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# CHARACTERIZATION OF EPIDEMIOLOGY DATA RELATING TO PROSTATE CANCER AND EXPOSURE TO ATRAZINE

July 17, 2003

[8:30 a.m.]

Sheraton Crystal City Hotel

1800 Jefferson Davis Highway

Arlington, Virginia 22202

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

DR. ROBERTS: Good morning and welcome to the July 17 Scientific Advisory Panel. The topic of our meeting is Characterization of Epidemiology Data Relating to Prostate Cancer and Exposure to Atrazine. My name is Steve Roberts, and I am chair of the FIFRA SAP. Today's session is going to be chaired by another member of the permanent panel, Dr. Chris Portier. And I would like to now turn the session over to him to introduce the Panel and begin the meeting. Dr. Portier.

DR. PORTIER: Good morning, and thank you, Dr. Roberts. And I want to also welcome you to this July 17 meeting of the FIFRA Science Advisory Panel. I want to thank the Agency for getting us here this morning and getting all the information to us far in advance of this meeting so we'd have a lot of time to digest it. I think we're in for a very interesting scientific discussion today on a topic of serious national public health concern. So I think it would be a very stimulating and interesting discussion for us and something I hope we can provide the Agency with some clear scientific advice on.

I want to begin by having the Panel introduce themselves. I'd ask that they give their name, affiliation, and a little bit about their interest and how it pertains to the topic at hand. Why don't we start

with you, Frank, if that's okay.

DR. BOVE: My name is Frank Bove. I work for Agency for Toxic Substances and Disease Registry in Atlanta. I'm a senior epidemiologist in the Division of Health Studies. My work has been in drinking water contamination with solvents and disinfection by-products. And I'm interested also in atrazine.

DR. KNOBELOCH: I'm Lynda Knobeloch. I'm a senior toxicologist at the --

DR. PORTIER: Lynda, if you could use the microphone, please.

DR. KNOBELOCH: I'm Lynda Knobeloch. I'm a toxicologist with the Wisconsin Department of Health and Family Services in the Bureau of Environmental Health. My primary focus is on drinking water safety and environmental epidemiology.

DR. REIF: John Reif from the Department of Environmental and Radiological Health Sciences at Colorado State University. I'm an environmental epidemiologist. I've worked in the area of drinking water, cancer in farmers, and other agriculture populations.

DR. SYMANSKI: My name is Elaine Symanski. I'm from the University of Texas, School of Public Health in Houston. My primary research interests are in exposure assessment; and, specifically, in the development of quantitatively based strategies to evaluate exposures

to both environmental and occupational contaminants.

DR. YOUNG: My name is Heather Young. I'm an assistant research professor at George Washington University in the Department of Epidemiology. My primary research interests are reproductive cancers, specifically ovarian cancer, and exposure assessment as it relates to pesticide usage data bases.

DR. SANDY: I'm Martha Sandy. I'm a senior toxicologist with the Office of Environmental Health Hazard Assessment in California. And I'm interested in carcinogenesis.

DR. HOPENHAYN: I'm Claudia Hopenhayn. I'm with the University of Kentucky School of Public Health and also their Markey Cancer Center. I'm an environmental epidemiologist, and I have an interest in environmental and occupational carcinogens and also other effects such as reproductive effects.

DR. GOLD: I'm Ellen Gold. I'm a professor in the Department of Epidemiology and Preventative Medicine at U.C. Davis. And my interests are in cancer epidemiology in women's health.

DR. MERRILL: I'm Ray Merrill. I'm a associate professor at Brigham Young University. I'm a biostatistician and have experience in modeling trends in prostate cancer.

DR. ISOM: I'm Gary Isom, professor of toxicology at Purdue

University. My area of interest is neurotoxicology and specifically chemical-induced neural degenerative processes.

DR. HERRINGA: I'm Steve Herringa, a research scientist and director of the Statistical Design Group at the Institute for Social Research at the University of Michigan. I am a statistician, and I specialize in the design of population-based studies.

DR. HANDWERGER: I'm Stuart Handwerger. I'm a pediatric endocrinologist. I direct the Division of endocrinology in the Perinatal Research Institute at the University of Cincinnati. I'm a molecular and developmental endocrinologist with the primary focus in fetal growth and development.

DR. ROBERTS: And I'm Steve Roberts. I'm a professor with joint appointments in the College of Veterinary and the College of Medicine at the University of Florida. I also serve as director for the Center for Environmental and Human Toxicology there. My areas of expertise are in toxicology and risk assessment.

DR. PORTIER: I'm Chris Portier. I'm director of the Environmental Toxicology Program at the National Institute of Environmental Health Services in Research Triangle Park, North Carolina. And I'm the associate director of the National Toxicology Program. My areas of interest are statistics and mathematics as they

relate to toxicology and risk assessment.

Now that you've met the Panel, I'd like to turn it over to Steve Knott, the Designated Federal Official with some logistical and other issues. Steve.

MR. KNOTT: Thank you, Dr. Portier. And good morning to everyone. My name is Steve Knott. And I will be serving as the Designated Federal Official to the FIFRA Scientific Advisory Panel for this meeting.

I want to thank, Dr. Portier, for agreeing to serve as chair for this session of the FIFRA SAP. And I also want to thank both the members of the Panel and the public for attending this important meeting to review the characterization of epidemiology data relating to prostate cancer and exposure to atrazine. We appreciate the time and the effort of the Panel members in preparing for this meeting.

By way of background, the FIFRA SAP is a federal advisory committee that provides independent scientific peer review and advice to the Agency on pesticides and pesticide-related issues regarding the impact of proposed regulatory actions on human health in the environment. The FIFRA SAP only provides advice and recommendations to EPA. Decision-making and implementation authority remains with the Agency.

The Federal Insecticide Fungicide Fund and Rodenticide Act established the SAP as a panel consisting of seven members. The expertise of these members is augmented through the use of a science review board that was established by the Food Quality Protection Act of 1996. Science review board members serve as ad hoc temporary members of the FIFRA SAP, providing additional scientific expertise to assist in reviews conducted by the Panel.

As the Designated Federal Official for this meeting, I serve as a liaison between Panel and the Agency. I'm also responsible for insuring that the provisions of the Federal Advisory Committee Act of 1972 or FACA are met. FACA established a system that governs the creation, operation, and termination of executive branch advisory committees.

FIFRA SAP meetings are subject to all of FACA's requirements. These include open meetings, timely public notice for meetings, and public availability of documents which is provided via the Office of Pesticide Programs public docket.

Another critical responsibility as Designated Federal Official is to work with appropriate Agency officials to ensure that all applicable ethics regulations are satisfied. In that capacity, Panel members will be briefed on the provisions of federal conflict of interest laws. In

addition each participant has filed a standard government financial disclosure report.

I, along with our deputy ethics officer for the Office of Prevention, Pesticides, and Toxic Substances, and in consultation with the Office of General Counsel, have reviewed these reports to ensure all ethics requirements are met. An example copy of this form is available on the FIFRA SAP web site.

Over the next two days, the Panel will review challenging science issues. And we do have a very full agenda. And please note that all times that are noted on the agenda are approximate. We strive to ensure that there is adequate time for Agency presentations, public comments, and Panel deliberations. For presenters, Panel members, and public commenters, please identify yourselves and speak into the microphones that are provided. This meeting is being recorded.

For members of the public requesting time to make a public comment, please limit your comments to five minutes unless you've made prior arrangements for additional time. For those that have not preregistered to make comments, please notify either myself or another member of the FIFRA SAP staff.

All background materials, questions posed to the Panel by the Agency, and other documents related to this meeting are available in

the public docket. Copies of presentation of materials and public comments that are presented today will be available in the docket within the next several days. Also, some background documents are available on the EPA web site. And the agenda lists contact information for obtaining such documents.

For members of the press, I believe Mr. David Degan from EPA's Office of Media Relations is available here today to answer questions about this meeting. Is David here yet? Okay. Well, should he be here later, please, do address your questions to Mr. Degan.

At the conclusion of this meeting, the SAP will prepare a report as a response to questions posed by the agency and related materials. The report serves as meeting minutes, and we anticipate completing these minutes within approximately four weeks after the meeting.

Again, I wish to thank the Panel for their participation in this session; and I look forward to an interesting discussion over the next two days. Dr. Portier.

DR. PORTIER: Thank you, Steve. And with that then, why don't we begin formal presentations by the Agency. I'd like to introduce Mr. Jim Jones, who's Director of the Office of Pesticide Programs within the Office of Prevention, Pesticides, and Toxic Substances of EPA. Jim, I'll let you introduce your staff.

DR. JONES: Thank you. Well, first I want to comment on the weather. It's not that typical -- those of you who have been to Washington in July -- to have such a beautiful day. Maybe every three or four years we get a day like this in July. So I thought I'd mention that since it's not too often I get to say, what a beautiful day in July in Washington.

First, I'd like to make a few introductory remarks before introducing the Agency staff sitting to my left. Mr. Chairman and members of the Scientific Advisory Panel, on behalf of the Environmental Protection Agency and the Office of Pesticide Programs, I want to thank you for your service here. We are deeply indebted to you for your considerable time and energy that you bring to help advice the Agency on complex scientific issues. The work doesn't start or end with the two days you spend in this public meeting.

The voluminous materials provided in advance of the meeting and the deliberations afterward are considerable, and we recognize the sacrifices that they represent. Atrazine presents some of the most complex scientific issues we wrestle with in OPP. It is also one of the most controversial chemicals we regulate. A few years back, this Panel helped us sort out the complex scientific issues associated with

atrazine's mechanism of carcinogenicity.

Just last month, another SAP panel met to consider the issues associated with atrazine's potential affects on amphibians. For the next two days, this panel will deliberate over the epidemiological data associated with atrazine and prostate cancer.

Although the Agency has a high degree of confidence in the sophistication and integrity of it's scientific capabilities, we recognize that we are not the sole source of scientific knowledge and expertise. We also recognize the value of seeking scientific advice from individuals who are independent of the Agency as well as any entity that may have a stake in the outcomes.

Over the years, the Office the Pesticide Programs has benefited greatly from the advice and expertise the SAP has afforded us. I expect this panel and this meeting will be no different. I hope each of you reap the many intangible but gratifying benefits of your public service. I know the Agency and OPP will benefit from your efforts.

And I want to introduce to my left Margaret Stasikowski who is the Director of the Health Effects Division who will be making some additional introductory remarks. And to her left is Dr. Jerry Blondell, also from the Health Effects Division. Thank you.

