficient, expedited means for identifying the known and possible cancer hazards that selected, well-tested chemicals may pose.

Many of us in the public interest community count on NTP to provide a document that reflects the scientific landscape in a way that's not censored by those who have a commercial interest in minimizing or obfuscating the evidence. This is particularly important since to develop such a compilation from the literature would be impossible for most public interest groups that have limited staff, resources, and access to the literature.

The proposal put forward by some industry representatives to expand the level of review and reporting to include more active participation of affected industries in the listing decisions is disconcerting.

Looking back to the time when

carcinogenicity of chemicals like asbestos and vinyl chloride were the subject of debate, the affected industries repeatedly refused to face the uncomfortable fact that these chemicals caused serious health effects in humans as well as laboratory animals. Nonetheless, industry already has a place at the table with at least one representative on the Board of Scientific Counselors, and we feel that's more than sufficient.

With all due respect to the need for scientific debate, we believe the strongest impulse of economically affected parties is to emphasize uncertainties and block consensus, delaying listings and the associated bad PR for as long as possible. The plain truth is that for most substances listed in the Report on Carcinogens, there's already consensus, at least among non-economically interested experts. There comes a time when enough debate is enough.

Unlike regulatory decision-making, the decision to list a chemical in the Report on Carcinogens does not in itself constitute a regulatory action. Often, experts within the regulatory agencies have already developed extensive risk assessments on chemicals before they

are listed in the Report on Carcinogens.

It's up to other agencies and their respective risk management decision-making processes, which are political as well as scientific in nature, to decide what action to take. Congress no doubt recognized this distinction when it chose to place the listing authority in the hands of NTP scientists rather than a regulatory agency.

Interested parties should lobby the specific regulatory agency about whether or not action should be taken on the basis of the facts referenced in the Report on Carcinogens, not the NTP, about whether the chemical should be listed in the first place.

The Report on Carcinogens listing process is one of hazard identification, not risk assessment. It is simply an admission of research findings that suggest that a chemical may cause cancer. Given that any method for identifying potential carcinogens necessarily reflects the many uncertainties in the existing data, it's critical that those engaged in the activity are not influenced by commercial interests in delaying or preventing such a conclusion.

Congress knew what it was doing when it

made government, and government alone, responsible for hazard identification, thereby drawing a distinct boundary between the scientific process of reviewing the knowledge base and summarizing it for public consumption and the political process of deciding what action such information warrants.

It's interesting to note that so many petitioners who expressed a problem with the current NTP approach are those organizations that have a commercial interest in keeping chemicals off the list. We, therefore, strongly object to any changes that would be made solely for their benefit.

Let us not forget that the Report on Carcinogens is a product of Congress's passage of the Toxic Substances Control Act in 1978, following on the Nixon Administration's War on Cancer launched in 1972. As that war is still far from won, we need to maintain, if not strengthen, our vigilance to identify and characterize compounds that may be contributing to this trend.

The Report on Carcinogens in its current form is one important tool that helps us bring chemicals that may be harmful into focus, just as it

helps steer us away from wasting precious research and regulatory dollars on controlling substances for which the evidence suggests no risks.

In our view, this review process must not be hindered. The more chemicals that undergo NTP review the better. The Report on Carcinogens offers an efficient approach to identifying chemicals that warrant further action. It's also a flexible document that allows for listing decisions to be revisited in light of new information.

To subject this process to more lengthy, encumbered politics of further committees and analysis would defeat its purpose in being a reliable, timely report with which to begin the more political process of deciding how to assess and manage risk.

Just a few years ago, these listing criteria were reviewed and changed. Presumably that process was open and transparent and enjoyed broad participation from a wide range of stakeholders. Yet, somehow we find ourselves here again, just three years later, to reopen the debate simply because a group of economically affected parties don't agree with some of the new listings. It makes one wonder if we will all find ourselves

here again after the next Report on Carcinogens is issued, suffering through this time- and resource-wasting debate endlessly, unless or until no commercial chemicals remain on the list.

But as we've learned from chemicals like asbestos, PCBs, and lead, an ounce of prevention is worth a pound of cure. It's society that has to pay for that pound; yet it's often industry that refuses the ounce. That's why we need tools like the Report on Carcinogens to identify carcinogens, if possible, before they saturate the chain of commerce.

The information in the Report on Carcinogens isn't earth-shattering. It's, basically, information the government and the scientific community already know. The public has a right to this information as well. The Report on Carcinogens provides it in a clear, digestible, not-hard-to-understand prose with appropriate caveats as to its tentative nature. For the public and Congress, this is no small benefit. To quote Thomas Jefferson, "Only an informed public can be trusted to govern itself."

What we think we see here is the affected economic interests objecting to the bad publicity

attendant to seeing their chemicals listed this way. Their tactic is to attack the basis of the listing as an unfair result of a flawed process. We think the words of another president probably fit the industry's campaign here: Self-delusion in face of unpleasant facts is folly, Ronald Reagan.

Regardless of how noble and reasonable they try to make it sound, good science, peer review, open process, transparency, let's not forget that the goal of the petitioners here is to prevent the public from getting information. That's profoundly undemocratic, and NTP should resist the impulse to go along with this unreasonable request.

Thank you very much.

DR. GOLDSTEIN: Our next speaker, our last speaker before the break, is Barry Castleman, who will be taking the place of Jane Williams of California Communities Against Toxics.

MR. CASTLEMAN: Thank you. I'm an environmental consultant. My background is in chemical engineering, and I'm here to speak with the people from the various public interest groups and consumer protection groups to urge that the Report on Carcinogens be kept where it is, where it's least endangered by improper corporate

influence.

The pressure to move this to the National Academy of Sciences or the EPA Science Advisory Board or the International Agency for Research on Cancer that's coming from the industry and public interest groups are consistent in wanting the current process retained and protected. NIEHS has a more open process than groups like the National Academy of Sciences and, certainly, the International Agency for Research on Cancer.

In the case of butadiene, the International Agency for Research on Cancer meetings were highly improper. There were two votes held on the classification of carcinogenicity of this major industrial chemical. The first vote, by one vote it was decided that butadiene would be graded as Class 1 by IARC as a human carcinogen.

Subsequent to that, one of the people who was present -- one of the experts who was present had to leave. That evening, a bunch of lobbying went on and an additional vote was held the next day, and at this point the votes were by one vote in the other direction. One person, I believe, was persuaded to change his vote. When the Chairman of the IARC panel asked that this be disclosed in

the IARC publication on butadiene, this was disregarded by the staff at IARC, including Americans who happened to be on the staff at IARC.

So I don't think that this is a model that we want to follow or rely upon too much if we have more open and public process for evaluating carcinogens. The meeting at IARC was also heavily loaded with people who were representing the affected industries who were there as observers by IARC.

There have also been criticisms about IARC's handling of (inaudible), another major industrial chemical used in gasoline, and the deletion of certain important animal studies in the IARC review on that chemical. Conflict-of-interest information received by IARC, by the experts who serve on IARC panels, is not publicly available.

I've been following these kinds of activities with the international agencies, the World Health Organization, the International Labor Office, the International Program on Chemical Safety, and with Dr. Richard Lemmon I've authored an editorial called "The Manipulation of International Scientific Organizations" that was published last year in the

International Journal of Occupational and Environmental Health. And it's usually the process that is at issue where the process is being grossly manipulated by financially interested parties, as Dr. (inaudible) used to call them.

At the EPA Science Advisory Board, I understand that participants disclose their potential conflicts of interest and then go ahead and vote anyway. I think that the industry preference for the National Academy of Sciences, for the EPA Science Advisory Board, and the International Agency for Research on Cancer, as venues preferred for evaluating carcinogenicity, reflects that the industry has greater ability and access to influence those so-called expert panels in those other venues than they had with the civil service and open public process of NIEHS.

And I guess I would only have to conclude that it's a shame that David Rall can't be with us today because I believe that he would also agree that this is yet another wave of corporate influence trying to overwhelm our democratic processes and expose the public to more carcinogenic agents for financial reasons.

Thank you.

DR. GOLDSTEIN: Okay. Well, we've got a break coming up, and we're scheduled to come back at, I guess, 3:20. Our first speaker may or may not be here. Is Joe Shapiro here? We'll be --

SPEAKER: I could probably do it for him.

DR. GOLDSTEIN: You have his material?

SPEAKER: I do.

DR. GOLDSTEIN: Okay. So we will start at 3:20 with --

DR. FREDERICK: -- with a discussion. We're doing the discussion first.

DR. GOLDSTEIN: I'm sorry. You're right. We will start at 3:20 with discussion.

(**WHEREUPON**, a break was taken from 3:00 p.m. to 3:20 p.m.)

DR. GOLDSTEIN: Let me make a couple of points about the discussion. I think the format -- from talking to people around in a very informal way, the format seemed to have worked reasonably well this morning, so we'll try to reproduce that.

We're going to first ask the NTP folks if

they have any real clarifications. Then I'll turn this over to Clay and to Lynn to see if they've got some specific themes they think they want to go over. I've got a whole bunch that seemed to have been developed, but we'll primarily depend upon the discussion here.

Let me make a few points about that discussion. Again, I would hope that we do not get into the chemical-specific, study-specific kind of issues. We really are focusing on a process here, and the motive of what we're doing is to improve the process.

I think that's the only motive that ought to be discussed here. I don't think it's helpful to discuss or try to impugn motives to everyone as to why they're doing this or not doing this. So let's focus it on the motive of trying to get things better.

Let me turn it over to George. Do you have any comments at all or any clarifications?

DR. LUCIER: None.

DR. GOLDSTEIN: Fine.

Okay. Lynn, Clay?

DR. GOLDMAN: Okay. I thought, actually, in the last series of comments -- probably

many of you appeared to be sleeping (inaudible), but I thought in the last series of comments there were a number of speakers and, really, coming from different points of view, on the one hand from the point of view of the tobacco industry in terms of the listing for tobacco smoke, on the other hand from the point of view of some of the public interest groups, that there was some interesting issues that I'd like to hear more discussion on with respect to the whole -- kind of the guts of what the process should be about in terms of not only documenting the initial scientific analysis that is done, which is clearly done very well, that, you know, that is provided, not only providing the comments that are received from members of the public at all stages, and, clearly, that's provided, but also then whether or not the process should include, you know, the kind of process that you see in rule making, for example, where then each of those comments is formally responded to and there's an opportunity for everybody to get kind of a formal response back.

And I really was very interested and it made me realize there really is a difference between an agency like the NIEHS that's a part of

the NIH Scientific Research Agency and, you know, obviously, Congress putting this process there and not at the individual regulatory agencies.

It didn't say: EPA will do this for the ones it regulates and FDA for the ones it regulates and OSHA for the ones it regulates. It said that this would be, really, housed in or coordinated by, because there's a lot of participation from any of those other agencies, the NIEHS.

And, you know, when you do science in a regulatory context -- and when I was at EPA, it was in the context of, for my office, either the Toxic Substances Control Act or (inaudible). You not only have to get the science side, but there's also a tremendous amount of process and procedure that you have to get right.

And we knew, for example, under TSCA that if we did a rule where -- I mean, all the science might be correct in the rule, but we failed to, say, respond to every comment or we failed to have proper docketing of every study, even if those comments or those studies were not even germane to the decision, even if, from a scientific standpoint, those were not important in terms of the ultimate judgment, that could have returned the

decision because in a legal context, and which is where you operate with rule making, in a legal context, I hate to say this, but, you know, process is actually sometimes more important than the substance, but that's not where this activity was placed. It was placed in an agency where, you know, substance wins out over process in a sense where science comes first.

So in listening to discussion, I really had -- you know, I didn't have any question at all, especially after Jackie Warren's presentation about what the intent of Congress was to have been, because she gave a very compelling argument, and maybe there are other lawyers here who could argue against, but she gave a very compelling argument that, in a sense, it had already been argued out whether or not, you know, a regulatory-type process is required, and it's not, but then even if it's not required legally, what would be the benefits of having, you know, a process that looks more like that, and, also, what would be the problems with it?

And I guess one thing I really worry about a lot, from some of the things I heard, particularly from some of those on the industry side, is just,

you know, my sense that it's a tremendous amount of time and resources to do those very meticulous kinds of notice and common processes.