DR. STASIKOWSKI: Good morning. I would like to add my

welcome to Jim's welcome. And as I've been the director of the Health Effects Division for almost the last seven years, and I must say that the highlights of my year in Health Effects Divisions are consultations with the Science Advisory Panel. To those of you who may be working with us for the first time, the consultations, reviews, by Science Advisory Panel certainly have added to the quality of this the science work that we do in the Health Effects Division.

This is a division that's responsible for, in regard to this subject, developing the risk assessment for atrazine as it relates to human health effects. As Jim mentioned, in the area of human health effects, we met with the SAP in the year 2000 where we considered mechanism of toxicity as it relates to cancer based on animal data base; and we are very glad to be here today to consider the epidemiology data base as it relates to prostate cancer.

There are other studies that are underway that relate to epidemiology of other cancers. And as we receive that information, as we assess it, we may be back to talk with you about that.

Well, welcome. And we are ready to begin. And I have the pleasure to introduce Dr. Jerry Blondell, our very experienced epidemiologist who has worked in this area for 25 years now. So thank you very much.

DR. BLONDELL: Thank you, Margaret. And welcome also to everyone that's here today, the Panel and the public. I appreciate the opportunity to give the presentation that will frame the questions that we will present at the end of my presentation this morning.

The basic approach as we see on the slide in the front there we're going to be primarily considering three studies: A study in Louisiana manufacturing workers at the St. Gabriel plant; a corelational or sometimes called an ecologic study that was done in California; and a study that I should say is being done, has been done, and will be done in Iowa and North Carolina by the National Cancer Institute with participation by the Environmental Protection Agency and National Institute for Environmental Sciences, and it's called the Agricultural Health Study. Then I'll give you EPA's conclusions, and then our questions to the Panel.

Now let me give you a little more detail about these three studies if I may. The first study, the St. Gabriel study, is a retrospective cohort study of atrazine manufacturing workers. And this study has been ongoing for quite a number of years now, and we've received reports on this study before. In fact, we've done reviews in 199O, 1994, 1996, and 2001. And it's only the most recent study, the 2001 study, that led to the concern for prostate cancer that

we'll be discussing today that is really what led to this meeting.

The second study, as I mentioned, the Agricultural Health Study, that's a study of commercial and private applicators. It's a prospective study. And they had their very first report -- actually, the study started recruiting people back in 1993. And this year was a very first report of a major cancer. And it just so happens that this study came out at the same time that the St. Gabriel plant report did in terms of timing. And part of the reason, of course, is because they waited until they had a large enough sample of prostate cancer cases. And that was the most frequent cancer in the cohort, so that's the first thing to come out.

Now in coming years, they are going to be reporting on other cancers. And we'll talk about that in a moment, about the future studies that are coming.

But the scope of the review for today is just on the epidemiology studies specific to atrazine exposure and prostate cancer.

Let me say a little bit about those future studies to put all this into context because there are some really major studies coming up and we need to know about them in terms of understanding how this evaluation is going to go forward.

First of all, I just talked about the St. Gabriel plant study. And as you see the first item on the list is a St. Gabriel plant study, a future study at that plant. And what that's going to be is a nested case-control analysis that looks specifically as exposure indices. And we're expecting to have the results of that study by the end of this year. One of the things I'll be talking about later is how in the process of reviewing the study, questions would arise about certain things. We'd go to peer reviewers, get comments from external peer reviewers, do another review. Then we got public comment and additional comment from peer reviewers. And as a result of all of this, Syngenta, the people that are the manufacturers at this plant, are now doing this additional work looking at exposure indices to see that they can further tease apart what's going on in terms of the exposure at the plant versus the prostate cancer outcomes.

And you just heard me say that the Agricultural Health Study just published on prostate cancer; and yet I have on as a second bullet they're going to reanalyze that study. Well, how did that come about? Well, the reason that came about is because they actually collected those prostate cancer cases a year and a half, two years ago; and it's taken them considerable time to get it analyzed and finally get it published. And this is the first major cancer that they have published

on.

But in that intervening year and a half to two years, there's been another 400 prostate cancers occur in that cohort. That nearly doubles the sample size. As a result, they're going to go back, redo the analysis starting this year. And they will have a report next year reanalyzing the whole data set for prostate cancer.

Another thing that the Agricultural Health Study is going to do is they're going to do an analysis specific to atrazine. That also is going to start this year, and is also going to be reported on next year.

Now I just said earlier that they were basing their studies on having a frequent enough number of cases and they're going to do prostate cancer. And coming up next year, we're going to have breast cancer, we're going to have non-Hodgkin's lymphoma. But what about atrazine? Well, the people at the National Cancer Institute are very aware of EPA's concern to address some of these major chemicals. And atrazine, in terms of the volume of use, in terms of pounds active ingredient, is probably the leading pesticide, period, used in the United States. And so that, along with certain other pesticides including 2-4D and chlorpyrophos, are chemicals that are on their list that they're going to do special analysis respecting the fact that EPA wants to get knowledge as quickly as we can and find out what risks

there may be associated with these particular chemicals. So that's the reason for the third bullet.

Then the fourth bullet is another Cancer Institute study, and it's about to be published in another two months. Now, this fourth bullet is based on earlier studies. It's a combination of the earlier studies they did in Kansas, Iowa, Minnesota, and Nebraska. And there, they've had a real difficulty trying to tease apart the exposure problems with multiple exposures to different pesticides. And they've come up with a much more sophisticated hierarchical technique where they adjust for the different exposures, look at combinations of exposures, and stabilize the variance in such a way that they can try to get and tease out what exposures may be associated with the non-Hodgkin's lymphoma in the earlier studies. And even more important than that in some ways, because it's a stronger study, going back to the Agricultural Health Study again will be the non-Hodgkin's lymphoma study that they'll have enough cases starting next year, to do the work, and we would certainly expect a report on that study by 2005 if not earlier.

So given the importance of incorporating these results into an evaluation of atrazine for prostate cancer and other cancer outcomes, the Agency plans future analyses and absent compelling information

in the interim will wait until all these analyses are in before addressing the broader question of atrazine exposure and all cancers.

Now if we get a study that is very strong prior to getting all the studies, we will not wait until all the studies. We will act on a strong study as it comes in. We do want to make that clear.

Let me now turn to the St. Gabriel plant study and introduce it, if I may. The inclusion criteria for this study was that a worker had to be working in the plant for at least six months prior to 1993 during the period 1970 to '92. 1970 was when they started to produce atrazine. They had to be a Louisiana resident in order to be captured by the Louisiana tumor registry which was the basis for capturing both the incidence and the mortality information. And they had to be, of course, exposed to triazines or their precursors, things used in making the triazines. And I want to emphasize, that at this plant, the main type of triazine produced was atrazine overwhelmingly.

As a result of these inclusion criteria, they had 2,045 subjects that met the criteria. And one of the interesting things about these 2,045 subjects that I want you to focus on for a moment and keep in mind is that 37 percent of them, 757, were employees of the plant. But most of the people in the cohort contract workers were either contract maintenance or contract production. And there's a big

difference between these two groups. And the big difference is the duration of time that they worked at the plant. The employees worked a median of 11 years, whereas the contract workers worked a median of two years. And this is going to be important to distinguish. And in some of the later tables that I'll show you, I'll only be showing you information about the employees instead of the contractors or talking only about the contractors. So it's important to understand the distinction there.

The 2,045 subjects included 1,263 white men, 598 nonwhite men, 99 white women, and 85 nonwhite women. One of the good things about this study is they were very vigilant in pursuing the vital status and the location of what happened to each of these 2,045 subjects; so that by the end of the study, they had less than a 1 percent loss to follow-up.

Seventy-four percent of these workers were no longer employed at the plant at end of the study which was at the end of 1997. And they did have a well documented report of their efforts to determine vital status and location and did the same both for the subjects, the cancer cases, and the reference population.

The overall result of the study was that there were 46 cancer cases versus 41 that were expected. And this results in a standardized

incidence ratio, standardized in the sense that it's adjusted for age and race and time period, was 113, which is not statistically significant. It has a 95 percent confidence interval, 83 to 151, where a hundred would be no effect.

The initial comparisons and the comparison I just presented, was based on the years 1985 to '97. And during that time period, there were 11 prostate cancers. And when they did the comparison, they did a comparison -- you see two comparisons given there. One for the Louisiana State population and another for the industrial corridor. The reason for the industrial corridor is there was a concern that maybe the Louisiana population wasn't a proper comparison. And one of the things I'm going to talk about a little bit later, is one of the problems with any pesticide study is getting a good comparison group, a group that is comparable in every way possible except for the exposure to pesticides. And this is something many of you already know. But this is something that's very difficult to do in agricultural studies or in manufacturing studies.

So the idea of the industrial corridor is this would be a group of people that have the same lifestyle, same comparable in many respects in terms of environmental exposures because they lived nearby. The industrial corridor consists of seven parishes. Louisiana,

unfortunately, is the only state that has parishes. Every other state in the country calls them counties. But in Louisiana we talk about the seven parishes, but counties is what we mean by that for those who aren't familiar.

So there was a statistically significant effect when you compare to the Louisiana population, there was an increase of 2.5 times more prostate cancer at the plant with a confidence interval of 1.2 to 4.4; but not for the industrial corridor. It was elevated 1.75 but with a confidence interval of .9 to 3.1.

But while they were developing the results, they found out something rather surprising. Another six cancers occurred in the next two years while they were developing the results, six additional prostate cancers. And they didn't just ignore these. And by the way, when they did these comparisons with Louisiana and the industrial corridor, one of the things that I thought was helpful is they always presented the results side by side for the two groups. So you could see what the difference was with the two comparison groups. And they went ahead and tried to develop some statistics so they could get some expected numbers to look at these prostate cancers.

So that's what we're going to talk about in the next two slides which go into just the prostate cancer cases. Seventeen cases total

now. And this is for '85 to '99. So we've added two additional years here. And what I've done for you in this slide is I've broken it down by age group because that's a rather important issue. What you see here is that the highest standardized incidence ratios are in the younger age group with a 6.7 for those in the under 50 age group compared to the Louisiana state population, 3.9 for the 50 to 59, and actually below expectation for the 60 year, 32, only a third of the expected cancers in that particular age group. But it's only based on one case. We're now dealing the small number problem.

And in the next slide for comparison we have the industrial corridor, so you can see it side by side. And, basically, you have the same results. There's no difference in whether you have statistical significance between these two slides. But when you did the comparison with the industrial corridor, the ratios are lower.

So moving on to the key question about why these numbers are coming out the way they are, they had a prostate specific antigen screening program in this plant that started in 1989. In 1992, it was reported that it was offered to all men 50 years or older and younger men at the physician's discretion. In 1994 even men as young as 40 were offered the digital rectal exam. Those 45 and over were offered PSA screening. And even those 40 to 44 if they were African

American or if they had a family history of prostate cancer, were offered PSA screening.

And the result of this is that over this '93, '99 time period, an incredibly intensive level of PSA screening occurred. For those that were 45 and over, 90 to 100 percent did receive PSA screening. And even for those in the 40 to 44 year age group, over a third received PSA screening. So this is a very intensively screened for prostate cancer group. And the question is: Did this intensive screening lead to increased detection?

Well, before I comment on external reviewers, I wanted to talk a little bit about how the process worked in terms of the earlier peer review that we did. I completed the first review of this study back in December of 2001 and immediately realized that there was a serious question about whether PSA screening might account for this increase, part of the increase, or all of the increase. And I did seek outside comment from two reviewers, Dr. Blair who's often assisted the Agency, he's at the National Cancer Institute, in reviewing cancer epidemiology studies. And then on the recommendation of our Office of Research and Development, I sought out Dr. Giovannucci at Harvard to also comment on this question.

And after I got their comments, we also had a round of public

comment which resulted in a comment from an expert panel that was hired by Syngenta, the manufacturer, to look at this information. And also we had a couple sets of comments in July of 2002 from the National Resources Defense Council that raised questions about the prostate cancer analysis.

So we went out -- we don't normally do this. But in this case, we had so much comment we went out for a third round of review. And it was this third review that went back to the two original reviewers plus two additional reviewers, Dr. Howard Morrison, who has conducted studies of prostate cancer epidemiology, and Dr. Richard Hayes at the National Cancer Institute.

So their comments, I would like to share the key comment from each of them. Dr. Morrison's comment was that "almost definitely some increased prostate cancer case finding occurred because of increased PSA screening. There was a suggestion, however, that this might not be the entire explanation." Dr. Giovannucci, on the other hand, said, "In my opinion, the magnitude of the increase is compatible with PSA screening being the explanation." So there's a difference of opinion here.

Dr. Richard Hayes, on the other hand, "While PSA screening may account for much of the excess, it would be premature to reject a

potential role of occupational exposure to triazines as a contributing factor." And Dr. Blair commented on the Syngenta review which the Panel has and which goes into some calculations as to whether PSA screening might account for the entire increase. He said, well, "suggests that PSA screening may well explain the excess incidence of prostate cancer." And then later on in his comments he said, "but we really have a problem here because we don't have quantitative exposure assessment." That really is essential. So he didn't focus -- he didn't exactly give a conclusion there. But he did emphasize the need for more information.

Other peer review comments, we talked about the fact that there was this inverse relationship, the younger you were, the higher the standardized incidence ratio. And, of course, for prostate cancer, the incidence increases with age. Well, one of the things of course were others to keep in mind is that those standardized incidents ratios are adjusted for age. And the proportion screened was so high one person commented, one of the reviewers commented, that it was 98 percent for those over 44 years of age. And, typically, clinicians do not screen people in their 40s. And even in states where there's heavy screening, I would be surprised if it rose as high as 50 percent for those 50 and over.

Although we don't know. We don't know exactly what the screening rate was in the Louisiana population or the seven parish, seven county industrial corridor. So that's a problem. So because of the screening and because screening detects results in people being detected much earlier, many years earlier than they otherwise would, you do get a bias such that you would expect more of a bias the younger the person was that was screened. So in that sense, the screening has the expected effect, that is, the standardized incidence ratios are higher in the younger age groups.

Another thing that was consistent with screening as being the explanation for this increased detection is that 12 of the 14 tumors among the employees -- and one of the things I should have mentioned earlier, the employees are the ones, the 37 percent of the cohort, those were the ones that were offered the PSA screening not the contractor workers. Contractor workers did not have that as a benefit. They were not part of the medical plan for the plant in that respect.

So the 12 tumors were asymptomatic and localized, and that's consisted with increased heightened detection. And another comment by a reviewer was that autopsy studies suggest that there are many more prostate cancers that go undetected than are actually detected as a result of either screening or visit with a physician or other

symptoms. So the screening itself is a limitation, but only in the sense that we don't know in the -- we don't have a comparison population that has similar screening.

The other thing that I and other reviewers commented on was lack of assessment of exposure levels. And one of the things that I asked for in my review comments was, if at all possible, could you at least rank the exposure of the prostate cancer cases. And Syngenta did that and sent us some additional results which you have received and we'll be commenting on those in a couple of minutes. It was relatively, as in all occupational cancer studies of this kind, of relatively small populations, limited years of follow-up. And in order to look at the 98 to 99 cancer cases, they didn't have rates from the tumor registry for those years. So what they did was they used '95 to '96 figures to estimate what it would be in '98 and '99.

Now for the industrial corridor, they actually had '95 to '97 figures to estimate what the expected rate would be. So if there was an increase or decrease over time, that's going to bias the results either up or down. And we don't know which way.

So now turning to the exposure data, they didn't have exposure data really for the contract employees. But in my opinion, I don't think that's a serious problem. There were only three contract

employees that had prostate cancer, and the expectation in that cohort based on Louisiana or the industrial corridor would be that it would be 1.8 or 2.7. So there's no statistical significance there. And I'm not sure we need to worry too much about the contract employees because it's not an increase.

On the other hand, for the other 14 of the 17 cases that were plant employees -- and remember this is 37 percent of the cohort, but this is also the cohort that had the longest duration of exposures -- 11 years versus 2 years for the contract workers. They were able to collect data on 12 of them. And they did look at the two they weren't able to get data on and get some information on job titles. And they have the expectation that they would have fallen into the low exposure group.

So let's look now at the categories that these cases fell into. The 12 prostate cancer cases -- well, first of all, let me talk about the methodology. I'm skipping ahead a minute. What they did, they had two methods of looking at exposure. The first was simply to look at job titles classified by proximity to the plant. They had 30 job categories, 5 classified as remote, 17 as low, 4 mid, and 4 high. And if you look at the map at the back of the technical report on this study, you'll see a map of all the buildings. And you'll find out that there are

really only two or three buildings out of the several buildings at this location that had significant exposure to atrazine. So that's one of the reasons why these categories come out the way they do.

And what they did, of course, is they took each cancer case and assessed job categories accumulated until the time of diagnoses. For the 12 cancer cases, we had the duration, 46 percent of the duration was in a low exposure, 26 percent in the medium, 28 in a high exposure category. So that was one method.

The second method of looking at this data was to take into account the airborne dust monitoring data. And with that data, they actually did have -- in the most recent years, they did have some atrazine levels in the dust. But for earlier years, they just know the level of dust. So to a certain extent, they're sort of back calculating based on later data to what the dust levels would be. And one of the things they noticed is when you look at the high versus the medium, the remote, and so on, it was about a order of magnitude difference. So this is very rough. This is very, I don't want to say back of the envelope. It's more than that. But it's at least an attempt to get at the question of where did these workers fall. Did they have high, medium, or low exposure.

And then they also adjusted for some changes they made at the

plant that resulted in reduced exposure among the employees. And as a result of that analysis, they ended up with three cases with high proximity, four medium, and five that were low. But one of the things they didn't tell me when they sent me these results is they didn't tell me what was true for all the rest of the employees. And, of course, my question is, well, if they are a very, very small number of working in high proximity, those three cases may represent a significant excess. So I need to know what is the distribution for the male Syngenta employees. And they did go back and get the information which is what you see on your next slide.

And here we find out the first group, the prostate cancer, the second group, all male employees that 25 high exposure in the prostate cancer; 21 percent high exposure among all male employees; 33 percent mid level; 6 percent for all male employees. And you can see the statistics for the low. And so a Chi-square to see if there was dose response, particularly for the high level, did not show evidence of dose response; although, obviously, there is an increase in the mid-level group. And, of course, the reason we look for dose response is that if it's present it can be very helpful to us.

But, of course, one of the concerns with a study like this is that, particularly if we're talking about something that might involve

endocrine effects, it may not be true that dose response operates in the usual way. It may be that there's a range of exposure that's critical, and that above that range there is not an increase in risk. So we have to keep that in mind when we look at these data.

So these data are kind of crude in a number of respects. And it's really not a substitute for doing the proper comparison where you look at employees and matching adjusting for age, adjusting for race. And that's what the nested case-control study, that future study I told you about, is going to do. So we will get that in the future.

So our conclusion for looking at the St. Gabriel study is no strong evidence of dose response, a proper comparison requires measuring exposure in cases and controls, the future study I just mentioned. Most increase appears to be likely due to the increase in PSA screening. However, the study is insufficiently large; and there are other limitations to prevent ruling out atrazine as a factor. However, in our opinion, the role of atrazine seems unlikely.

Now, I'd like to go on to the next study which was in California. And this study looked at six pesticides and a priori. They decided that there were certainly pesticides which there was already a concern that they were carcinogenic. And atrazine was one of the six. So there was a suspicion of carcinogenicity that was used to select the

pesticides.

Then the other key part of the study was to get county based data based on pesticides usage for all six of these pesticides and also to get county cancer incident rates adjusted for age and for race.

Now they did find one that was significant, and that was a borderline significance where the correlation coefficient 0.67 for 95 percent; .01 to .97, a very wide confidence interval to say the least. And that was true only for black males. That was not true for Asians, not true for Hispanics, or Whites, all of whom had inverse point estimates. But again the estimates are very wide.

Atrazine is not widely used in California. Even though it's widely used in most of the other states in the country, it's because of the use on corn and other crops. And corn is not a big crop in California.

So this study has a problem in that you don't know if the black males are actually exposed to atrazine in these counties. You don't even know for sure if they lived in the counties when the atrazine was being used or whether they moved in or moved out. It's the problem of aggregation bias which is sometimes called ecological fallacy. I prefer not to use the term ecologic fallacy because there are so many other things we do at EPA that are ecologic and we don't want to cast

dispersions on that idea. So that pretty much sums up the results for that study.

And I'd like to talk about the Agricultural Health Study. In this study which was designed because of the problems they had with earlier studies, the earlier case-control retrospective studies particularly starting out in Kansas, Iowa, Minnesota, Nebraska, they kept getting conflicting results. They had problems with small sample sizes. They had problems with recall bias. And part of the idea of Agricultural Health Study was to do a prospective study where you'd measure exposure in advance and then find out who gets cancer to overcome those limitations.