At EPA, one of the major costs in rule making was just that piece of, you know, every single comment that came in, you know, docketing, responding, having lawyers review it, frankly, you know, and all of that is an enormous amount of effort.

And I just thought it would be useful to hear a little more from people about, you know, why -- you know, if that's what they're looking for, why they'd want something like that, how they think it would actually improve the scientific process. As you can probably hear, I'm pretty dubious about that, but, you know, whether this would truly be enough addition of value in that that it warrant the effort.

DR. FREDERICK: Let me pick up on what Lynn was saying. This process is clearly focused on the substance of the science. And I participated in the reevaluation of the listing and delisting guidelines a few years ago, and we intentionally wrote those -- the group worked with George and others, (inaudible), who we wanted

these guidelines to be guidance to bring in the full body of information.

Quite honestly, from industry's perspective, there's a real opening there for doing good-quality science to effect these listings. It's not taken advantage of nearly as often as it should by industry. There's a clear opening there to put good-quality science on the table to support the position that industry is taking, and this could involve very new technology.

It wasn't even in -- it was not more than a twinkle in our eyes back when we wrote those listing and delisting provisions years ago. (Inaudible) technology certainly holds a lot of power with regard to the (inaudible) expression of many genes at the same time as a manifestation of a toxic response or to say that there's not a toxic response, either way.

But the point is that this is a scientific evaluation. It's not a rule-making process. I've participated in EPA peer reviews from time to time. That's a very different sort of thing. Takes a lot more time. There's a lot of wordsmithing involved and all those sorts of thing.

In this process, you look at the body of

information and you form an opinion, yes, no, up or down. We don't wordsmith. We don't get into all the nuances of what goes on in a regulatory agency. It's just a recommendation (inaudible) on what the clear scientific signal is on the motion on the table. Is it a probable human carcinogen? Is it a known human carcinogen? That's all.

Now, I'd like to come back to a couple of the comments that were presented because they bring up some important points. Michael Bird's presentation -- Michael, the background document is not an all-important document. It may be an all-important document to some people on the outside who are looking at it and want to focus on it and obsess on it, but it's not an all-important document. It is a part of the information on the table that's evaluated with regard to the decision-making at hand.

There is a full body of information there, and it includes all the outside comments that come in and all the papers we look up, all the peer review papers, the full listing of the IARC listing, if we want of go back and look at that. It's the full body of information on the table. There's not one piece that's all-important. It's the full body of

information on the table, and I think it would be inappropriate to describe the background document as being all-important.

And this is really highlighted when we get to Richard Carchman's comments with regard to picking one element of the background document on one specific listing discussion, which happened to be on environmental tobacco smoke, and what you did there was focus on one aspect of the animal data that, from my perspective, was totally incidental to the meat of the discussion at hand.

It's well acknowledged that the animal models are very poor with regard to tobacco smoke for a variety of different reasons, which I won't go into, but the point is that the meat of discussion really related around other aspects of the scientific information.

And to focus on not only -- you know, just one aspect of this background document and say that the whole process is flawed because you picked one, more or less, incidental element of something that was discussed there is just an inappropriate characterization of the decision-making process.

And I think it's the sort of thing that Lynn

got into on this notice of rule making and getting tripped up because you didn't appropriately respond to some insignificant detail along the way. We're clearly looking at the important scientific signal on the problem at hand, the full body of evidence that relates to that. And if the background document doesn't handle something properly or is insignificant, then we can generally deal with that.

I'd like to come back to one thing. Susan Nathanson and William Kennedy brought up some points with regard to pharmaceutical agents that particularly focused on Tamoxifen. What I'd like to say, and is this is something that was discussed by the board at the time we discussed Tamoxifen, is it's clearly a problematic area. It was discussed as a problematic area.

There are a variety of pharmaceutical agents, immunosuppressive agents, that sort of thing, that are very important, very useful. Some of these can induce secondary cancers, and if they're placed before us, we have to respond to that issue.

I think there's a legitimate question on whether we should be evaluating those materials, and if we evaluate those materials and respond to a

scientific signal with regard to carcinogenic risk, then how that information should be communicated to the public.

And I think we all have some concerns in that particular area because this is an advisory document, and I would certainly urge Ken Olden and NTP staff, even as we did in the discussion on Tamoxifen, to try to find the way to appropriately communicate this information to the public because we want to do the right thing. It's not to just follow some written process and have some negative consequence.

I think that's -- those are all my comments.

DR. GOLDSTEIN: Okay. Thank you.

I'm going to suggest, to start with, that we focus on what Lynn has brought us into. That's sort of an underlying issue. Should the general approach be changed into more of a regulatory, if you will, approach, for want of a better term? If that were to happen, then the whole discussion that Clay just had about the background document would inevitably change. So this would be central to us of the issues.

There's a number of the people who have

presented a number of the documents which point out that the NTP listing has implications as strong to their particular products as does a regulatory agency's action. There are others who have been here who pointed out -- who, basically, strongly said that, no, this should be kept as a scientific approach by the National Toxicology Program's group of scientists and only have this relatively minimal, compared to IARC or EPA, review of the Board of Scientific Counselors. So that seems to be a generic issue. Anybody want to comment on that, speak to that?

Sara, please give us your name.

MS. SCHOTLAND: Sara Schotland. I am Counsel to CMA's Ethylene Oxide Industry Council. I do want to respond to Dr. Goldman's points.

Let's not set up a false dichotomy between process and science. Process need not be the enemy of science. On the contrary: Good process leads to good science.

If, referring to something that Clay Frederick alluded to earlier, the decision is made to take mechanistic data into account in considering whether to upgrade or downgrade a chemical, there

may be a question as to whether (inaudible) market data justifies upgrade or whether it doesn't. It may be questionable to the extent to which human genetic studies versus animals genetic studies are relevant. These are scientific issues and (inaudible) should be encouraged.

Now, I understand Dr. Goldman has a concern and NTP must surely have a concern not to be dragged into the kind of lengthy process that has made it so difficult and so burdensome for EPA and OSHA to issue standard-setting rules.

Again, let's not make a false dichotomy between the current status quo of virtually no meaningful process and going into a 400-page regulatory justification needed for an OSHA standard. That's not the necessary conclusion.

EPA's SAB and EPA's (inaudible) Committee give a better opportunity for all different sectors to present their comments. They respond on numerous occasions. There's more of an iterative opportunity. They consider maybe four substances in a day rather than eighteen.

This is the kind of compromise model which would provide better process, giving greater acceptance to the decisions, and I think actually

reducing your legal burden because it would reduce the vulnerability on judicial review.

Let's not forget that, in fact, the minute NTP makes a classification decision, it has the impact of a rule because it is absolutely mandatory, mandatory on our clients to change the OSHA hazard communication and to change EPA community right-to-know.

This isn't some voluntary little thing that we do because we think it may or may not be appropriate. We are required. It has a regulatory impact, and if you click on the NTP website, NTP is proud of the use to which its classifications of carcinogens are put and recognized. So it's used for OSHA and community right-to-know purposes.

I want to also make a comment, again, on SAB. It provides an instructive model about the role of industry science. I cannot emphasize enough how inappropriate I find disparaging attacks on industry science. It is just as inappropriate as it would be to disparage the contribution of the scientists from the environmental movement or to denigrate the government scientists, any one of whom can have problems with their credibility, can appear to have

their own axe to grind, but that applies to lawyers, scientist, doctors from all different sectors.

The EPA Science Advisory Board invites the participation of qualified scientists. The scientists it's been my privilege to be associated with in industry, when they serve on these kinds of panels and present to these kinds of panels are terribly important to -- terribly conscious of the need to be credible. In many instances, they are the authors of peer-reviewed published literature. I know with ethylene oxide, the scientists my client presented were leaders in the field on that subject, including one who's now at EPA.

So I absolutely reject disparagement of the contribution of industry scientists, and I really think that we have to move beyond the black hat/white hat and say that there ought to be, instead, a balanced sector representation both on the Board of Scientific Counselors and that we should welcome stakeholder efforts to improve the process and stakeholder involvements to provide comments, as the OMAN (phonetic) Commission on Risk Assessment has recommended.

Thank you.

DR. GOLDSTEIN: Are there other

comments on the subject of the extent of stakeholder involvement and the process?

MR. AUERBACH: My name is Martin Auerbach (phonetic). I represent the makers of Sweet-N-Low from time to time, but I'm also a father. I'm also a consumer, and I live in America.

And, first, I'd like to thank all of the people from NTP for taking the time to have this kind of forum, and I know that this forum was expanded from its original one day to two days, and I think that's reflective of what I think the best of all the comments I've heard here today were about.

I think there's actually a surprisingly large degree of common ground between industry and between those who appropriately believe that they are representing the public of America, and that is how the process of analysis and review becomes an open and fully credible process so that the very significant impacts that a listing or delisting decision by the NTP has, whether they are technical or simply practical or fully the result of a balanced process.

And, you know, for us as an industry member, we were quite pleased that RD1 and RD2

and the Executive Committee all voted in favor of delisting, and we were dismayed that the BSC process seemed to be a rushed process. It seemed to be a process in which although we had made a submission a year in advance, most of the people who were called upon to deliberate were only given the briefest period of time to review the material, and the actual discussion session was so compressed and so abbreviated that the kind of dialogue that has existed here today on the process didn't exist on complicated scientific issues that go on and have gone on for over a century.

Now, we take great comfort in the fact that there is a final review process and that all of the other input within the organization will be ultimately reviewed by variable scientists, but I do think that everybody benefits from having a process that everybody can unequivocally acknowledge is one that takes a due amount of time -- and here it's two days instead of one day to hear the comments.

If we're talking about two weeks or a month before a BSC hearing or meeting takes place so that people really have an opportunity to reflect so that we never hear, as we've heard today, that

on some issues, members of the panel were ultimately called upon to vote and do vote say that they haven't really had time to review and understand the issues.

So I think there's actually a lot more common ground here than would ordinarily is perceived by the people who come from either the environmental side or come from the industry side. We are actually all living, breathing human beings in this society, and we really do have a lot of common ground, and I welcome this opportunity to share that thought.

DR. MIRER: Frank Mirer again. Just a couple of points brought up by the discussion on the process issues.

First, Mr. Coogan and I had a long discussion of a misquote from the IARC document on silica, and the fact is that when we review these things, we have the IARC document in front of us, and I reviewed the IARC document on silica, which has been an interest of mine since '75, when I first walked through a (inaudible) representative boundary. And I think we're hearing exactly what the problem is with excessive concern for the process, like a little quote being used to try and

discredit the effort of the whole review committee.

I don't think anybody on the committee who does these reviews would object to getting the review material earlier, having more time to work on it, but there has to be -- I think there's a rhythm on which these things work.

And the fact is, again, the background document is a layering on top -- usually, on top of IARC, which is a pretty complete review, which has been available to people for quite a long time before.

With regard to the saccharin issue, which was just raised and we shouldn't be talking about, let's talk about the impact of the process. I was prepared to vote for the listing of saccharin until I read the review materials and saw that the picture of the epidemiologists was substantially different than you think it is when you haven't read the individual papers and had the analysis done in the committee.

And those of us who recall that, there was an extensive -- I think we're not talking about a five-minute presentation by Dr. Cohen. He went on for quite a long time presenting his life's work – or not his life's work but a major piece of work as a

major advocate of saccharin not posing a risk to people.

So I think that what we're getting here is a very consistent negative, incorrect picture of the degree to which the Advisory Group gets the information, works on the information. And the fact is, remember, we are, like, the third step in a six-step process. We are advisory to NTP. We give what I view as peer-review comments on the background document, peer-review comments on the level of evidence, and we do, in writing, justify our positive -- certainly, if it's a negative vote, we are required to submit that in writing, and there's a record of it.

So there's plenty there for anybody to review who wants to review it, and there is a transcript because I see myself quoted in some of the comments that are here. So there is a transcript of it. It's a very well-documented process.

DR. GOLDSTEIN: Other comments?

MR. FINKEL: Adam Finkel from OSHA and OSHA's rep on the Executive Committee. There hasn't been much talk about that group's role towards the end of the process, and I just -- and I

apologize for having to leave almost as soon as I finish this little minute or so to catch a plane, but there are times when I have felt hurried as a rep on the Executive Committee, but I think hurried has to be thought of in a context that, you know, there are times when I would like, as an academic with academic aspirations, to understand more about an issue, but as Clay said there, very often times issues come before us where we know enough to know that -- for the purposes of the classification decision, that there are already enough unanswered questions raised by the provocative information that further discussion of how interesting it would be to know more than we know would be helpful but not germane to making the decision.

So I think, you know, to say just how many days did somebody get to read some piece of material wasn't enough given the thickness of the document is not really the question. You know, the question is: Is there an issue that is really dispositive to decisions that are being made?

At OSHA, when we did one of our rules a couple of years ago, we spent almost a year on a set of scientific papers because we had to make a quantitative determination about adjusting potency

estimates based on the possibility of the inner-species differences.

If I had gotten those same papers to make a determination on the Executive Committee, it would not have taken a half hour to begin to ask myself enough questions about holes in the argument to know that it was not going to be, in my view, enough to change a classification.

And I just wanted to pick up on something Bill Kelly said earlier in the day, which I think has been a subtheme running through the whole day so far about the appropriate scope of the BRC. And, certainly, I agree that there are other ways to present information to make it more consumer-friendly, if that was, in fact, part of the original Congressional intent, but, again, from a personal perspective, I always have to put aside my intense interest in potency in special circumstances of signals of carcinogenicity being not universally applicable, the issue, as Clay pointed out, of ancillary benefits of pharmaceuticals, a very important issue that I think NTP ought to talk about real seriously before new categories are carved out because of the slippery-slope aspect of this.

There are ancillary benefits to all kinds of

other categories of agents, but, really, ultimately, a consumer-friendly document would have a lot more information about substitutes, about industrial processes, about costs of control, about the profitability of the firms making the substance, things which consumers might have a lot of intense interest in but would clearly not be the province of NTP. There's a role for a document that talks about qualitative signals of carcinogenicity, and there are roles for other kinds of documents that other agencies or federal bodies or public private bodies could engage in.

DR. GOLDSTEIN: Don't go yet. I, basically, think you've answered this question. This is some of the -- these are some of the issues that I, again, thought I heard, and one is the issue of hazard versus risk, risk being, obviously, exposure plus hazard, and to specify the circumstances is, really, a subset of that. And, of course, the issue of exposure criteria, is it just simply for inclusion in the NTP selection process or, again, is it part of the process, part of the dose?

What I think I heard you say, Adam, is that from the point of a regulator at an agency which is part of the group that takes the information from

NTP and guides NTP in its lecturing process -- did I hear right, you saying that to specify the circumstances and inclusion of exposure is really your job, not their job?

MR. FINKEL: Well, I don't want to be dogmatic about it. Certainly, if there is information that a particular agent exists in a bunch of forms and that there's affirmative information that one or more of those forms is qualitatively different from the main form, then that becomes a qualitative, very key ingredient in the classification.

But, you know, part of my remarks about being hurried versus having enough time related to that. If I have enough time to realize that people are calling into question that there are multiple forms, but there's no affirmative information to suggest, you know, compelling evidence of noncarcinogenicity for those forms, then I think that that would be deferred to the regulatory agency that would have to be making decisions about whether all those forms would, in fact, be subject to controls. Same goes, I think, with high dose/low dose issues.

I'm somewhat persuaded by the discussion on beverage alcohol. I gather that that was made

part of the record, that there may be a qualitative difference caused by some biological phenomenon that can be distinguished at high or low doses, but when you get into, again, as Clay said earlier, these issues about: Is it several hundred or several thousand people being exposed? Is it parts per million or thousand or hundred? where there may be non-linearies, I think all of that is the province of the regulatory agencies and not this particular exercise in classification.

DR. GOLDSTEIN: Okay. Comments on this issue of exposure or the extent to which specific circumstances might be cited?

DR. OLLER: I guess as a member of the (inaudible), I think I am very interested in finding out what compounds -- what substances around me are carcinogenic and try to avoid them. And if the NTP document and listing is going to be used for the public to make those kind of decisions, I think it is important to consider that we do need to put more information into that document, and I would just illustrate for the case of nickel.

I looked into the 9th Report, and I see nickel and nickel compounds are (inaudible) known carcinogens, and I may ask them, "Well, what

should I do about my stainless steel sink in my kitchen? Should I get rid of it? What about the pitcher where I keep my water? Should I get a filter so that if there is any nickel in the water, I can decrease it? What about the multivitamins I'm giving to my child that have nickel in them? Should I worry about all of those things?" And perhaps we do need to consider that the route of exposure and the circumstances should be part of the narrative on that document.

MR. KENNEDY: Bill Kennedy, AstraZeneca. I'd like to respond to the comment made about let's be careful about going down a slippery-slope on pharmaceuticals.

I think with NTP having in their mandate information on risk management and public health, you have to take into consideration the information in the public health aspects of it and the risk that is generating a lot of fear in the minds of people who are currently taking medications.

And I can only share with you an experience that we had when the IARC information -- IARC classification was being used to push Proposition 65 in California. After it was all over, we saw a decrease in the use of Tamoxifen on a

nationwide basis. It coincided with the discussion that was going on on Proposition 65.

We checked further and found out there was an inordinate decrease in the western states. It calculated out to be a reduction of 30,000 women had stopped taking Nolvadex, and it coincided with Proposition 65 discussion. If you consider Nolvadex having a 35 to 50 percent positive response in treating breast cancer, we're putting 10- to 15,000 women at risk of not having appropriate therapy.

We took this one step further and followed up with physicians who were treating breast cancer patients in California, and they did confirm that at the time of the Proposition 65 discussion, there were women who stopped taking their Nolvadex without discussing it with their physician.

So we do think that there is an appropriate use of a pharmaceutical category. We shared this information, just for information, with the FDA about 18 months ago, and they have used it in a document that the Deputy Commissioner exchanged with the State Department in supporting a pharmaceutical category on a worldwide basis, not just in the NTP classification.

DR. GOLDSTEIN: Thank you.

We've got about four or five minutes. Anyone --

MS. WIND: Marilyn Wind from the Consumer Product Safety Commission.

I have to agree with Adam Finkel that it is within the realm of the regulatory agencies to deal with risk analysis, and I think that it would be a huge mistake to extend what the Report on Carcinogens does beyond hazard assessment.

For any given chemical, there may be three or four of the regulatory agencies that deal with various aspects of that chemical use, and each one of us has a different act under which we regulate, and there are different criteria that we need to fulfill. And, believe me, the NTP does not want to get involved in this.

DR. GOLDMAN: Yes. Just a point of information. We're sitting here chatting, but on the nickel issue -- I thought it was interesting that you put your five cents in on it -- that, actually in that listing, that the alloys -- the metal forms are not included.

DR. FREDERICK: That's right.

DR. GOLDMAN: That's my understanding. So there is already some

consideration of exposure and that forms where – like nickel alloys, nickel metal, it's supposed to be clear, at least, in a listing that that's not where the cancer assessment was, and I would assume that's because of the lack of exposure.

So I'm not sure that the question is really whether there should be any consideration at all because I think from that it's obvious there is already some consideration, but whether that's going far enough or, you know, there needs to be more information than that --

MS. NUNLEY: Carolyn Nunley from Consumers Union.

This question about exposure, I just want to remind everybody that chemicals are not limited in how they're used. Just because a chemical is used for a pharmaceutical product today doesn't mean it's not going to be used for something else tomorrow. We don't approve chemicals solely by their use or limit their use once they're on the market.

So, you know, my concern, I guess, with taking an exposure-based approach to this listing is that, you know, what's going to happen tomorrow when somebody decides to use Chemical A that was

delisted because it's only used in these uses that don't cause a lot of exposure today, you know, down the road tomorrow when somebody puts it in something else that is much more exposure-intensive?

DR. GOLDMAN: That's actually right. There are some pesticides that -- fungicides that are also anti-fungals as pharmaceuticals. So it's not clear-cut. It's not absolutely simple, but if people are aware of that, it might be a way of dealing with it, too.

DR. GOLDSTEIN: Let me ask if there's any further comments.

(No response.)

Good. Why don't we go into our next group of presentations. Joseph Shapiro, I'm told, is here from the Unimin Corporation and Crystalline Silica Panel.

MR. SHAPIRO: My name is Joe Shapiro, and I'm here to talk about the NTP process concerning crystalline silica. Crystalline silica, in its most common form, is quartz. It's the second most abundant substance on the landmass of the earth, and I brought a sample with me.

This is sand like you find on a beach or in

a sandbox. I brought it in a little sandbox toy cup, and I guess I'll give it to the Chairman, Dr. Goldstein. I was on the beach in New Jersey just last month, and I missed my opportunity to retain a sample of the sand. That actually is from Minnesota, I must say.

Now, the sand, of course, is predominantly crystalline silica, and, of course, it includes in it some respirable crystalline silica. And lest anyone have any fears about it, this is the same stuff that hundreds of millions of Americans are exposed to every day because it's in the air we breathe, and it's those Americans who will be asking about your decision-making process: How did you decide that crystalline silica ought to be classified as a known human carcinogen?

I'm here to talk about silica, or sand, because of the 9th Report on Carcinogens because NTP is on the verge of classifying silica as known to cause human cancer without having meaningfully looked at the data.

Our government's pronouncements about the carcinogenicity of the second most abundant substance on the crust of our planet deserves to be based on a process which looks closely at the

available information and at public input.

At my company, we try to keep our employees up to date on the science and on the government's pronouncements and on the health issues concerning silica. The U.S. Department of Labor chose my company's CEO to make the industry plenary session presentation at the government's conference two years ago on how to eliminate silicosis. That's a disease well known to be caused by silica.

With regard to cancer, what can we tell our employees and the people who live near our plants about how NTP reached its conclusion in the 9th Report on Carcinogens? What can we tell the millions upon millions of people who breathe sand dust in the air every day in the natural environment?

Do we tell them that the U.S. government agency charged with evaluating published studies didn't think the second most abundant substance on the landmass of the earth was important enough to read about before making a decision or that their health wasn't important enough to merit a serious look at the health science or that their health was not important enough to allow meaningful public

input?

I came here today to talk about the NTP process and silica not just as an executive of Unimin Corporation. I'm also the Chairman of the Crystalline Silica Panel housed at the Chemical Manufacturers Association, the CMA.

Now, let me turn to some recent history. Silica was nominated for the recent NTP process because of IARC. At IARC, a Working Group meeting in late 1996 issued a -- the issue was very hotly debated at that meeting. There was a sharply divided vote of the committee experts. Of the 19 experts in the IARC Working Group, 10 supported the reclassification of crystalline silica; seven noted against; one abstained; one was not present.

Silica's reclassification, though, was carefully circumscribed, an issue that I think has been raised, and that's quite unusual for IARC. The reclassification was based on an evaluation that found, quote, "sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the forms of quartz or cristobalite from occupational sources," closed quote. Whether non-occupational exposures may present a comparable risk was not addressed. The Working Group further limited its

conclusion by noting, quote:

"In making the overall evaluation, the Working group Noted that carcinogenicity was not detected in all industrial circumstances studied," closed quote.

Now, despite the obvious need, as shown by the IARC deliberations, for NTP to conduct its own careful assessment of this difficult-to-interpret evidence, we have seen no indication that such a review ever occurred at NTP.

Now, it has long been clear that respiration of excessive silica dust can cause this form of pneumoconiosis called silicosis. However, assessing whether crystalline silica should be determined to be a known human carcinogen is a complex scientific issue.

Numerous epidemiology studies have been connected in different occupational settings, and they focus on two different questions. One is whether silica exposure increases the risk of lung cancer and whether silicosis, the disease, increases the risk of lung cancer. Each of these studies has to be carefully examined.

Accordingly, following the IARC meeting, the CMA Crystalline Silica Panel asked a

distinguished epidemiologist who attended the IARC Working Group meeting, Dr. John Gamble of Exxon Biomedical Sciences, to review the silica epidemiological studies and prepare a report to assist NTP in determining whether silica should be classified as known to cause human cancer. We submitted his lengthy, well-documented, and carefully considered report to NTP in November of last year.

The record in this matter, though, contains no indication that NTP ever wrestled with the principal scientific issues concerning silica, the issues on which Dr. Gamble focused in his report. As far as we can tell, NTP participants may have never read, let alone assessed, the Dr. Gamble report.