And not only did they collect information on the exposure to pesticides, and I invite anyone that's at all interested to get on the web site, www.aghealth.org, aghealth all one word, and look at the questionnaire. It's really very thorough. It goes into lifestyle. It goes into all kind of exposures to other things besides pesticide on the farm. And it goes into family history and personal characteristics that might influence cancer outcomes. This is a very thorough effort to use the best techniques available to measure what's going on it with cancer and pesticides in the agricultural environment.

And the other thing about the exposure is that EPA is

participating in doing some field measurements to help validate the information that's collected by questionnaire.

So this study started enrolling people in 1993. And as you'll see in the next slide, the enrollment continued up until 1997. And as soon as they had people enrolled and had filled out their questionnaires, they started collecting information on cancer incidents and mortality starting in 1994 through to the present.

So for this study, the exposure information collected, as you'll see in the next slide, they collected information on 50 individual pesticides. And these were selected ahead of time in consultation with EPA. And as you see on the next slide, they did three different things in looking at exposure. And of course I think I mentioned earlier about the problem of comparison. The number two problem with any pesticide study is measuring exposure. And at the National Cancer Institute, they haven't actually gone out and taken biological measurements on each subject; but they have been very careful about getting information on duration of use, frequency of use, and intensity of use. And these are three very different types of things that go into exposure.

And the intensity includes application methods, protective equipment that the workers used, work practices, whether they might

have had a sudden exposure, an overexpose. And they've actually published about 10 studies on this study already. I mentioned that the prostate cancer was the first and only study on prostate cancer. But there are 10 other studies that have been published. And if you go to the web site, you can find out about the 50 studies they have that are ongoing based on this huge tremendous effort.

This is the largest study of it's kind ever done. I don't think I've mentioned the sample size yet, but it involves 90,000 commercial and private applicators and their spouses. One of the advantages of this study is, like the St. Gabriel study, they have been very good at doing follow-up. Less than 1 percent lost to follow-up. And that's because they have a variety of address registries, and they're doing everything they can to follow up everybody to determine vital status.

So again for the prostate cancer study, the study that was just reported, we have 55,332 males in the study in Iowa and North Carolina, commercial and private applicators. And the overall result was for atrazine an odds ratio of 0.94 for those who used atrazine in the cohort versus those who had never reported using atrazine.

And the confidence interval on that estimate is 0.78 -- let me just give it in round numbers -- 0.8 to 1.1. That's a very narrow confidence interval. And they didn't just stop at that. They also did a

test for trend. And I adapted these -- Dr. Alavanja, who is the lead director for the study at the Agricultural Health Study, kindly provided these slides by the way that I've copied from that I've just shown you.

And in the next slide, I've adapted one of his slides for a different chemical for atrazine. In the next slide, you can see the test for trend for atrazine. And you can see there were 202 prostate cancer cases with no exposure. And then they have these five groups. And the way they did it, the first two groups is one-third; the first group is one-third; the second group is one-third. And then they took the third third and divided it into three parts, one-sixth, one-twelfth, and one-twelfth, to really tease out whether high exposure might have been a factor.

And as you look at the numbers there, you see that they got fairly good numbers of cases. Atrazine is widely used, so that's not unexpected. And as you look at the odds ratios, you don't see any evidence of trend. And indeed, the linear test for trend did not show any significance. If anything, the higher exposure groups actually in three and four appeared to have a little lower point estimate. But on the other hand, the interval is wider, too, the 95 percent confidence interval.

So that shows a very different result from the St. Gabriel plant study in the respect of no evidence whatsoever in a group of farmers that would have significant exposure but very different kind of exposure from the manufacturing plant. We'll talk about that in a moment.

Let me summarize, first, the three studies that we just looked at. There was the Alavanja study, the one that we just discussed, with the 0.9, 0.8, the 1.1, based on 364 cases versus 202 that had no exposure to atrazine. There was the Louisiana manufacturing plant where, if you're just talking about -- now here, I just selected the plant employees. I didn't show you the result for the contract employees, just the plant employees. And there you see significance whether you do a comparison with Louisiana state or the industrial corridor. And, again, this includes the through-1999 data. Then we had the marginal result from the Mill study in California.

So our conclusion, EPA's conclusion from all three of these studies is that the available data do not support a likely relationship between atrazine exposure and prostate cancer. Again, the St. Gabriel study had limitations to prevent ruling out atrazine as a potential contributor. But on balance, the role for atrazine seems unlikely.

The California study we feel is inconclusive. And the

Agricultural Health Study did not support a finding of risk among farmers. But farmers are very different. They have the opportunity perhaps for intensity of exposure. But certainly they don't have the duration of exposure that the manufacturing plant had. So you need to take into account that we're looking at very different exposure scenarios between those two studies.

And that leads me to the two questions that we have for the Science Advisory Panel today. And everybody, I believe, has a copy of the full question. But I have copied just an excerpt. And just to set the stage, we'll read what it says here.

"EPA has concluded that the increase in prostate cancer observed at the St. Gabriel plant workers could be explained by the increase in PSA screening for these workers. Due to the lack of detailed exposure analysis based on job history and the limited statistical power due to small sample size, atrazine could not be ruled out as a potential cause but a role for atrazine seems unlikely. Please comment on EPA's conclusion. Please identify any additional data or additional analyses, particularly with the St. Gabriel cohort, that you would recommend that we look at."

Then the second question is: "Also, please, comment on comparing the results of the epidemiology study of prostate cancer at

St. Gabriel to the results of the Agricultural Health Study considering that participants in these two studies were likely to have experienced different exposures. Discuss what a comparison indicates about a relationship about exposure to atrazine and prostate cancer."

Now, one of the things I would like to mention before I conclude is that we did get a letter from the National Resources Defense Council. On July 7 they sent EPA a letter asking EPA to expand the scope of issues being considered at today's meeting. The National Resources Defense Council identified approximately 15 studies and reports concerning atrazine and offered their interpretation of the scientific significance of this information. In addition, they requested that several additional questions be posed to the Panel about the cited studies.

Yesterday, July 16, EPA responded to the National Resource Defense Council request in a letter explaining the basis for our decision not to broaden the scope or the charge before the Panel. EPA has made copies of both NRDC's, National Resources Defense Council's, letter and EPA's response available to the Panel. And we have also placed copies of this correspondence in the public docket for this meeting. We understand that NRDC has asked to speak during the comment period later this morning. And we hope that the letters

will be useful to the Scientific Advisory Panel as you consider the NRDC comments. Thank you.

DR. PORTIER: Thank you, Dr. Blondell.

Are there any questions of clarification from the Panel? Dr. Roberts.

DR. ROBERTS: I probably missed this in my reading. In the description of the St. Gabriel study and the stratification by exposure, did that include consideration of personal protective equipment that might be used by workers in different areas?

DR. BLONDELL: No, it did not.

ATTY2: So it was based on some sort of anticipation of ambient dust levels, those kinds of things?

DR. BLONDELL: Correct.

DR. ROBERTS: But not what they would have worn as protection.

DR. BLONDELL: Not to my knowledge, no.

DR. PORTIER: Other questions?

DR. REIF: Dr. Blondell, in your presentation you referred to the nested case-control study that is underway on a couple of occasions. Did you or your agency review the protocol for that study and comment on it prior to the initiation of the study in Louisiana?

DR. BLONDELL: Only in one sense. We didn't do a formal comment. We didn't provide written comments to them about their protocol. But when they initially came and talked to us and presented what they were planning to do, we did discuss the key thing that we wanted to see which was the exposure data, improvement on the exposure analysis.

DR. REIF: The Panel was provided a copy of a draft of that study produced by Exponent. To your knowledge is the study ongoing as the draft that the Panel has in hands?

DR. BLONDELL: Yes. My understanding is that study is underway.

DR. REIF: Thank you.

DR. PORTIER: Dr. Knobeloch.

DR. KNOBELOCH: I had a question about the St. Gabriel plant study. Has there been any statistical power calculation for that study, assuming, for example, a doubling of risk among the exposed workers?

DR. BLONDELL: I believe some of the peer reviewers may have done a power calculation as a matter of fact. I can't remember which one right now. And that would be attached to the comments to my review, my January 2003 review. But as far as the study itself

doing power calculations, I don't recall any.

DR. PORTIER: Dr. Bove.

DR. BOVE: I'd like you to expand a little bit on why we're restricted to evaluating just prostate cancer given the fact there was a recent study also at the St. Gabriel plant that found excess mortality with non-Hodgkin's lymphoma and there was a study done in 2001, looking at a sub-group of non-Hodgkin's lymphoma findings associated with atrazine as well.

There were, in the previous Science Advisory Panel back in 2000, we wanted the EPA to do a better job of evaluating the epi data. And it would seem that it would be important to evaluate these as well. So I want to get a sense of why a restriction to prostate cancer.

DR. BLONDELL: I have some additional slides that I'd like to show to help address that question.

And you mentioned non-Hodgkin's lymphoma first, and that's the one that has the most studies. So let's go with the very first slide there. Now, before we get -- I do have a slide at the very end of this that will give what occurred at the St. Gabriel study as far as the other cancers are concerned. But that was one of the comments, one of the earlier comments from the 2003 -- I'm sorry -- the 2000 review by the Science Advisory Panel. And I was going to look and quote from what

they said. But anyway, that is one of the things they said.

The very first study that sort of led to the concern about non-Hodgkin's lymphoma was the study in Kansas by Sheila Zahm, at the National Cancer Institute, et al., published in 1986 in the Journal of the American Medical Association. The main result of that study, actually, had more to do with 2-4D. And there was an earlier Scientific Advisory Panel review of that information.

But anyway, for atrazine there was a statistically significant, somewhat borderline but statistically significant, result. However they didn't find that as strong a relationship in eastern Nebraska or in Iowa and Minnesota. And then they did a combination of those four studies. And here I do want to comment on what we came up with.

The review of that study did a comparison taking all four studies into account and found that, after you adjusted for exposure to other pesticides, there was no statistical relationship, that they did not think atrazine. And, in fact, that was part of their conclusion, which as soon as I find it after a few minutes, I'll maybe read it at a later point. I don't want to take up your time by looking for stuff. But they did say that there was no significant relationship when you took all four studies together.

Now the next slide on non-Hodgkin's lymphoma, they also

looked at women in Nebraska. Did not find a statistical relationship there. But then there's a new study or a fairly recent study that came out two years ago where they looked at a subtype of non-Hodgkin's lymphoma. And that study did find again a borderline association but did find an association with atrazine. However, they found five associations. There were five different chemicals in that study that were associated with atrazine.

And so the comment was that more substantial or more analysis is needed. Quoting from the study, "We found relatively strong association between many agricultural exposures in this particular subtype." But they did not adjust estimates for shared agricultural exposure. So they are, in a sense, setting the stage for the Agricultural Health Study which will eventually supplant this.

And in the mortality study at the St. Gabriel plant which was the -- well, I should say the first one is the incidence study. They had three cancers, and that was not significant. And then the mortality study that was done, had been done earlier, they had four cases. And that was statistically significant but again very borderline.

And so looking at all the non-Hodgkin's lymphoma cancer studies together, there's conflict. We can't say one way or the other what's going on. And we know that there are two studies coming up in

the near future involving the Agricultural Health Study that will really help resolve this conflict. And so we decided not to bring this particular cancer forward.

Now at the same time that people talk about splitting cancers, for example, if we have a subtype there and it may turn out -- one of the things they'll do in the Agriculture Health Study, they'll look at that subtype specifically. But there are also other cancers. Let me give you a quick overview of those studies.

Leukemia in the Iowa Minnesota study that was done, they did not find a significant relationship. In the Mill study in California, that was not significant. Multiple myeloma, no statistical significance there. There were two separate studies in Iowa that overlap. And one is reported. The second one by Brumeistere is reported as an abstract. And that was not statistically significant for triazine use

By the way, in these slides I'm giving you studies that involve either triazines or atrazine, not studies that involve herbicides overall. So that's the hematopoietic.

But of course with atrazine, one of the concerns has been the endocrine disruption. And for endocrine-related cancers, the key one that the panel discussed was the ovarian cancer study on the next

slide. And there we did have a significant excess, 2.7. And there they used a 90 percent rather than a 95 percent confidence interval. And it's borderline significant. Had they used a 95 percent, it probably would not have been significant. But in any case, that was based on seven cases and seven controls that were definitely exposed to triazines. Three of the seven didn't actually know, recall, whether they were exposed to atrazine or triazine specifically. We just know they worked in crops where atrazine was used.

And the second result there, the county correlation in Kentucky, they developed an index based on drinking water sales and acreage and did not find a relationship. But that's another one of these ecologic studies with is subject to aggregation bias.

Then for breast cancer, again, we have two ecologic studies, both in Kentucky. And the first one, the earlier one, 1997, by Kettels, did find a significant increase. And as a result of that, they did do a follow up and developed more sophisticated measures and looked again to see if they could show whether high versus low and did not find a significant relationship.

And then there was a study of testicular cancer that was part of the Mill study. And they didn't find a statistical relationship. It was elevated for Hispanic males but not necessarily for other groups.

So that covers the endocrine-related cancers. There were a couple of others. There was one on brain cancer, not statistically significant. That was again the Mill study in California. There were a couple of studies that commented on colon cancer, triazine use in farmers. And then the other one on drinking water levels in Canada, not significant. Or in one case, a negative correlation.

And, finally, for stomach cancer, a positive correlation that was significant, fairly significant, for males. The P value was .046.

And then, finally, let's look at the St. Gabriel plant results. And, basically, what you have here, you have the problem of, I think, of the occupational mortality study in a plant. You have small numbers. For all the cancers listed on the left-hand column, there's an elevation but not statistically significant. And the elevation often would go away if you removed even one case. It's based on one or two cases at most.

And on the right-hand side, you have four cases where you have the opposite. You have a reduction. And my conclusion from looking at this pattern of data, this is not outside the realm of chance. There's nothing I can say, nothing more that I can really say. And, therefore, I've elected to recommend that this not be brought to the Panel, particularly in view of the future studies that are going to be coming

that will look in much more detail with much larger problems and avoid the problems that we've discussed. Thank you.

DR. PORTIER: I will allow continued discussion of this for a few more minutes. But since the Panel doesn't have these studies in front of them for a detailed discussion, I'm not sure the Panel can give you any type of scientific comment on your presentation or its validity or nonvalidity. I will note for the record that we will get copies of the slides and have them distributed.

Let's start with Dr. Hopenhayn, and then we'll come around.

DR. HOPENHAYN: Yes, actually, my question or comments is not related to the presentation but related to one article that I believe was in the package we received today which is the prostate cancer paper by Mills and colleague which is a case-control study of prostate cancer. And I wonder if the Agency has any comments on that.

DR. BLONDELL: Let me locate my copy of that study so I can comment properly on it.

DR. PORTIER: While you're looking for that, I'll ask Dr. Handwerger.

DR. HANDWERGER: I have a question other risk factor among the people --

DR. PORTIER: Microphone, please.

DR. HANDWERGER: -- in the St. Gabriel of family. Among the young people who were the ones who had the remarkably increased incidences, was there a increase of family history of prostate cancer among those patients?

DR. BLONDELL: I'm sorry. Could you repeat that question?

DR. HANDWERGER: About other risk factors in the St. Gabriel population who got prostate cancer, I'd like to know about family history. Particularly among the young people who had the highest risk to develop prostate cancer, was there an increased family history relative to the general population?

DR. BLONDELL: I don't recall any discussion in the study of prostate cancer history for those 17 cases. So I don't have an answer to that question. I'd have to go back and look, and I don't recall. So I don't know the answer.

Let me go back to the earlier question, though, now, if I may, on the study that just came out this year on prostate cancer risk in California farm workers. One of the advantages of this study is that it involves the cohort of the United Farm Workers Union. And the comparison is within that cohort as to whether they were or were not exposed to a pesticide.

But the way they measured whether they were exposed or not

exposed to a pesticide is that they selected 16 pesticides in advance and they got data on the total pounds of active ingredient from the early 1970s through the year 2000 for these 16 pesticides. And they selected them on the basis of whether they were a B2 carcinogen based on EPA's evaluation, Proposition 65 in California, which evaluates carcinogenicity. And apparently, I think, they also took volume of use into account as well.

And this study did not look specifically at atrazine. However, it did look at simazine. One of the things -- and for simazine, they did have a statistically significant elevated risk of 1.5. Again it was borderline. The confidence limit was 1.02 to 2.3. And one of the problems I have with this study is that if you compare atrazine and simazine in California, it's confusing how come they didn't do atrazine again since the earlier Mill study had found a significant result in black males for atrazine. But they didn't. They didn't include it in the later study. And I think the reason is probably because of the fact it's just not widely used enough to warrant analysis on.

Simazine, on the other hand, I looked it up. And there are over three-quarter-of-a-million pounds applied in one year. Principally, over half of that was to grapes and citrus. And grapes and citrus are two crops that get heavy pesticide usage, particularly insecticides and

fungicides. Now the simazine that would have been used on these two crops was a herbicide. And the exposure would have been to the soil, not to the foliage, not to the grapes, not to the trees.

And so the question comes, well, the United Farm Workers that go to these crops are doing primarily thinning and harvesting. They're not doing -- they may be, some of them, doing application. And we don't know, of course, who had which exposure. But we do know that there were many other pesticides that simazine would be an indicator for. So the fact that they just looked at the 16 and didn't look at all the other exposures -- I mean, there are so many other things that it could have been that they didn't study, I really can't put a lot of weight on a study like that.

DR. PORTIER: Dr. Merrill

DR. MERRILL: I also wonder if they considered the multiple comparison problem, that there was an inflated type or the probability of a type one error especially given that this was just a marginally significant result for blacks. And it's also interesting to me that it is just significant for blacks and not significant across races.

DR. BLONDELL: Well, now you're talking about the earlier Mill study, not the study I just talked about.

DR. MERRILL: Right.

DR. BLONDELL: And you're right. The way they dealt with -- in the earlier study what they did they only had six pesticides and, a priori, there was a suspicion of carcinogenicity. And that was the justification for even though they had the multiple comparison problem. In the later study, they had, you know, 16 again, but a priori, some suspicion that these were carcinogens.

DR. PORTIER: Dr. Isom.

DR. ISOM: With regards to the St. Gabriel study, I have two questions. First, it seems to me that not only the level of exposure based upon job classifications is important or could be an important issue but the duration of employment in that position or total duration of employment in the plant. Has that been taken into consideration?

DR. BLONDELL: Yes. The exposure measurements that I presented earlier actually do take into account both job category and the duration together so that they would cumulate. That was the part of the second exposure method that I had up there was to cumulate the exposure and to assign this relatively arbitrary value of order of magnitude difference so that they could come up with a sum total. And that's what resulted in identifying three cases as high exposure, four medium, five low.

DR. ISOM: Secondly, looking at the information in the

publication, it considered employment after 1985. Was that when the study started? Yet the plant started production of atrazine with triazines pesticides -- when was it? -- in the 1970s.

DR. BLONDELL: 1970.

DR. ISOM: So there's a 15-year period before the study started.

DR. BLONDELL: Right.

DR. ISOM: Has there been any follow-up on employees that perhaps were in that period of time before the study was initiated that may have stopped employment?

DR. BLONDELL: That's an interesting --

DR. ISOM: And moved on.

DR. BLONDELL: Right.

DR. ISOM: Because these are the longer term people, aged employees theoretically where you would see perhaps a higher correlation of prostate cancer.

DR. BLONDELL: It would be nice to be able to do that. That would be an ideal situation if you could. But in order to do this study and do a proper comparison, they wanted to have a sound like basis for collecting the information. And that meant they have to rely on the Louisiana Tumor Registry. And the general consensus was that until -- I forget the exact year -- 1986 or '87, that wasn't uniformly in place

around the entire state to the point that you would want to rely on any data prior to those years. So in order to collect the information fairly, both on the comparison and on the workers at the plant, they had to wait until that tumor registry was up and running.

DR. PORTIER: Dr. Knobeloch.

DR. KNOBELOCH: I also have a couple questions about the St. Gabriel plant study. The first is regarding screening frequency. And I'm just wondering. It appeared to me from what I read that screening frequency was similar among all three exposure cohorts. And I just wanted to confirm that that was the case.

DR. BLONDELL: Yes, that would be the case. All the employees had, as far as we know, equal, over 90 percent.

DR. KNOBELOCH: My other question was, if you look at the prostate cancer rate among the men that were classified as low exposure, how did that rate compare if you did age and racial matching to the industrial corridor of Louisiana?

DR. BLONDELL: We don't know. We didn't have them calculate prostate cancer on that basis, so we don't know the answer to that. That's one of the things that the nested case-control study should do, however, is enable us to say, well, for the low, what is their rate compared to the industrial corridor. Is it equally as high?

And I think the answer would be, you know, preliminary information suggests that might be the case. But we have to wait and find out.