We obviously do not know what occurred in the RG1 and RG2 meetings since they were closed to the public, but we have seen the background document that forms the basis of the RG1 and RG2 recommendations. And as you know, we are told that the background document presents the scientific information and arguments upon which the opinion of the BSC Subcommittee is based.

Well, the background document on silica

does not discuss in any detail all the available studies; nor does it assess which of those studies provide the most relevant data for assessing a potential causal relationship between silica exposure and human carcinogenicity.

Nowhere in the background document is there a careful review of potential biases in the various studies, most significantly whether confounding exposures, most importantly, cigarette smoking, a powerful known carcinogen, precludes reaching a valid conclusion regarding the potential carcinogenicity of silica. Nor does the background document provide a careful assessment of whether the studies demonstrate a dose-response relationship, although that's the central criterion for assessing human cancer causation.

In his report, the Dr. Gamble report submitted to the NTP, Dr. Gamble meticulously looked at all these issues. We don't know why RG1 and RG2 rejected this.

We do know what happened at the NTP Board of Scientific Counselors Subcommittee meeting. In his five-minute presentation -- he had only five minutes available to him -- Bob Glenn attempted to summarize Dr. Gamble's 72-page

report, an impossible task. He did point out that in the studies of silicotics, there was no consistent increase in lung cancer risk found when risks are evaluated by comparing silicotics with nonsilicotics, persons with high severity of silicosis with those with low severity of silicosis, silicotics with high silica exposure versus those with relatively low silica exposure.

And he did observe that classifying an agent as a human carcinogen in the absence of an increasing risk by gradient of exposure or disease severity is counter to long-standing scientific criteria, yet there was virtually no discussion of these points following Mr. Glenn's presentation. We don't find any discussion in the record that we see.

Now, if the NTP Report on Carcinogens is meant to be only a rubber stamp of IARC, which, in fact, it wasn't because it didn't even have IARC's limitations, even an IARC decision with a closely divided vote, as happened in this case, then the report doesn't serve a useful purpose to the American people. On the other hand, if the Report on Carcinogens should be meaningful, then a much more complete, independent assessment of the data must occur than has occurred with respect to

crystalline silica.

The decision now facing NTP and DHHS is this: The arm of the U.S. government charged with advising the American public on the carcinogenicity of substances is making a decision about the cancer-causing effects of the second most abundant substance on the landmass of this planet.

There is crystalline silica dust, sand dust, in all the outdoor air we breathe, presumably in the indoor air as well, but according to a 1996 EPA report, about 95 percent of the respirable crystalline silica that Americans find in their ordinary outdoor air does not come from manufacturing or mining. We are talking about exposure to sand dust that neither the government nor private industry can control.

We must remember that when we are talking about crystalline silica, it's a major component of our farm soils, of the surface of paved roads and unpaved roads. It's used in all construction projects. It's the major component, of course, of beach sand and play sand, yet when the American people ask NTP why they classify this pervasive substance as a known carcinogen, all NTP will honestly be able to reply is, We basically

rubber-stamped an IARC decision made in (inaudible) 1996.

DR. GOLDSTEIN: Mr. Shapiro, you have one minute.

MR. SHAPIRO: Thank you.

Now, I firmly believe that before NTP and DHHS advise the American people that respirable crystalline silica, the most commonly found form of sand dust, is a known human carcinogen, the agency owes it to the American people to study the issue seriously. Accordingly, we request that no report on crystalline silica should be published in the 9th Report on carcinogens. NTP should implement a new, improved process and then give the science concerning this ubiquitous substance the attention it deserves.

Thank you very much.

DR. FREDERICK: Clarification point, Bernie.

You said there's a 72-page paper report. I don't remember exactly what all the documentation package was we had on the table for silica. We were working with a ton of stuff there. Was that paper submitted well ahead of time before the meeting?

MR. SHAPIRO: It was.

DR. FREDERICK: Okay. Then it was reviewed. The five-minute summary was a recapitulation of material that was already submitted and should not be considered to be the whole --

MR. SHAPIRO: My comment was we saw no evidence that any of the studies --

DR. GOLDSTEIN: Basically, let's get to the process issues.

The next speaker is Ralph Gingell from the Shell Chemical Company representing the Ethylene Oxide Industry.

DR. GINGELL: Good afternoon. I'm Ralph Gingell, and I'm speaking as Chairman of the Ethylene Oxide Industry Council's Toxicology Group, otherwise known as the EOIC. The EOIC is a trade group of ethylene oxide manufacturers operating within the Chemical Manufacturers Association.

I want you to rest assured, Mr. Chairman, I haven't brought any free samples of ethylene oxide with me today.

The Ethylene Oxide Industry Council understands that EO, ethylene oxide, is being

proposed to be upgraded from the reasonably anticipated to the known to be a human carcinogen classification in the 9th NTP Report on Carcinogens.

I want to address one specific procedural problem that was experienced at the Board of Scientific Counselors public hearing on ethylene oxide in October of last year, which led to, I believe, the erroneous recommendation for upgrading to known human carcinogen.

The EOIC does not argue with the current classification of reasonably anticipated to be a human carcinogen. However, there is a distinction between reasonably anticipated and known human carcinogen which can have significant regulatory and legal repercussions for which I believe conveys very little to the general public.

The criterion for known human carcinogen simply states, and I quote: There is sufficient evidence from carcinogenicity studies in humans which indicate a causal relationship between exposure to the agent, substance, or mixture and human cancer.

If (inaudible) epidemiological cancer data was the sole information considered, then ethylene oxide, I believe, would not be upgraded to known

human carcinogen. There's a rich database which includes 12 independent studies, over 33,000 workers, and the conclusions are that there was no increase in cancer overall or in muscle or organ sites of interest and only weak or inconclusive evidence of data for leukemia and lymphomas.

And, overall, there is limited evidence of human carcinogenicity which does not support upgrade to the known category, and all this data has been recently submitted and accepted for publication in the journal, as noted at the bottom here.

However, recent clarification by the NTP of the criteria for the known human carcinogen includes, and you can see the direct quote here: Data derived from the studies of tissues from humans exposed to the substance in question and useful for evaluating whether a relevant cancer mechanism is operating in people.

For ethylene oxide, this relevant data was cytogenetic changes in the peripheral lymphocytes of workers, manufacturing workers predominantly, exposed to high levels of ethylene oxide.

I won't try to recapitulate here all of the discussion at the public hearing, but there was

considerable disagreement among the members of the Board of Scientific Counselors on whether these effects did, in fact, indicate a relevant mechanism for human cancer.

At this board meeting, Dr. Julian Preston, who was (inaudible) EPA, stated that these human cytogenetic studies were small, subject to confounding, and of questionable validity for various technical reasons. He also went on to state, and I quote from his journal article which has been published, at the bottom: Chromosomal changes in peripheral lymphocytes are markers only of recent ethylene oxide exposure, not predictors of carcinogenicity. These assays are typically conducted and not appropriate for chronic exposures because they assess nontransmittable alterations.

As I mentioned earlier, and as the transcript of that October meeting shows, the NTP reviewers differed in their recommendations. The primary reviewer, Dr. Balinski (phonetic), (inaudible) reasonably anticipated classification for ethylene oxide. The second reviewer, Dr. Yamasaki (phonetic), proposed upgrading to known based on these questionable cytogenetic monitoring studies.

After much discussion, and it was a protracted discussion, the board was still divided, and several members had difficulty forming an opinion on this complex issue in the time available. The disagreement is exemplified by the split vote of the board, six votes for to five against to recommend upgrading to the known human carcinogen category.

In summary, the EOIC have a few recommendations, and we believe that when a consensus of the board or at least no convincing majority can be obtained, then no classification should be made. Especially for the known classification, the chemical should be deferred for further consideration in a future report, emphasizing those issues on which agreement could not be reached or at least a consensus or a majority decision could not be reached.

As this pertains specifically to ethylene oxide, we believe that because of the split vote, EO should not be upgraded to the known human carcinogen at this time, and we believe continued classification as reasonably anticipated adequately protects the public.

I think you've heard lots of issues raised

here, that the NTP process certainly could be improved, and we would recommend that the 9th Report not be published at this time until many of the issues raised here could be addressed and corrected.

I understand you have a Congressional mandate to put out a report, so if you feel that the 9th Report must be issued at this time, I suggest that it go forward at least excluding those chemicals for which we're showing a contention here today, one of which is ethylene oxide.

Thank you.

DR. GOLDSTEIN: Thank you, Dr. Gingell.

Our next speaker is Sara Schotland of Cleary, Gottlieb, Steen and Hamilton and the Ethylene Oxide Industry Council.

MS. SCHOTLAND: Good afternoon. NTP, thank you, thank you for holding this hearing. This particular day and tomorrow are an example of good process.

Skip to the second slide. That's of no interest to anyone but my mother.

You have sought comments on the criteria for listing as well as on review procedures, so I'd

like to focus in on three different issues, that known criteria should be reserved for chemicals – the known category should be reserved for chemicals where there is direct evidence of carcinogenicity. I'd like to address, as Counsel, the point that the criteria constituted agency rule, and then talk a little bit more about the process issues.

EO is illustrative of a chemical which could not possibly be upgraded to known carcinogen on the basis of the epidemiologic data. Everybody agrees that it's limited. The question is whether cytogenetic studies provide data indicative of carcinogenic risk. As Dr. Gingell mentioned, the two NTP reviewers and the BSC were directly split on this question down the middle.

We think that the cytogenetic data is terribly problematic, small-scale population monitoring data on one hand or SCE bio market (phonetic) data on the other. We think that under these circumstances there is a criteria problem. We are not adequately communicating to the public that a chemical is a known carcinogen if we're using such data to make that determination when there is a rich epidemiologic database with one follow-up, exceptionally long follow-up and exceptionally large

size, that does not indicate that ethylene oxide presents human cancer risk.

Being a known carcinogen is serious business. There's a branding of the chemical. Workers are unduly alarmed. Most seriously, the point that was raised earlier about nickel, possible misleading of the public. And there should be no doubt but that there is a mandatory regulatory impact in terms of OSHA has a communication and EPA right-to-know.

I don't want to reiterate or belabor the deficiencies in the peer-review process that we saw with respect to EO. I do want to mention the first point. We felt that the first pages of the process, because they were internal to NTP, did not really provide for an independent peer review.

When there was a peer review, it was before the BSC, and although we appreciate that the time was a little extended on EO, we really did have a situation there, as the transcript will reflect, where there were comments from the members of the Board of Scientific Counselors asking Dr. Lucier for clarification on the criteria, where people wanted to ask more questions, Chairman Brown gaveling them down. It was a circus. It was not

adequate opportunity to present scientific information.

I emphasize we had people like Jane Peda (phonetic) and Julian Preston, the leaders in the field on epidemiology and genetic toxicology, that there was informed debate. Members of the BSC included some very distinguished people, including some here today. There were questions asked. There wasn't enough time.

And we are concerned that NTP has not indicated whether it has responded to our comments, appreciated our comments. Again, I would focus on the most significant comment. Nobody is suggesting NTP needs to respond to every little nit.

As a lawyer, it is my opinion that the NTP decisions constitute agency rules. They are statements of general applicability. The annual report indicates the secretary's judgment as to carcinogenicity. It is used by a broad range of regulatory agencies. In particular, it is automatically used in OSHA hazard communication, and it is automatically used in EPA community right-to-know.

Yes, there's a case which said: We agree,

in the particular instance, that NTP was right in the way it treated mechanistic data in the chemical listing decision under challenge, but the decision is very clear that what NTP is doing is agency action by rule.

I don't really think that there's reasonable level doubt about it, and as I indicated earlier, the fact that the agency is engaged in a rule-making-type activity, putting out a classification criteria as a rule, does not mean that it needs to go through the same extended process that is used by EPA in a TSCA rule or used by EPA in some other decision or by OSHA (inaudible), but it's got to get more process than it is now.

And this is not just a matter of a legal defense. I think the OMAN Commission was a wonderful report. Dr. Goldstein, I don't recall. Were you part of that commission?

DR. GOLDSTEIN: Yes, I was.

MS. SCHOTLAND: Indeed. And I think David Rall was part of that report, too, and I congratulate the people who were part of that report.