DR. PORTIER: Dr. Young.

DR. YOUNG: Yes. It appears from the reading that the PSA screening began at a high level around 1992 or 1993. I was wondering if you knew if there were any plans or discussion about subdividing the analysis and looking at those cases that were before 1993 as opposed to those cases that were after. I know there might be a sample size problem, but I don't know. Has there been any discussion about that?

DR. BLONDELL: As a matter of fact, there most certainly has. And unfortunately the screening is actually earlier than that. I think it's 1989 that it started. And basically all the prostate cancer cases, except for perhaps one or two at the most, and I have to admit, I haven't been able to double check on a couple of cases, but basically for nearly all of the cases, they did have PSA screening. I know what you're leading to which is wouldn't it be great if we can compare the ones that did have screening versus the ones that didn't and do a comparison. But unfortunately there's not a sample there to do that kind of comparison.

DR. PORTIER: Dr. Bove.

DR. BOVE: Maybe I don't understand Table 4 in the study. There it seems that the testing really gets off the ground and tests a high percentage of workers starting in 1993. Before that, hardly anyone is tested in any of the age groups according to Table 4. And then there were also five cases, I think, of prostate cancer with about two or so expected before 1993 -- or four or five depending on which document I was reading at the time. So I'm a little confused as to why you keep saying that the testing started in earnest in 1989 when the intensity really started in 1993 according to this table. Am I interpreting this properly?

DR. BLONDELL: I'm not sure. Let me look at the table again. Actually, we might even pull up that slide so we can look at it. That would be number 15.

That's not the one that gives it by time line, though. Let's see.

DR. PORTIER: It's slide 12.

DR. BLONDELL: Yeah, that's right. Well, again, you're right. It starts in 1989. I don't have data for you. And I think there is data available, actually, in an appendix to the technical report that tells the percent employees year by year that were screened. And I would refer you to that table. That's in the appendix to the St. Gabriel Technical -- the thick report, the 170 page document. There are different tables

at the end that give the rate of PSA screening for the cohort through the years, year by year.

DR. BOVE: I didn't see that. But is it different than the information provided in Table 4 of the published article?

DR. BLONDELL: Not that I know of, no.

DR. PORTIER: Dr. Sandy.

DR. SANDY: Just a follow up with the question Dr. Young asked. I remember reading, maybe it was in the technical report, that of the prostate cancer cases, they had about five detected before screening started in earnest and then six while it was gearing up and then another six, if I remember correctly, in the last two years of extension. And I'm wondering, did I hear you say that all but maybe one of the prostate cancer cases had PSA testing screening?

DR. BLONDELL: Yeah. I will say the information that I've seen in the report except for at most one or two, they all had screening, yes, prior to diagnosis of their prostate cancer.

DR. SANDY: At the plant.

DR. BLONDELL: At the plant.

DR. SANDY: Because that doesn't seem to correlate with the information presented in Table 4 of the publication. And then in the appendix, what is very few people that are being screened in those

early years. I wonder, do you have information on the age of diagnosis?

DR. BLONDELL: Well, there may have been fewer people screened in those earlier years. But the few that were screened were where they located the prostate cancer cases is my reading of the report.

DR. MERRILL: Nationally, PSA screening took off, I guess, was approved by the EPA in '87, '88.

DR. BLONDELL: EPA doesn't --

DR. MERRILL: I mean the FDA. And Artie Petoski did a study that showed about 21 percent of the population in, was it '89, by that point had adopted PSA screening. By in 1992, it was up about 30 percent according to a study by Ed Cioni, it was up around 50 percent by '94. And so even though the company offered PSA screening widely in '92, I'm sure quite a few of these men were receiving PSA screens prior to '92.

DR. BLONDELL: Yes. And the other thing that -- one of the other studies particularly I remember the one in Olmstead County in Minnesota, they noted that there was a three-fold, three-and-a-half-fold, I think it was, increase in prostate cancer incidence that they felt was associated with the increased detection

due to the screening.

And part of my question to the Panel, then, is okay, well, if you can screen 50 percent and get a three-fold increase, can you screen 90 to 100 percent and get a six-fold increase. That's part of the question that we're asking.

DR. PORTIER: For the record, the previous commentor was Dr. Merrill. And I would note that we're recording this. And in order to get the minutes straight, make sure either I announce your names or you use it so we get it exactly right.

Just for my clarification on the issue we're talking about here, do you actually know whether the prostate cancers that were seen in the St. Gabriel plant were identified through a PSA screen, confirmed through a PSA screen, or identified in some other way in terms of initial diagnosis of potential prostate cancer?

DR. BLONDELL: It wasn't spelled out as clearly as you phrased your question. I wish it had been so that I could say affirmatively. The indication is that, yes, the way these cases were identified was by that. But, no, I don't know the answer to that question specifically.

DR. PORTIER: Any other questions for clarification from the Panel? Dr. Symanski.

DR. SYMANSKI: In the supplemental data that was received on the regular employees who were diagnosed with prostate cancer, was any information provided on whether job titles changed over the worker's working history; and if so, how exposures were classified particularly if the job titles were categorized into different job categories based on proximity to where atrazine was manufactured, handled, or packaged? And then I have another question.

DR. BLONDELL: Yes, they did, certainly, take into account the fact that people would change jobs from time to time and recategorized them. And then did that cumulation to come up with what percent of time did they spend in a job that was high exposure versus low exposure. And then the other thing they did was the second method. Which again, depending on what the job title was, they might have had a job title that was remote and then suddenly had one that was high. But then they would cumulate that to the time of prostate cancer diagnosis.

DR. SYMANSKI: The second question, as I understand it, the exposure data that were collected at the plant were collected using what's commonly referred to as the "worse case sampling approach," not only workers whose exposes were presumed to higher were sampled most often. Was any information given as to how they came

up with the relative rankings which I think indicated about a thousand-fold difference in exposure between the lowest to the highest job category?

DR. BLONDELL: Was any information given on --

DR. SYMANSKI: As to how those relative rankings were determined?

DR. BLONDELL: No. No, they were not.

DR. PORTIER: Any final questions for clarification? Dr. Herringa.

DR. HERRINGA: I have a modest amount of exposure to prostate epidemiology studies through a study that we did in Genesee County in Michigan. And I'm sensitive somewhat to the race ethnicity issue particularly as it applies to African American populations. And I presume that Tables 19 and 20 in the Syngenta report break down the PSA testing experience in terms of total employees and percent tested. It's quite evident if you look at this high age group that a heavy amount of testing occurred within the African American or nonwhite workers in this plant.

That, again, depending on -- I don't want to speak to the progression of disease and disease course because that's not my area of expertise. But I'm concerned a little about the estimation of these

standardized index ratios particularly if the plant worker population is substantially different from the standardized population. Have you seen the calculations for those indices?

DR. BLONDELL: I'm going to say from what I know about the demography of Louisiana and the surrounding industrial corridor, I would expect that they would be fairly similar. There wouldn't be that much difference.

DR. HERRINGA: Okay. It's a question and a concern. Because we have certainly a differential ascertainment bias here through the PSA screening mechanism for African American men.

DR. BLONDELL: Right.

DR. HERRINGA: And that would follow the American Cancer Society guidelines and plant policy here evidently, too. If there were in fact highly differential employment ratios in combination with this differential ascertainment bias -- these are just issues that I don't have explanations or I'm not going anywhere with it other than to understand this from a mathematical and an estimation standpoint.

DR. BLONDELL: Right. It certainly could add to the questions about comparability.

DR. PORTIER: Dr. Hopenhayn.

DR. GOLD: I'm Dr. Gold.

DR. PORTIER: I'm sorry. Dr. Gold.

DR. GOLD: This is sort of a follow-up to Dr. Sandy's and Young's question. When I look at the 2001 report in Table 20, it shows that by 1994, certainly by 1995, the screening is at 100 percent for everyone, all men, over 45. And I think that what the point was that was being made earlier is that there's a five-year period of '89 to '92 that had five cases; and in a five-year period '93 to '97, that had five cases. And then just a two-year period of '98 to '99, just two years, when they will six cases. By then they were already up at full screening for several years, 100 percent screening.

So is there some explanation? Granted we're missing denominators and a reasonable way to get expected numbers of cases. But why you would expect in half the amount of time, less than half the amount of time, to see an additional case even?

DR. BLONDELL: That's a very good question. I hadn't noticed, hadn't focused on the timing year by year like that. Yeah, I don't know. That's a very good question.

DR. PORTIER: Okay. I think we're going to move on. There's still an opportunity to ask any remaining questions as we move into the discussion this afternoon. But I think it's time we go ahead and proceed. It's now 10 minutes after 10. We're going to go ahead and

take a 10-minute break instead of a 15-minute break. And we'll be back at 10:20 to start the public comments. Thank you.

[The morning break was taken;

conference resumed at 10:22 a.m.]

DR. PORTIER: Thank you all for coming back from break. Our first set public comments in morning will be presented by Syngenta Crop Protection and their expert panel. Dr. Charles Breckenridge, I assume, will introduce the members of the panel and their affiliations. I've been told that you would like to run through the entire panel before we have questions from the SAP. And I assume they will all sit up here when we start the question and answer period. I would note that you take down your notes on questions, and we'll come back to all of the presenters at the end. Dr. Breckenridge.

DR. BRECKENRIDGE: Thank you. I'm Charles Breckenridge. I'm a senior researcher Syngenta Crop Protection, and I'm here today to discuss the prostate cancer questions that are before the SAP. We have with us a number of people, both from the human safety assessment group, who principally worked on the mode of action research for atrazine. And our entire epidemiologic panel who was charged with the task of conducting the case-control study. In fact, I would invite those panel members to come to the table right now so

that we can proceed in an efficient way once we get into the presentation. So if you'll just give us a minute.

While they are coming to the table, I'll just introduce who the members are. And I'll let the chairmen of the subgroups actually introduce their own panel members as we proceed through this.

As I had discussed, we had two principal groups of activities associated with atrazine. We had a long time activity associated with mode of action research. And we had a number of expert advisors who helped design and conduct and interpret studies in mode of action research. Some of that was discussed in the year 2000. And we're going to present a little bit more today relative to the prostate cancer and the question of plausibility of getting a prostate cancer effect with atrazine.

Just to run through this, Dr. Simpkins is chairman of the panel. And he will be speaking today for that group: Dr. Mel Anderson, Dr. Brusick, Dr. Eldridge -- next slide please -- Dr. Steven Safe, Robert Sielken who is here today as well, James Swengberg, Lee Tyrey from Duke.