Let me just read that quote, and I -- the word risk management is used in a quote. If

anyone has any doubt when you read the report, it includes risk assessment in its context: Experience increasingly shows that risk management decisions that are made in collaboration with stakeholders are more effective and more durable. Stakeholders bring to the table important information, knowledge, expertise, and insights for crafting workable solutions. Stakeholders are more likely to accept and implement a risk management decision they have participated in shaping.

Of course, of course.

The Commission acknowledges concerns, costs, and additional time needed to involve stakeholders can be considerable. However, risk management by government agencies has been costly anyway, and investment in stakeholder involvement can bring long-term savings and reduce litigation.

Again, we have successful models, and I ask NTP to consider in the form of EPA-SAB, EPA Eagle (phonetic), IARC, with respect to a more reasonable process.

Dr. Olden, I would volunteer to work with you and your staff regardless of the decision made on ethylene oxide, regardless of whether I have a

client, to donate my time to the process on this matter. I think it's so important, and I think it is possible to find a process that is a compromise between giving people of all sectors a fair shake and avoiding an excessive burden to NTP is critical.

Is that it? Well, then I'll sit down. Thank you very much.

DR. GOLDSTEIN: Thank you.

In the interest of fair disclosure, the author of that is probably sitting in the room here, Gail Charnley, who is the Executive Director of the Risk Assessment Management Commission.

I'm not sure -- is George Alexeeff here? He came in from California for the last one?

DR. GOLDMAN: He may be here tomorrow.

DR. GOLDSTEIN: He may be here tomorrow. Okay.

Our next speaker, then, is Rudolph Valentine of DuPont Dow Elastomers.

MR. VALENTINE: Thank you, Mr. Chairman, ladies and gentlemen. My name is Rudy Valentine. I'm an employee of the DuPont Company. However, I'm here at the request of Mr. Michael Lynch of DuPont Dow Elastomers to

express our learning, specifically, with regard to the RoC process (inaudible).

I've heard a lot of discussion today, and I must say that our interest in this material was tweaked roughly three years ago when the draft report on chloroprene was issued. It was a contentious issue for us from the standpoint that it had contradicted a number of toxicology studies that had been done, and our subsequent involvement with the NTP was geared to understand the science behind the decision.

What I'd like to do, based on those learnings, is suggest some things that the NTP may wish to consider, some improvements that may be indicated in the pre-study planning phases, including compound nomination and selection, during the course of the actual animal testing for study conduct and results communication, and, finally, after the data is all collected and it's time to look at it and interpret what it means, review of that data, and, finally, the RoC classification itself.

In terms of compound nomination and selection, it may be presumptive on our part, but we think the objective of the NTP ought to obtain the best available information that justifies testing

on a particular material. We're aware that the NTP has certain exposure criteria, including poundage as well as a number of people potentially exposed.

And what we encountered in our review of the information was that the NTP categorization of worker exposure was grossly exaggerated based on the quality of the National Occupational Exposure Survey. We didn't fully understand the impact of the NOES survey until we began to ask questions about how many people were actually exposed, and we found considerable error in there.

The same applies for air-monitoring data. Some of the air-monitoring data recorded was not exactly consistent with our own experience. We provided the NTP information regarding what our experience has been in air monitoring.

Additionally, certain constraints on other sorts of data was an issue for us. We understand the NTP prefers using only peer-reviewed data. However, as many of you will attest, there is probably a great deal of information available from various manufacturers that could impact NTP interpretation at issue. To that end, DuPont Dow Elastomers had a considerable body of information as it related to epidemiology, toxicity, and exposure

assessment information, which would have been gladly provided to you.

In terms of study conduct and results communication, again, if I may be so presumptive to suggest why we might want information, it would be to conduct studies in a manner consistent with chemical use and to communicate study findings in a timely way.

With regard to our experience, particularly with chloroprene, we think it's important that the testing group fully understand how the material is used and processed so that whatever regimen is used in the animal testing represents actual use conditions the way that people might be exposed. I may point out that many of the comments I'm making are discussed in much more detail in the written comments which have been submitted, also.

An item, again, of interest for our company was communication of the results. We understand that the studies were going for several years, particularly in the animal bioassay, and what we don't fully understand is if significant results were observed in the conduct of that study, why they weren't expressed sooner in the process rather than at the time they were.

It is well known that if industry were to generate such toxicologic information, that we are required by law, in addition to adherence to responsible care commitments, to communicate within a very rapid time frame the significance of that information, particularly if it constitutes an adverse health effect. What we don't understand is why that information wasn't communicated sooner.

Should the NTP decide that information should not be presented in a timely way, something we'd like to encourage, obviously, and points that have already been brought up numerous times before, we think there should be ample time in advance of the dissemination of that information for review by appropriate folks.

Okay. What we think an objective ought to be for data review and interpretation is to ensure that the process is open to stakeholders, the people on both sides of the fence here, that it should be equitable and that procedural checks are followed when the review is taking place.

If the data that is derived by the NTP is contentious -- and from what I've heard today, much of it is -- there should be lots of opportunities where the NTP should openly seek -- solicit

contribution in terms of what might be a responsible next step to take as well as comment upon the data that was generated.

In our case, specifically, we are very interested in understanding the mechanistic basis behind the results that were observed, and, to that extent, we are taking appropriate steps by developing additional epidemiological data as well as mechanistic studies, which we are openly sharing with NTP and EPA and anybody else who is interested in listening. Again, as it's already been described earlier, there should be ample opportunity to comment. There should be some acknowledgment of those comments.

An issue that came up last year after the RG1 and RG2 met was that certain critical pieces of information were developed in relatively rapid succession, including the data and IARC review of betachlorophren (phonetic), and we are uncertain whether this information was communicated within the Board of Scientific Counselors and if, indeed, it was considered. We are somewhat out of the loop on that, and I don't know if they were considered.

This is an item for consideration. We think that perhaps there may be some discussion

around whether the NTP could harmonize the cancer classifications with other regulatory agencies and that by not harmonizing, by not considering the other classification schemes, that perhaps we compromise our ability to fully understand the human health impact of those decisions.

I'd also like to suggest something perhaps rather heretical, based upon some earlier discussions, was that the delayed classification pending would be with supplemental information. Again, our interest is making sure that the right scientific information is there to make a coherent, cogent estimation of the hazard that a chemical may present, and if this means developing sufficient epidemiological or mechanistic data in a timely way -- and I must underscore that it must be timely -- especially if there is no indication of significant exposure to people, that that might be an item worthy of further consideration.

I suggested several things that the NTP might want to consider, but two of them hinge upon actively involving representatives from industry in the process. We believe that that participation will assist in the reform of the process by a key stakeholder.

We think that by sharing exposure toxicity information that studies can be designed better (inaudible). We can expand participation and perspectives in scientific overviews, and, most importantly, we can communicate in a timely way the hazards and risks posed by chemicals to the regulators and the public.

And lastly and most importantly, we certainly embrace the idea of developing research partnerships with the NTP to understand the hazards of these materials presented.

Thank you.

DR. GOLDSTEIN: Thank you.

Our next speaker is Michael Gipko from the J&L Specialty Steel, Incorporated. He's representing the Specialty Steel Industry of North America.

MR. GIPKO: Thank you.

I guess the first question is: Why is the stainless steel industry here? And the reason, we are a consumer of chemicals, primarily metals. And our concerns are that the NTP process has not adequately paid attention to the scientific data presented to them by one of our suppliers, which is the nickel industry and, in addition, has not adequately paid attention to the requirements of the

public because the public, as we see it, is confused what nickel data means because they don't understand what alloys mean.

With that, I will begin. My name is Mike Gipko, and on behalf of the Specialty Steel Industry of North America, I am pleased to have the opportunity to comment on the procedures used by NTP in the preparation of the Report on Carcinogens.

SSINA is a national trade association comprised of 15 producers of specialty steels and products which account for over 90 percent of the specialty steel manufactured in the United States, including stainless and other alloy steels that contain nickel and chromium, substances that recently have been the subject of NTP's attention.

The Specialty Steel Industry globally consumes 90 percent of the ferrochromium and 65 percent of the nickel produced annually worldwide. And if you look at the alloy industry, the stainless and alloy industry combined consumes about 80 some -- 84, I think, percent of the nickel production globally.

Stainless steel itself is 100 percent recyclable. 85 percent of the raw materials used

by the stainless steel industry are recyclable, making the stainless steel industry one of the largest recyclers in the world.

SSINA, which is one organization, has been concerned with the listing process employed by NTP, particularly with respect to the potential listing of nickel compounds currently under consideration. The current recommendation to list nickel compounds as known human carcinogens was plagued by numerous procedural and substantive errors that raise serious questions about the reasonableness and legal and scientific adequacy of the recommendations. These concerns have already been detailed at length by other presenters and are addressed in the written comments presented by SSINA.

Instead, today I would like to touch on a particular concern of SSINA's as a user of nickel and other substances subject to NTP's review process. That is, the significant downstream regulatory and economic impacts of what we believe to be the NTP's flawed decision-making process.

NTP's decisions are very important because while the agency maintains that it is not a formal regulatory agency, in fact, NTP's decisions are the

first step in the regulatory process. For example, NTP's website catalogs some of the formal regulatory actions taken by EPA, OSHA, and the FDA on the basis of NTP classifications.

California has identified NTP as one of five authoritative bodies under Proposition 65 for identifying carcinogens. NTP's actions also influence classification decisions made by regulatory agencies and scientific bodies in Europe and other regions of the world.

Beyond federal and state regulations, identification as a carcinogen has widespread social and economic impacts. For example, carcinogen listings may spur toxic tort litigation and consumer product deselection and impact material purchasing decisions by manufacturers and other users of chemicals.

Let me say that again. Carcinogen listings may spur toxic tort litigation and consumer product deselection and impact material purchasing decisions by manufacturers and other users of these chemicals. In some cases, however, these elements, such as nickel and chromium, provide great public health benefits through the properties they bring to the products into which they are

incorporated. Substitutes for these elements either may not be as effective or may themselves present other risks to human health and the environment.

Stainless steel provides a good example of what I'm talking about. Nickel and chromium impart to stainless steel properties -- such as exceptional hardness, strength, resistance to heat, corrosion, chemicals, and abrasion -- that make it essential in a number of applications related to the protection of public health.

The medical industry is particularly reliant on stainless steel instruments, equipment, and implants for their hygienic qualities. Stainless steel is similarly essential for food preparation and chemical processing equipment and in the aerospace and defense industries, which are crucial to the U.S. economy and national defense.

In alloy forms, such as stainless steel, nickel and chromium are essentially benign, as the nickel and chromium are essentially bound within the alloy and unavailable for exposure.

Despite the benign nature of stainless steel, were nickel and chromium to be identified as carcinogens, whether in alloy form or not, the use of stainless steel could be adversely affected.

Consumers would be less likely to purchase stainless steel products, particularly with Proposition 65 and similar labels attached.

Manufacturers would be pressured to limit uses of materials containing nickel or chromium for public relations reasons and out of fear of toxic tort lawsuits. Let me say that one more time. Manufacturers would be pressured to limit uses of materials containing nickel or chromium for public relations reasons and out of fear of toxic tort lawsuits. Did you hear any safety there at all? No. No, you didn't. European stainless steel producers already are experiencing such product deselection as a result of inappropriate, non-scientifically-based regulatory treatment of nickel.

In place of stainless steel, substitutes would be utilized that are not likely to be as efficient and combine all the characteristics of stainless steel, such as corrosion resistance, strength, health protectiveness, and environmental friendliness. Product quality would suffer, but even more importantly, these substances are likely to generate their own risks to the public.

This could happen in many ways. One example would be if a substitute is less corrosion

resistant than stainless steel, then it could expose the public to health risks resulting from less hygienic conditions. Likewise, an increased risk of physical injury could result from the use of less strong substitutes for those that corrode more easily and compromise product integrity.

In addition, who is to say that substitutes would not be inherently more risky than stainless steel due to their chemical makeup? While nickel and chromium alloys are essentially risk-free, this may not be the case with substitutes containing other substances.

NTP's listing decisions have especially significant downstream impacts due to the agency's historic refusal to recognize inherent toxicological differences among various metal species, including those of nickel and chromium. As a result, NTP promotes an inaccurate notion that all compounds of a metal may be linked to cancer in humans, resulting in the serious economic and public relations problems I just discussed.

Recently, SSINA has been encouraged by NTP's decision after publication of the 8th Report to list only hexavalent chromium compounds rather than all chromium compounds and the similar recent

decision to consider nickel compounds separately from nickel metal and nickel alloys.

While a step in the right direction, SSINA remains concerned by NTP's failure to list specific metal compounds as they do for individual organic compounds. SSINA would be very happy to discuss this issue further with NTP.

In conclusion, SSINA understands that it is not the province of a strictly scientific body to consider policy issues, but by acting as part of the regulatory process, NTP should be wary of the impacts of its listing decisions, including those on downstream users and on consumers of the substances NTP addresses, such as the specialty steel industry.

Because of these impacts, NTP has a legal duty to ensure that its decisions are based on sound science and the product of reasoned decision making before stigmatizing a substance as a carcinogen. NTP should address technical issues such as speciation, and NTP should address property changes associated with alloys.

Thank you again for the opportunity to speak, and my organization would be happy to work with NTP in the future to address these issues more

thoroughly. Thank you.

DR. GOLDSTEIN: Thank you, Mr. Gipko.

Our next speaker and, actually, our last speaker today, because I understand Sylvia Kieding is not here, will be Gail Charnley of Health Risk Strategies, here representing the Chlorine Chemistry Council.

MS. CHARNLEY: Last and possibly least, I am Gail Charnley. I am President of the International Society for Risk Analysis, and I have private practice involving environmental (inaudible) policy matters. I am speaking today on behalf of the Chlorine Chemistry Council, but my views, as always, are my own.

I would like to start by thanking Dr. Olden and NTP staff, the Executive Committee, and the Board of Scientific Counselors for this opportunity to express my views on the carcinogen listing process.

I know you all work hard to honor the right of the public to know what chemical exposures might cause harm. The process you have employed to do so is not perceived to be in the same spirit of right-to-know, however. There is clearly, as

we've all seen today, a perception that the process used to evaluate carcinogens is ancillary and exclusive. We've debated that point all day, and all I can really add at this point is that whether the process is open and fair or ancillary and exclusive, as long as there is such a strong perception that the latter is the case, I think that you have a problem that needs to be addressed. It is instructed to compare the carcinogen listing process and the process used by the new NTP Center for the Evaluation of Risks to Human Reproduction.

At the August 1999 meeting of the expert panel charged with evaluating the reproductive and environmental hazards of phthalates, for example. Three half-hour formal scientific presentations to the panel were made by independent groups of stakeholders of all stripes (phonetic). An additional half-hour was made available for unscheduled stakeholder comments.

Presenters were invited to remain throughout the three-day meeting to serve as scientific resources for the expert panel. And, in fact, they weren't just invited to remain. They were strongly encouraged.

By contrast, we've heard a lot today about

the perception that stakeholder input is not taken seriously by the Board of Scientific Counselors Report on Carcinogens Subcommittee, and, in fact, it is not really taken at all. As the world famous Commission on Risk Assessment and Risk Management pointed out -- by the way, Dr. Goldstein is far too modest in terms of his (inaudible). I thought the only person who called it the Oman Commission was Oman.

As the Risk Commission pointed out --

DR. GOLDMAN: It was the Oman-Goldstein Commission.

MS. CHARNLEY: -- a good risk management decision emerges from a decision-making process that elicits the views of those affected by the decision so that differing technical assessments, public values, knowledge, and perceptions are considered.

While you may argue that carcinogen listing is not the same as risk management decision-making, it does trigger risk management. The NTP carcinogen listing program should acknowledge the increasingly valuable role that stakeholders are playing in risk management efforts, as NTP did when it created the Reproductive Hazard

Evaluation Program.

The latter program is a good model for assuring that valuable scientific expertise is available to the expert panel and that panel decisions are made after a careful evaluation of all the available scientific evidence.

My recommendation, then, is that the process used by the NTP to evaluate carcinogens should be reevaluated in view of the perception that a more open process that fosters dialogue among scientists and that values and encourages diverse scientific input is needed. The NTP's own Reproductive Hazard Evaluation Program for process is a good model.

Secondly, identifying carcinogenic hazards absent the evaluations of human health risk adds little value to risk management and public health protection. The NTP Report on Carcinogens does not provide information that is useful for public communication regarding carcinogenic risks to health.

As we have discussed, the goal of the NTP carcinogen listing procedure is just that, listing. It's a hazard identification procedure. And the problem with identifying hazards absent the risk context is

that doing so is sometimes not very useful. Everything, as (inaudible) told us, is a hazard, and whether everything poses a risk, of course, is another matter.

Devoting emotional and other resources to worrying about a hazard when it is not a risk reinforces fear and misunderstanding of risks and leads to misallocation of risk management resources. As the Risk Commission once again put it in its final report, risk assessment integrates information about toxicity or intrinsic hazard and information about exposure in the specific context of a particular receptor to produce a risk characterization.

The purpose of a risk characterization is to provide qualitative and scientific information about the nature, severity, and likelihood of a particular risk in a form that is useful for risk management decision makers. If the purpose of the NTP's carcinogen listing process is not to provide information that is useful to risk management decision makers, then what is the point?

It is useful, I think, to compare the authorizing language for the NTP carcinogen listing process and NTP's announcement of the

developmental and reproductive toxicant evaluation process.

Bill Kelly did his homework much better than I did and actually went back to the actual report language, but I just looked at the legislative language.

With regard to carcinogens, as we all know, Congress requires a list of substances known or likely to be human carcinogens and information concerning the nature of such exposure and the number of persons exposed. Congress does not require information on how much exposure occurs.

Taking the proposed entry for TCDD from the 9th Report on Carcinogens as an example of NTP's interpretation of Congress's intent, we see that there are exactly two sentences devoted to exposure analysis, neither of which is particularly useful for helping to judge TCDD's potential risks.

By contrast, the Federal Register announcement of the Center for the Evaluation of Risks to Human Reproduction states clearly that the reports produced by the center, quote, will provide a timely, scientifically sound source of information to the public and the scientific communities on the reproductive risks of environmental agents.

Similarly, we can compare the preamble found in the 8th Report on Carcinogens to the charge to the expert panels convened by the Center for Evaluation of Risks to Human Reproduction. As Bill Kelly noted earlier, the preamble states the listing of a substance in the report is descriptive and qualitative in nature and represents an initial step in hazard identification, which is generally considered the first step in the analytical process known as risk assessment.

It is necessary to conduct a risk assessment in order to estimate the potential for any substance to harm human health. The listing of a substance in the report, therefore, does not establish that any such substance presents a risk to persons in their daily lives.

By comparison, the charge of the expert panels evaluating reproductive and developmental toxicants states: Integrate information about toxicity and exposure using a weight of evidence approach. Determine how human, animal, and other data can reasonably be used to predict reproductive or developmental defects in humans under particular exposure conditions. Provide judgments that an agent presents a potential risk to human

reproduction and/or development.

What is clear from these comparisons is that we have an institutionalized risk versus hazard problem. The risk versus hazard problem probably results from the real difference between the NTP approach to carcinogens and to developmental and reproductive toxicants, which is 22 years.

Back in 1978, we didn't have a National Academy of Sciences Red Book or Science & Judgment or the Risk Commission Report. We didn't have members of Congress actively promoting the use of risk assessment. We didn't have a president who read Against the Gods - A Remarkable Story of Risk on his summer vacation.

Back in 1978, Congress's intentions were honorable, and NTP carries out those intentions as best they can, but times have changed, and there needs to be a way for the NTP program to change with them, which, of course, is why we're all here.

Congress did not prohibit NTP from including evaluations of risk in its Report on Carcinogens, and I see no reason why it cannot. Absent evaluation of risk, I believe that the Report on Carcinogens does not add as much value as it could to our efforts to manage risks and

assure public health protection.

In the case of reproductive and developmental toxicants, NTP saw an empty niche and filled it. By comparison, listing carcinogens is a potentially overworked and misplaced niche. Now, I'm not saying that NTP should venture into the regulatory realm. Regulation should be left to the regulators, but risk assessment should not be confused with regulation.

My recommendation, then, is that the NTP should broaden its mission beyond one of simply listing potential human carcinogens to one that evaluates whether public health is at risk as a result of exposure to such carcinogens.

Alternatively, NTP could consider pointing out to Congress that EPA, FDA, OSHA, ATSDR, (inaudible) IARC, and others already identify human carcinogens and evaluate human cancer risks from chemical exposures and that perhaps the public's right to know about such potential risks is being adequately served by others.

Instead, redirecting NTP resources towards strengthening its efforts to make better connections between environmental exposures and public health outcomes would make a very valuable contribution

towards improving public health.

Those are my thoughts. Thank you for listening.

DR. GOLDMAN: I have just a point of clarification. I was both a consultant on the board when it looked at the Center, and I also attended the Phthalate Panel meeting, and that effort does look at exposures in the sense of trying to understand what the relevant exposure scenarios might look like. It does not quantitate exposure. It does not do a risk assessment. It does not, for example, compute reference doses or, you know, the cancer equivalent. If it were doing cancer, it would not be doing the modeling and developing risk numbers for different scenarios.

So what she said is accurate in terms of that the panel does put the toxicity information into kind of a context in terms of possible exposure scenarios. It does not actually do a risk assessment. I don't think it would be accurate to say that.

I don't know if you want to add to that, but --

DR. LUCIER: I think that's a good depiction of it, Lynn, but the bottom line is that

the Reproductive Tox Center, which is in the process of evaluating reproductive risk of phthalates now is not doing a quantitative risk assessment. It's not deriving specific uncertainty factors. It's meant to establish the science base, however, on which a risk assessment could be made and where the scientific underpinnings for such a risk assessment have gone through a rigorous scientific peer review so their credibility would be enhanced.

MS. CHARNLEY: But does it not draw an ultimate conclusion with regard to (inaudible)?

DR. LUCIER: It's hard to say because we haven't seen the first report yet. You'll have to wait until sometime in '00, but it's our intent not to do a quantitative risk assessment to describe, certainly under some exposure circumstances, when a risk might exist, however.

DR. GOLDSTEIN: I think we can agree that it does go a little beyond where NTP currently is right now.

Let me just -- we're about 15 minutes early in terms of the discussion, which is scheduled to go to 6:00. I'll stay as long as anybody else wants, but I guess the real end of time is when our

expert transcriber will leave. I don't know that we'll need all that time, but, basically, I know I'm here and the NTP folks are here. We're completely open for discussion of any kind.

Let me again start with the NTP to ask if there's any other clarifications you want of anything that's come up during this period of time, anything you'd like to speak to. Great. And then turn it over to Lynn and to Clay in terms of any specific themes they think might be useful at this time.

DR. FREDERICK: I did want a couple of clarifying comments. Mr. Gipko, nickel metal and nickel alloys are explicitly not included in the discussion of the nickel compounds that were evaluated in the last listing, and I think it is important to emphasize that, but I think the text of the listing does do so.

Coming back, actually, to David Guston's comments with regard to industrial participation in the process and I'll say me sitting on the board, those of us who are involved in the industry do understand that there are economic ramifications of these listings.

And I would say to the extent that we understand that, we may evaluate the data more

carefully, possibly, to be sure that the decision is right than somebody who may not be as mindful of the economic consequences of the decisions. I don't necessarily put that in the category of bias. I'd say you'd put it into the category of being aware of all of the ramifications of the decision making of the process. In my experience, and I don't think there's any difference in the way the votes go because the essence is definitely the scientific evaluation, but that's what it is.

One thing -- Rudy Valentine's comments I thought were very good in the sense of offering the partnership of NTP scientists on scientific investigation relative to these listings. In my experience, NTP scientists are very open to scientific evaluations of the issues at hand, and I think that the meat of this -- can't really decide that. The meat of this is the scientific information. We can never forget that.

And if further research, additional data, on the table suggests that the wrong decision was made, for whatever reason, I think the NTP scientists have demonstrated that they would be willing to support a delisting petition if that is the appropriate thing to do based upon the appropriate

scientific body of information. And that, to me, is the right answer.

I mean, at one point in time, the appropriate -- the body of information may suggest one answer. As more data is put on the table, it may indicate that a different conclusion should be reached. And the appropriate thing is to have this process (inaudible) and provide the appropriate advice for the public. I think those are all my comments.