And now I will go just briefly to the second group of experts that we have today. And this is an independent group of science who were charged with the question of conducting and designing and

interpreting the case-control study. This group is headed up by Dr. Mandel. The members of the group are Dr. Adami, Dr. Colditz, Dr. Hessel, Dr. Pastides, Dr. Smith, and Dr. Trichopoulos. All of these individuals are here except for Dr. Colditz, and they will be available for detailed questions as we get there.

Briefly our plan for this morning is to try to go with some efficiency and speed through a rather complicated set of information. I'm at the introduction right now. Dr. Simpkins will follow with a brief discussion of biologic plausibility. We expect that should take about a total of 15 minutes. Then Dr. Mandel will review some of the information that Dr. Blondell has already presented relative to the Delzell Epidemiologic study. We will follow up with Drs. Adami and Trichopoulos talking briefly about PSA screening bias. Drs. Hessel and Smith will actually present the results of the case-control study which we have just, by the hard work of these gentlemen, managed to get this put together for this day's meeting. And, finally, Dr. Pastides will comment on the Ag Health Study and summarize the overall viewpoint of the expert panel.

We will then be available for questions on any and all questions that the Panel might have here. We noted several questions this morning for which we probably do have the answers, and we'll come

back to those. And perhaps those that were answered this morning maybe could be readdressed to us.

Basically, beginning in 2000, the Science Advisory Panel considered a mode of action related to the occurrence of cancer in the female Sprague-Dawley rat. And first most important point about this consideration is that there's not a genotoxic mode of action operating. And that is important for not only mammary cancer in the rat but also for all cancers in humans. And we just wanted to at least make the Panel aware of that decision both by the SAP and the EPA.

In regard to the specific cancers in the female Sprague-Dawley rat, there was a mediation through a pituitary-hypothalamic axis effect. It translated to higher exposure to endogenous estrogen which people believe would not occur in the human under these conditions. And, therefore, the female Sprague-Dawley rats results were considered unique and not relevant to humans. At that time, the SAP and the EPA concluded that atrazine should be classified as not likely to be a human carcinogen.

We are now going to turn to the attention the animal bioassay work relative to the prostate specifically. And we have a large battery of studies where prostate was certainly part of the examination. And in all of these studies, except for perhaps one that we have seen, the

prostate is not indicated to have been a target organ.

There are shorter-term studies at higher doses, specifically developmental studies, where we do demonstrate an effect of atrazine on the male reproductive system. And specifically Dr. Zerkin from Johns Hopkins University in collaboration with us has conducted a study on high doses of atrazine to male development. And we observed reduced testosterone levels, prostate weight, and a delay in onset of puberty as demonstrated by a delay in preputial separation. This has been described extensively by us as well as by EPA scientists in the Research Triangle Park.

Secondly, also in that group at the Research Triangle Park, Stoker, et al., conducted a study where they observed prostatitis in male rats that had been exposed -- or not exposed to atrazine but whose dams have been exposed to atrazine during lactation. And the interpretation of this finding was that the effect on the mother was consequent to a prolactin reduction. And that prolactin reduction impaired lactation, in fact, in these animals; but it also, according to the interpretation that was rendered, caused a failure of transfer of prolactin to the rodent through the mother's milk. And that had secondary effect later in time on the prostate.

We have presented a paper today that discusses the role of

prostatitis and prostate cancer in humans for your consideration.

Just so you have a concept of the dosimetrics relative to these no-effects level in animal studies versus the expected point estimates of exposure coming from different sources in the environment, we start with an LD50 for the product of about 3090. The mode of action research studies generally are conducted in the range of 100 to 300 milligrams per kg. And these are short-duration studies, which, if you attempted to administer those compounds at those levels for long duration, the animal would not survive. So these mechanistic studies are effectively done at very high doses.

The longer term studies that are typically done in toxicology are done at more modest doses. And the no-effect levels for the most sensitive studies conducted are represented there.

And it should also be noted as far as human cancers in the prostate, the rodent isn't a particular good model. The dog is the only other species that gets prostate cancer spontaneously other than man. Rodent models can be developed to elaborate prostate cancer under special conditions especially with mutagenic substances and promoters combined.

In regard to exposure opportunity, point estimates of production worker exposures coming from the urine monitoring program which

people have probably read about and some of the background material. We made a guesstimate of range of possible doses in those production workers from those urine monitoring programs. And I should say that urine monitoring and the characterization of internal dose for atrazine is based on a fairly good and solid knowledge about metabolisms and metabolites. In some of these studies, we have up to 30 percent of the total applied dose accounted for as we're calculating or back calculating total atrazine dose as measured by 24-hour urine collection.

In regard to pesticide handlers, because the Ichouse study has been underway and is underway, the range of exposure in those individuals is obviously less as indicated here. It's for a shorter duration of time during the year. These point estimates here are based on a study we did in Iowa and a second state which I don't remember off the top of my head. But there's approximately 125 workers there where we collected 24-hour urine samples over three days. And these are the estimates of atrazine burden in those individuals.

You can see that we're looking at approximately two to three orders of magnitude difference between the no-effect levels and the highest expected exposure for agricultural workers and production works.

With respect to incidental exposure via drinking water and diet, the differences are as many of seven orders of magnitude between no effects and the occurrence of exposure.

Finally, just to conclude relative to this section which has to do with toxicology and plausibility, we perceive that, if anything, there would be reduced androgenic stimulation of high doses of atrazine on the prostate, and we would expect that there would be actually, if anything, a decrease prostate cancer risk. There's large margins of exposure between human exposure and the no-effect levels from these animal studies. And that also comes to play into consideration in terms of relative risk.

I'll turn the presentation over now to Dr. Simpkins who will elaborate a little bit more on some of the animal data. And then we'll go to Dr. Mandel.

DR. SIMPKINS: What I'll be presenting is really the result of now approaching a decade of work on the part of our mode of action panel, first, to deal with females toxicity issues and then later with male issues.

In 2000, the Scientific Advisory Panel as well as the EPA agreed that this was the likely mode of action by which atrazine was affecting reproductive function in rats. Atrazine appears to be

working at the level of the hypothalamus through most likely neurotransmitters or neural peptides to have two major effects. One is to reduce the secretion of GnRH, or gonadotropin releasing hormone, which thereby secondarily reduces LH secretion and in males results in a reduction in testosterone secretion.

A second action described by Dr. Ralph Cooper's lab is that atrazine appears to increase activity of tuberil and fendibular dopamine neurones which then reduce secretion of prolactin. And then that reduces a trophic influence in males on the prostate gland.

The panel assessed in males, and that's what will be presented today, a variety of potential mechanisms or modes of action of atrazine. And we will conclude at the end of this that this is the most likely mode by which atrazine is having its affects, if any, on prostate.

Now, there have been conducted a variety of subchronic, chronic, oncogenicity, and reproductive studies using both rodent models as well as dog models. Testing concentrations of atrazine up to 25 to 50 milligrams per kilogram per day. And in some studies, for as long as two years.

To date there have been 14 studies in rodents and four studies in dogs. And the overall, the observations that have been made are on organ weights and histopathology. And today we talk simply about

the testes and prostate. In all those studies with one exception at one very high dose, a thousand parts per million, there were no effects of atrazine on organ weights. There were no histopathological observations in the prostate. And in none of the studies was there any evidence that prostate cancer occurred in the rodents or in dogs.

The panel recommended that a series of studies be conducted to look specifically at atrazine effects in developing male rats. And so Barry Zerkin at Johns Hopkins University designed; the panel reviewed, revised. And then he conducted a study in which atrazine was dosed to male Sprague-Dawley rats. Doses ranging from 1 to two hundred milligrams per kilogram from post-natal days 22 to 47. Animals were sacrificed on day 48, 24 hours after the last atrazine dose. And then a variety of indicators of male reproductive function were assessed, and the results are summarized here.

At doses of a hundred milligrams per kilogram per day or higher, the observation was that there was a reduction in serum and intratesticular testosterone; there was a decrease in ventral prostate and seminal vesicle weights; there was a decrease in the serum luteinizing hormone; a decrease in sperm count; and a decrease body weight.

And these are the data or part of the data from that study. And

shown in the top two panels are ventral prostate and seminal vesicle weights, again at the hundred to 200 milligrams per kilogram per day doses. There were reductions in weights of those two androgen-responsive tissues. Consistently at those two doses, there was a significant reduction in serum testosterone. And at the highest dose only, there was reduction in sperm count in these animals.

Now the panel noted that the doses of atrazine at which these reproductive effects were happening were a hundred to 200 milligrams per kg. And those were the same doses at which body weight gained during this critical developmental period was happening. So we recommended that a study be done in which the body weight gain reduction was matched by pair feeding a separate control group. And these are the data, the matching of body weights at the end of the study to that seen when atrazine was administered.

And the question being asked here was what part if any of those reproductive effects were contributed by this reduction in effectively growth of the animals over this period.

And the results are summarized here. There was in the food restrictive group a significant decrease in both serum and intratesticular testosterone. Most of the reduction in androgen levels, circulating androgen levels, could be accounted for by the weight gain

reduction seen during development. And most of the reduction in prostate and seminal vesicle weights as well as in serum LH levels were also secondary to the weight reduction.

And here are the results from that study. This is for intratesticular testicular testosterone levels. That is the amount of hormone in the testes. This is the reduction seen with a hundred milligrams per kilogram per day of atrazine. This is a reduction achieved by simply matching body weights to those in the atrazine group. The same is true for serum testosterone, where not all, but a good part of that reduction seen appears to be secondary to body weight loss.

Seminal vesicle weights were reduced similarly as were ventral prostates and serum luteinizing hormone when the atrazine animals were paired for body weight gain reductions.

Now, mode of action of atrazine. This slide shows the regulation of testicular testosterone secretion. The hypothalamus is the ultimate regulator of the testes in males through, again, this GnRH secretion, which stimulates anterior pituitary gonadotropes to secrete LH. LH then acts on special cells in the testes called Leydig cells, which in response make and release testosterone. Testosterone then feeds back on both the pituitary and the hypothalamus. This is a

negative feedback loop. And the testosterone then shuts off this axis.

The observation from a variety of studies is that at a NOEL of 50 milligrams per kilogram per day of atrazine which, by the way, is at least a thousand times higher than the expected maximum human exposure to that herbicide, atrazine blocks the release of GnRH from the hypothalamus. Secondarily, reduces LH secretion, which then reduces secretion of testosterone. And we believe it's this reduction in testosterone that accounts for the reduction in androgen-responsive tissue weights in those animals.