DR. GOLDSTEIN: Let me point out a follow-up on Clay's comments. We've heard two different opinions as to, if you will, what the default assumption is, the discussion of a six-to-five vote and that's not really a consensus, and we really should have a consensus before we move something to the full classification from the reasonably anticipated classification. Basically, it has implicit in it a default assumption that says that until we're reasonably certain, we don't go to a full approach.

On the other hand, we've also heard from people who say that the default assumption is for protection of public health. And my goodness. If you've got even a one-person majority that says

that this is a known carcinogen, that the direction ought to be going absolutely, certainly, in the direction of that should be treated as a full carcinogen.

We've heard these two different views as to, if you will, a default. I'm not going to put words in George's mouth or ask him to respond. I'm sure if George or Ken responded there, their answer would be, "Well, our default is good science, and we're going to good science," but, in essence, we've heard these others. Does anyone want to comment further on those two?

Dr. Bingham, please identify yourself. We all know who you are, but there's a transcriber here.

DR. BINGHAM: Eula Bingham. I have thought about that. You know, it works -- something is proposed to be raised, let's say, to a known human carcinogen from the reasonably anticipated, and the vote is six to five against doing that, so there had to be five people who thought it should be done, but six people thought it shouldn't be.

It's the same situation that you've described, and I'm wondering whether or not in the

NTP report one ought to consider putting in there, in those situations -- and I don't know what the numbers are, unanimous or ten to two or -- let's say a six to five. You actually describe what the committee came up with.

It would say, for example, Dr. Olden having to say, "Well, I agree with this one. It was six to five," or, "I agree with" -- or, "I don't agree." It's a very tough burden, I think, but if you put down in writing the way the vote went, it would provide workers, for example, with information. They'd say, "Well, they didn't really put it all the way up into that category, but some people were nervous," or some of the workers would say, "Well, it only was put up there by one vote."

I think it gives a little information, more information than we have now. I don't know. Maybe it's a bad idea, but it does get at the issue you brought out.

DR. FREDERICK: Eula, let me just chip in on that. I think it's a bad idea to put the text in, but that's okay. I actually think the vote on EO, and I don't care about EO, the fact that it was a mixed vote, six-five, it was exactly the right vote, and it doesn't make any difference if it was

six-five either way.

The point I'd like to make is I think you got it right that there's a mixed scientific opinion on this type of body of information. This is an advisory group. The advice to Dr. Olden is that looking at this body of information, there's a mixed scientific opinion here.

DR. BINGHAM: Then put it in the report.

DR. FREDERICK: Well, we could do that or not. I mean, that would be his choice, but the main thing is I think the recommendation to him was exactly right on the money. Some people might get hung up on the fact that it was 6-5 one way or the other. That wasn't the point. The point is it's a mixed vote.

DR. GOLDMAN: I just want to add to that, Bernie, because this is the area that, actually, I thought might be interesting for more discussion but broader in that it seems to me, from a lot of the comments that we've heard over the course of the day, that there is a greater richness of information, whether it's about the vote or whether it is about the database or whether it's about, you know, issues such as the nickel issue,

about the difference between different forms of the substance that people would like to see more fully reflected in the report.

And whether -- and a couple of people said things like, "Well, you know, actually, the conclusions of the NTP, the listing could be longer. Instead of a couple, you know, it could be longer. It could be two or three times longer." A couple of people have said that. And it just seems to me that's another area where we could get more input, in general, not just on this issue about votes, but also on other issues like the exposure issues.

DR. MIRER: Frank Mirer. I hope that sentiment on a split vote for ethylene oxide would also be reflected in the split vote on saccharin and the action to be taken there. And, actually, in the saccharin debate, we had one scientist who had done the epidemiology and, Clay, had been unsuccessful in producing tumors in mice, I believe, and that colored his opinion. So the split votes are really at issue.

Let me make a couple of points from the discussion. First, I served on the Red Book Committee my first two or three with Ken Olden, and at that point we separated risk assessment from

risk management. And, to me, the taking quotes about risk management being something that's a consensus process of bringing all the stakeholders, that -- you know, it does not translate into risk assessment being the same kind of thing or hazard identification being the same kind of thing. We make the effort there, and you can't just jump over that. So I think that those remarks are actually inappropriate to make.

The other issue has to do with how this data is treated. We represent a lot of foundry workers. Foundry workers suffer excess mortality from lung cancer almost uniformly. Most of that comes from silica exposure. That's a real thing. This argument about whether it's carcinogenic or not has real public health impacts.

I read through Dr. Gamble's summary. We read through all that material. There is a vast body of information on silica and carcinogenesis, and to stand here and joke around about beach sand and all that stuff and to try and denigrate the findings or delay the findings, this is a very important material the workers are exposed to every day, and if you don't think known human carcinogen makes a difference in whether management takes

precautions or not, I agree with our industry colleagues. It makes a big difference. Reasonably anticipated to be a human carcinogen means they don't have to control the exposure, and they apply that every day.

Similarly, the first mortality study we did ourselves in the UAW had to do with a nickel and chrome plating in an automotive hardware plant. Those employees suffered excess mortality from lung cancer. In trying to devise a control strategy, it makes a difference which -- whether you look at the dye-cast smoke, the chromium gas mist, or the nickel plating mist. It's an important issue.

And, again, as we raise the distinction between nickel metal and nickel compounds, people take a nickel rod. People weld a cast-iron casting with a nickel rod. They weld on stainless steel. It may be steel when it's sitting there, but it's nickel compound when they breathe it in. And steel welders suffer excess mortality from cancer.

So this hazard identification step is the first entry into risk assessment, and we can't, like, play around with all of the, "It will scare people," because that's what we have the rest of the regulatory process to deal with.

And then the final point, and this goes more to the pharmaceutical issues which were raised, and it came up at the time we heard the Tamoxifen issue in the meeting, the scientific purpose of this determination of what's a human carcinogen and what's an animal carcinogen and so forth, we're constantly reevaluating the predicted value of the bioassay in the face of epidemiology and epidemiology in the face of a bioassay.

And if we allow nonscientific considerations such as, "Oh, somebody might get" -- we recognize people might not take their medication, but if you allow those extra scientific considerations, you distort the body of evidence that we have to work with and you cause real problems down the line with the next chemical. And so I would not want to see that change of the classifications, then. Thanks.

DR. GOLDSTEIN: There's a comment in the back.

MR. GIPKO: Mike Gipko from the Specialty Steel Industry. And I thank you, Dr. Frederick, for your explanation. I just wanted to be clear what this means in the real world. Okay?

We understand how the listings of nickel

and nickel compounds. I mean, we can read, but the problem is some of our mom-and-pop customers can't. We get questions from Ford Motor. We get questions from Mercedes. We get questions from some of the big boys, and I said mom-and-pop to be funny. The big boys are calling our membership and saying -- and have implemented (inaudible) queries, asking whether nickel is present in our stainless steel. Well, of course it is. And they are considering deselection processes because of potential NTP ramifications.

So these are real. And, you know, we may say, "Well, you know, alloys aren't included." In the real world, that's what's going on, and I just wanted everyone here to be aware of that. Thank you.

DR. GOLDSTEIN: Okay. We have two folks over there, then Dr. Guston.

MR. TORSON: Mark Torson (phonetic) from NIOSH. I'm on the RG2, and when we finish voting -- or deliberating on a chemical, we always ask: What happened at RG1? What was the vote and why? We're most interested in the dissenting vote or the minority vote, and I think that there's always a minority opinion with our

group and I see it with the BSC (inaudible).

It shows up in the discussions and it often shows up in the presentations at the BSC where people give arguments as to why it should be listed and why it should not be listed. And this "why not" seems to be lost later on in the documents, and it might be helpful that the minority opinion be included in the discussion of why something is listed.

MS. WARREN: My name is Jackie Warren. I've been a career public interest advocate for environmental groups. I just wanted to respond to some of the statements that have been made here. This statute was passed in 1978, and I agree it's been 22 years, almost, but Congress did not change the agency's mandate when it revisited the statute in 1993.

And it's not appropriate for the agency to go off on a frolic of its own to do something that it might think is more timely now. I think it doesn't actually have the authority to deviate from the mandate that Congress gave it, and that is to produce -- first of all, to do toxicology studies, but to base the Report of Carcinogens on scientific conclusions, that they're not colored by conflicts of

interest or by the (inaudible) interest in the outcome of an evaluation but to just come out with the best scientific judgment they can make, which is, at bottom, going to be protective of public health.

And it's not going to be a majority, but if you took the majority vote of the people in this room to decide whether NTP should go one way or the other, it's clear to me that they would being going to some sort of formal ruling, you know, regulatory agency mode. I don't think that the agency really has the discretion to make that kind of change without a clear signal from Congress, which it definitely has not gotten in the past.

I think that the report's purpose is to come out with a list of substances which also includes how adequately they are presently being regulated or whether they are being regulated at all, and it's an alert. Look at these next. It isn't really the regulation itself, and it isn't risk assessment. The risk assessment stage comes later.

That's the thing with respect to the Tamoxifen example. I think that the downside of taking Tamoxifen is a factor that a woman needs to be considering when making the decision of whether

to take it in the first place. I don't think that that is served by keeping that information from people, and one would think and hope and expect that a woman's doctor would inform her of what the downside and the contraindications may be along with the very great benefits that would come from it, but I think that to, effectively, shoot the messenger of bad tidings so that people don't hear it and don't trouble their little pretty heads about it is not an appropriate response.

So I think, in general, the agency, as I said earlier, should not move to transform itself into a regulatory agency holding formal rule makings. I mean, there's plenty of opportunity for public input already, as this shows, but if every inch that's given results in a demand for another foot, you will be in a regulatory agency mode before you know it. I think you're halfway there already.

DR. GUSTON: David Guston, Rutgers University.

Two points, one on the Chairman's question about the default assumption. That seems, to me, to be something that's more properly pushed up the chain. We've, I think, had a somewhat unfortunate

focus simply on the Report on Carcinogens Subcommittee to the exclusion of the rest of the process of decision making, as was described at the beginning of the meeting, that there is an RG1, that there is an RG2, and there are several layers of political administrative review on top of this advisory process.

The decision about whether something, you know, to put it crudely, should be innocent until proven -- whether a substance should be innocent until proven guilty or guilty until proven innocent strikes me as exactly that kind of decision that we want to put in the hands of a responsible political decision maker who is subject to direct political controls. That's the first point.

Second point, I want to highlight something that Dr. Frederick said about this being an iterative process, and I want to highlight by way of a question that most of the presenters this afternoon who have spoken about the process with respect to individual substances have called for a delay for the 9th Report until all these procedural flaws, in their eyes, should be fixed. And I guess the question I have in that respect is: Well, what's wrong with the 10th Report or the 11th Report or

the 12th Report?

And the answer to that question -- you know, why is the option not move for delisting in the 10th Report rather than delay the 9th Report? And I don't think the answer to that question can be: Because it will confuse the public. Because I think the public, since the filming -- the screening of Woody Allen's Sleeper, is perfectly comfortable with the idea that science is a moving target, and, you know, what may be carcinogenic one day may not be carcinogenic the next day.

So I think that that's an important question for people whose initial impulse right now is to delay the 9th Report. Why not petition for delisting or a change in status in subsequent reports?

MR. KENNEDY: Bill Kennedy, AstraZeneca. I have to comment that in no way, I think, should our comments be taken as shooting the messenger. The issue of listing Tamoxifen we didn't address. We were talking about -- using Tamoxifen as an example for a (inaudible), and that's the inclusion of a pharmaceutical category.

I do recognize that there's a precedent, but I also recognize that the precedent has already

been accomplished by the FDA having made an evaluation of this compound as well as other compounds 25 years ago when the initial approvals were granted.

Coming back to the -- I think what the initial mandate of what Congressional intent was on the mandate, and that was to provide information to the public so that they would be aware, and I think the balance of the benefit and risk is terribly important in fulfilling that mandate. When a physician and patient are making that decision, they should have the information. I've already cited the example we've had on 30,000 patients leaving.

But an important piece that I like to keep in mind is that we're talking about compounds. If we're talking about a compound, there are restrictions that are placed upon unqualified statements of efficacy. There has to be a fair balance when the pharmaceutical industry is talking about efficacy. The agency requires -- the law requires us to provide evidence of comments on the safety.

I think when you're talking about a compound, the same should happen if you're talking about safety. There should be fair balance on the

efficacy side. Thank you.

DR. FREDERICK: Could I say one thing about the 30,000 patients leaving? That really troubled me when you said that, and the reason why it troubled me was, one, was the process in California wrong or whatever it could be or does this represent 30,000 cases of poor doctor-patient communication and inappropriate briefing of people with regard to the issues at hand relative to the benefits of the medication?

I don't think we can necessarily resolve that question here today, but I think there's more to that observation than might be -- you can say something about it if you wish, but I'm not sure in this particular case -- I think with regard to what's going on here, that -- this whole issue of communication -- appropriate communication of information like this is, basically, more complex than a superficial analysis might indicate.

MR. KENNEDY: Well, I think that the 30,000 number is very close to real. These were patients who were on five years of therapy. They're in contact with their physician. An initial meeting with their physician could have taken place a year ago, two years ago, three years ago. That

placed over a background of sensationalism as Proposition 65 is being argued in California, there was a significant impact.

If I could provide one anecdote on this –

DR. GOLDMAN: When did Tamoxifen come on the market for cancer chemotherapy?

MR. KENNEDY: Twenty years ago. In the United States, twenty years ago.

DR. GOLDMAN: So that was well prior to Prop 65. I mean, I'm confused by the timing. The history, as I remember it, is different than this, so -- you know, in terms of timing.

MR. KENNEDY: If you're confused, imagine what it's like for a woman out there who has, perhaps, a mother who has been treated for breast cancer with Tamoxifen, a sister who's had Agiden (phonetic) therapy and just finds out that she is at high risk and goes on Tamoxifen as a way to reduce her risk and then reads that this drug that is being used to treat and reduce the risk of cancer is identified as a carcinogen. She's going to be very, very confused.

DR. GOLDMAN: I was there then and I just didn't see that media. I mean, I just --

that's the thing. I mean, I was in the middle of it and not personally involved, but I worked for the State then, and I -- you know, so the history just doesn't mesh with, you know, what I remember hearing and seeing, but that's okay. It's just -- you know, I'm finding the example -- I think the point is a good one, that there could be a separate listing for therapeutic drugs that are regulated by the FDA, but the anecdote, you know, we're having trouble understanding. I think both of us are.

DR. GOLDSTEIN: You've greed to the point. Let's --

MR. KENNEDY: Okay. So you're not going to shoot this messenger?

DR. GOLDMAN: Not at all.

MR. KELLY: Bill Kelly with Federal Focus.

A couple of times now I've heard references to Congress revisiting the Report on Carcinogens in 1993, and it sounds like the inference to be drawn there is that Congress really deliberated on this subject and had decided that the way that the report is being prepared is just fine and it was going to leave everything unchanged.

And my recollection in trying to look into

this (inaudible) history materials is that what happened in 1993 is they changed it from an annual to a biennial report, and that was done in one sentence in miscellaneous provisions at the end of an extremely long bill that wouldn't even have the strength of something like an appropriations (inaudible), for example.

And I think it's a very weak argument to try to argue Congressional acquiescence on something like this unless there is some evidence, which we haven't seen, that Congress really did deliberate on this some time recently, and if that does exist, I'd love to see it brought forward. As I've said before, I haven't seen it so far. And if all they did was change it from one year to two years and stick it one sentence at the end of a bill, I doubt very seriously that Congress has really focused on this issue since 1978.

DR. GOLDSTEIN: Jackie Warren is up to make a comment. Sara Schotland would like to make a comment. And then I'm going to call this subject closed.

MS. WARREN: I want to make a quick response. What he said, it's very true about what Congress says with every statute that comes

before it. It doesn't reopen the statutes very often, and when it does, it has the opportunity to make any changes that it thinks should be made. The fact that it didn't make any changes says what it says.

DR. GOLDSTEIN: I thinks that the NTP folks will take a look at this more than they might have before, and I appreciate the fact that people have brought it up. It's something that I'm sure they will look at the issue.

Are there comments?

MR. LEBER: Phil Leber from Good Year.

I just wanted to get back to a point that Dr. Valentine made, and I think it may have been part of your slide, Dr. Goldstein, at the end of the last session with regard to the criteria for exposure, the importance of that as far as listing.

This morning I made the comments that there was some question about the exposure criteria for listing in an isoprene example. Dr. Valentine brought it up again. I understood from Clay Frederick saying any exposure is significant exposure. Is that an NTP position? It says clearly in the act that a significant number of people have

to be exposed before a chemical is listed. Is that being discarded? Is that not an issue any longer? Because it will save me time next time the (inaudible).

DR. GOLDSTEIN: That's a good question. Yours was about the only comment we had on this and Gail Charnley's comment, which is, you know, clearly NTP shouldn't do this unless it has some risk management input. Obviously, maybe that first step is the step in which, basically, the hurdle is: Does it have risk management input?

Let me ask the NTP folks to sort of describe what happens. How does a chemical get on the list to be evaluated?

DR. LUCIER: I'll backtrack and come back to the exposure issue, but there are a number of entries one could get into consideration for the Report on Carcinogens. The bottom line is anyone in the world can nominate something to us, and we do get nominations from all around the world. That doesn't mean we take all those nominations through this very lengthy process that we described today.

The charge we have from Congress is to list substances as known or reasonably anticipated

to be human carcinogens to which a significant number of people in the U.S. are exposed. How one defines that significant number of people, obviously, is difficult to do, but some people may consider 100 people a significant number. Some people may consider it more. Some people may consider it less. Obviously, if you're the one person who is exposed to a high level of a carcinogenic substance, it's of concern to you, but, obviously, that issue is debatable.

Often, the exposure information they're working from, I think the point has been made, is based on some outdated exposure information that may exist from the NOES Survey or something, and whenever those surveys are updated and we have information available, they, of course, are considered by us. We can only go on the information that we have at hand.

DR. GOLDSTEIN: Of all the chemicals that get nominated, can you give us some numbers as to how many make it through the process? Are we talking about most of them, a few of them?

DR. JAMESON: We currently have a list of chemicals or exposure circumstances or

mixtures that we're looking at, and I think the number on that particular list is about 198 that there is scientific literature available that we want to look at to see if it meets the criteria.

As far as outside nominations or nominations that come in from reviews from people other than an NTP review of the literature, every one of those goes through at least review by the RG1. And I would say probably, in my experience with the report, which is for the 7th, 8th, and 9th and now the 10th, probably at least 90 percent of those go all the way through -- have gone all the way through the review process. In other words 90 percent have enough information available to us that we feel we need --

DR. GUSTON: What percent?

DR. JAMESON: 90 percent.

DR. GOLDMAN: Where do they come from? Who nominates them.

DR. JAMESON: Where do they come from? We get nominations from other government agencies, from OSHA, NIOSH. EPA has nominated materials. We get nominations from some environmental state organizations, and we also have gotten nominations from private citizens and

industry. Nominations -- let me qualify. Most of the nominations we get from industry are for delisting.

DR. LUCIER: There are a number of things that will stimulate the priority for something. One is, obviously, if we have just completed an NTP study that's undergone rigorous peer review in terms of the chronic bioassay and that's given a strong carcinogenic response, that's something that we want to consider very soon for the Report on Carcinogens, and we need to do that for public health reasons.

The other triggers would be priorities of various kinds of regulatory agencies that might nominate things to us. If something has recently been upgraded or established as a known human carcinogen by IARC, that might be another trigger for us.

DR. GOLDSTEIN: Another comment there?

MR. TORSON: Mark Torson from NIOSH. I hate to take a step back, but just for the record, I want to let people know that the patient is not the only concern with exposure to the pharmaceutical. We have people involved in the

manufacturing, especially the healthcare workers that are exposed to these chemicals and affected by them.

DR. WADDELL: Bill Waddell, University of Louisville.

It's bothering me a little bit about relegating hazard identification to lack of consideration of the conditions of use, namely dose. It's my contention that we must have some consideration of dose to identify it as a hazard.

Water, sugar, and salt ingested in sufficient quantities will kill so that they are a potential hazard. They're not a risk under ordinary conditions of use at an ordinary dose. So the notion that dose must only be considered in risk assessment is not correct. You have to consider dose in a broad quantitative sense, at least, to identify something as a hazard.

And I think a lot of the discussion we've heard today saying, "It's not risk assessment. It's hazard identification," does not recognize that in order to identify a hazard, we must consider the conditions.

There are many things that we use ordinarily, and a lot of the problems would be

resolved if we're simply admitting that we have to consider dose, at least in a broad sense, to identify a hazard such that there are many things in low dose that you've identified as a carcinogen that are not carcinogens (inaudible) the only carcinogens are hazardous. So if you recognize this distinction in hazard identification, then it all resolves itself.

DR. GOLDSTEIN: Dr. Waddell, would you continue with that? Because Gail Charnley raised the same issue, and I guess just to follow up on it, the issue, I guess, would be -- as I understand what NTP is trying to do is first agree that everything is a hazard but that not all things are carcinogenic hazards and that their goal is really to narrow down which chemicals intrinsically can act as carcinogens.

DR. WADDELL: The problem is that many things are carcinogenic in high doses, and those same substances are not carcinogenic in low doses. And the problem that NTP is shackling itself with is saying, "Well, if it's carcinogenic at any dose, then we have to classify it as a carcinogen," and I don't think they have to be shackled with that.

I think that they can say it is a carcinogen

at the high dose, recognize that and say that, instead of saying it's a carcinogen and implying that it's a carcinogen at any dose, and that's somebody else's job. It's not.

DR. GOLDSTEIN: So you would support, basically, some degree of explanation or --

DR. WADDELL: Absolutely.

DR. LUCIER: Let me just make one quick comment. This issue was addressed in significant detail when we went through the two-year review for the criteria by which we would determine which substances should be listed or not listed in the report, and it's really addressed in the criteria itself in the last paragraph in which the Board of Scientific Counselors as well as the other review groups and the NTP Executive Committee operate under.

It says conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment with consideration given to all relevant information. Relevant information includes -- it does not limit it to – dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, and so forth.

So that's sort of the Bible which the various review groups use in determining which substances should be listed.

DR. WADDELL: I understand that, and I have read that, too, but what I'm saying is you're not using that. If you consider dose and you have named dose as part of the consideration, you're saying that only at high dose something is a carcinogen, and you ignore the facts that at low dose it may actually be essential.

So what I'm saying is, you point to that, and I read that in the document, but my contention is you're not using that as far as your decision if only at the high dose drives your decision.

MR. JANKE: My name is Ron Janke, and I'm with Jones, Day, Reavis & Pogue. My comments are purely personal.

It strikes me as only logical that if NTP has information that there are special circumstances that special populations are going to misinterpret what NTP says in the normal way, that NTP should speak differently on that subject.

I'll use Tamoxifen as an example. My wife began taking that drug about five months ago, and she now reads all reports about breast cancer and

breast cancer treatments far different than she did ten months ago. And if it's brought to NTP's attention that women may make ill-advised medical choices because of a classification, it would do my wife and a lot of women a great service if you said, "We've classified this drug as a carcinogen. We recognize it's FDA approved for certain treatment, and we make no statement one way or another whether FDA should do anything different as a result of what we're doing today."

DR. GOLDSTEIN: Thank you.

MS. MILLER: Karen Miller. I just want to make a comment that it is about the process, but it's about how you communicate what you do, and that's really what's at stake in terms of communicating to the public. I've dealt with the media for six years and all these issues around Tamoxifen and the sensationalism any time there's a story about endometrial cancer. So I just urge you to think about how you communicate the listing, not that you communicate it.

To the man's comment about whose wife has breast cancer, it's really not what you say but how you say it. And it's very complex to talk about these issues and listings, and the press

frequently gets it wrong. So please be as clear as possible in how you communicate the listings because that's what women will take away from the press is the misinterpretation, not necessarily what you say.

DR. GOLDSTEIN: Thank you.

Okay. Other comments on any subject?

My goodness. There's still about 30 or 40 people here. It's amazing. Let me thank you all.

(**WHEREUPON** the Public Meeting was adjourned at 5:45 p.m., to be reconvened on October 22, 1999 at 9:00 a.m.)

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C A P T I O N

The Public Meeting in the matter, on the date, and at the time and place set out on the title page hereof.

It was requested that the Meeting be taken by the reporter and that same be reduced to typewritten form.

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