Now, the panel went through a series of iterative thinking processes and review of the literature to ask the question, if atrazine were doing a number of other things in this loop or in the effects of testosterone on androgen-dependent tissue, would we get -- we can predict the results that we would get and are they the same as the empirical results that have been generated in studies.

And this is used as one example of five or six processes that we looked at. Here the proposal is that atrazine is interrupting the negative feedback of testosterone on the hypothalamus or pituitary depicted by these red lines. Now if that happens, the following would occur. You would get an increase in secretion of LH; and, secondarily, an increase in the secretion of testosterone. One would

see an increase in weight of the testes and the prostate if atrazine were working on this.

The fact is that one sees the opposite, that is, atrazine is decreasing LH and testosterone and decreasing the weights of androgen-responsive tissues. And through all of these processes, we came to the conclusion that atrazine is indeed affecting release of GnRH; and that LH, testosterone, and changes in reproductive tissues are secondary to that mode of action.

Now, the conclusions of the panel relative to male reproductive effects of atrazine are indicated here. The likely mode of action is in the hypothalamus or pituitary with a reduction in GnRH; secondary reduction in LH and then testosterone. High doses of atrazine do indeed reduce testosterone levels in male rats. The reduction in androgens are not a risk factor in prostate cancer. In fact, the opposite is true. And this is supported by a variety of clinical data because the major clinical approach to the treatment of prostate cancer is to try to reduce androgen stimulation of the prostates either by reducing its conversion to dihydrotestosterone through alpha reductase, by antagonizing androgen receptors, or by shutting off release of GnRH either with agonists or antagonists.

So our conclusion is that we can identify no biologically

plausible mechanism by which atrazine leads to an increase in prostate cancer.

DR. BRECKENRIDGE: Thank you, Dr. Simpkins. We'll now turn the presentation over to the chairman of the epidemiologic panel, Dr. Mandel. And he will take us from there. Thank you.

DR. MANDEL: Thank you, Dr. Breckenridge. Mr. Chairman, members of the Panel, thank you very much for the punt to present the results of our work. I'm going to review briefly, and I will make it brief since Dr. Blondell did a very good job of reviewing the St. Gabriel plant study. Not knowing what was going to be shown today, I did prepare an overview of the published study at the St. Gabriel plant. I'll run through it. I'd like to just highlight a few points, some of which came up as questions during the earlier presentation. I'll try to respond to some of those as best I can recall them in going through this.

Then I would like to ask Drs. Adami and Trichopoulos, both prominent cancer epidemiologists, who have worked in this area for many years. Dr. Adami recently has published in the New England Journal of Medicine on prostate cancer, to address the issue of the PSA testing of prostate cancer.

And then Dr. Hessel and Dr. Smith will provide the results of

the nested case-control study. In anticipation of this meeting, we accelerated the work on that study and we are able to share you with today the results of that study. And then Dr. Pastides will provide some summary comment.

Just a quick comment on procedure and how we carried out this activity. Initially, we reviewed the report of Dr. Delzell on the epidemiologic study at the St. Gabriel plan and addressed in particular the issue PSA testing. And we submitted a report providing our findings on that evaluation. And concurrent with that, we initiated the case-control study to look at exposure.

In the course of setting that up, we appointed a scientific advisory panel changed by Dr. Pastides, who is the dean of the Arnold School of Public Health at the University of South Carolina, the interim vice president for research. And the advisory panel consisted of Dr. Pastides, Dr. Trichopoulos, Dr. Adami, and Dr. Smith, who is well renowned in the area of retrospective exposure assessment in these kinds of undertakings.

So if I may, I'll go through this fairly quickly since you've seen most of this. But I would like to just highlight a few things.

The background the Novartis Crop Protection plant, also known today as Syngenta, began in 1970. There was an unpublished study of

cancer incidences from '85 to '93 that was referred to earlier by this panel reported five observed prostate cancer cases and two expected. The PSA testing program quite unique in my experience to have been introduced a program that early and to have been so successful in getting virtually a hundred percent of the men to participate least once in the program. The current study was published in November of 2002. And the study largely was focused on trying to evaluate the impact of the PSA testing program on the increase in prostate cancer incidence.

The exposure classify classification, and this is what was used in the published study. This does not relate to what we did in the case-control study. But as Dr. Blondell mentions, there were three groups essentially, the company employees, the contract production employees, and the contract maintenance employees. These were the three groups that were used by Dr. Delzell in analyzing the results of the study.

It was a retrospective core incidence study from '85 to '97. They subsequently had reports on some additional cancer cases in '98 and '99 that Dr. Gold referred to. To construct the cohort, they used computerized records and hard copy corporate records. They had detailed information on job title and work areas for the Novartis

employees. These are data they reviewed, but they did not abstract and did not use them in the study itself. 2,213 workers identified. A few were eliminated because they weren't eligible. And there were 2,045 in the core for analysis.

The inclusion criteria, this issue about 1985 just to clarify, that individuals who worked from 1970 were included in the study. To be eligible, they had to be resident of Louisiana in 1985. So the study does include to the response to the question earlier, it does include workers who worked there prior to '85 and left so long as they were resident. They had to be resident in '85 in order to be eligible for detection in the tumor registry. The tumor registry was the primary means used to detect incidence cases of cancer from '85 through '97.

These were selected because they worked in jobs involving the potential contact with triazines or precursor chemicals. And this defines the three groups. The company employees worked any time since 1970; the contract production employees, any time since '77; contract maintenance employees, any time since 1983. And the reason for those dates as explained in the paper is that's when the records were available through which they could identify the worker.

As Dr. Blondell pointed out, just over a third of the workers were actual employs of the company and about two thirds were the

contract workers.

For the cancer cases, they were diagnosed between '85 and the end of '97 which were the years for which the Louisiana tumor registry had incident data available. They focused only on invasive cancers. They excluded only the nonmelanoma skin cancers. They had to have been diagnosed after starting work at the plant and before any known or estimated exit date from Louisiana. I think the authors of the paper did a remarkable job of trying to establish residency, used a lot of different sources such as driver's license records, Lexus-Nexus, death certificates, to try to establish the residency on a particular date for everyone in the cohort who was no longer actively employed.

The incident cases were identified, as I mentioned, largely from the tumor registry. They looked at plant medical records. The cases that were identified through the plant medical records were also in the registry. And they also checked death certificates. And there was death, an esophageal cancer death, that was included. The death occurred post 19 -- it actually occurred in 1990. And they made a decision, based on an estimate of survival for esophageal cancer, that the case could have been diagnosed post '85. So there's an esophageal cancer case in there that was ascertained from the death certificate.

They calculated the standardized incidence ratios. They

compared the incidence rate of the cohort to that of the general population of the corridors as Dr. Blondell pointed out. In the report, they present results for both the state and the corridor. In the published the paper, they elected to present only the corridor. This was largely used by the Louisiana Tumor Registry. They thought it better represented the area from which the workers would have been drawn and, hence, would be more comparable. But the results tell essentially the same story.

Here are the results. Again you've seen these earlier. There were 46 total deaths and 40 expected from all cancers. I'm sorry. Cases not deaths. Prostate you see the elevation, the SIR of 175, the confidence limits lifts which include 100 for the corridor comparison. And it's interesting to note that if you subtract the prostate cancer observed and expected from the all-cancer observed and expected, then the remainder, which represents all other cancers observed and expected, are about the same. And you see that the increase in prostate cancer is largely in the Novartis employees.

The contract workers, the SIRs are 129 and 108 respectively compared to the employees with the 217. So the 175 is largely driven by the employee finding.

Dr. Blondell showed you these data. They're most interesting.

Drs. Adami and Trichopoulos will comment later on the age issue. But you see in particular the excess is driven by the cases at a younger age under the age of 50, particularly under the age of 60. And you see actually a deficit based on only a single case. You would have expected almost three in the men over 60 years of age.

The authors broke down the data by year since hire to get an idea of latency and years work to get an idea of dose, a proxy for dose, using duration, years of employment. And their interpretation of these data was that you do not see the patterns typical of an occupational exposure where you'd see higher rates among those who worked on average longer and might be expected to have a higher dose. So this was an indication to them that this argued against a work-related exposure.

They also looked at employment status. And as you can see, again, the excess is driven almost entirely by active employee as opposed to inactive employees. Of course, the active employees, you have to be an active employee in order to benefit from the PSA testing program.

So a summary of results, the SIR is elevated at 175. It was significant statistically for overall cohort aged 50 to 59, for company employees, age 50 to 59 and, for active employees. Ten of the eleven

observed cases in the published study occurred in men with 10 or more years since first hire.

PSA testing program, it started in '89. It really expanded by '93. And the rates of testing were exceedingly high from that point forward. It was offered to all men over the age of 50. It was offered initially to younger men at the discretion of the plant physician. In '94, they offered a digital rectal exam to all men age 40 and older. PSA was offered to all men age 45 and older. And there was a question about family history. And Dr. Blondell respond appropriately. We don't have data on family history. It wasn't collected to my knowledge in the study. And I have no data other than what's in the published paper or the report. But they were offering the PSA testing to younger men 40 to 44 if they had a positive history of prostate cancer or if they were African American. So it may be that some of the three cases that were diagnosed in the men under 50 may have resulted -- may have. I don't know. But may have resulted from individuals with one of those risk factors.

The participation was high overall. It was fairly low prior to 1993, about 20 percent, but probably relative to the general population. It may have been in the similar ballpark. After '93 you see what happened. It approached a hundred percent in men over 45,

38 to 43 percent in men aged 40 to 44. And by the end of '99, the proportion of men in the study who had at least one PSA test, 86 percent for those who reached age 40 while actively working and 98 percent for those who reached aged 45. A remarkably successful program.

In the paper, they provided some data on the stage of the tumor based on the SIRD designation, for stage, localized, regional and distant. They pointed out that 9 of the 11 tumors were localized, 82 percent, which was quite a by the higher than was what seen in the State of Louisiana. Sixty-percent of tumors in the State of Louisiana were localized. And not unlike what you see in a screening program is you see a shift in the stage towards earlier stage cancers.

There are a number of observations that the authors believed were consistent with the screening or surveillance effect. There was an unusually young average age of diagnosis of prostate cancer. A median age of 51 in the U.S. The average age is about 73. All the 9 cases, of the 11 cases, they had medical information on 9. And there was a question about how many of the cases were screen-detected. And this is perhaps as close was we can come to an answer. Nine of the case, that is all nine for whom they had medical information, were asymptomatic at the time of diagnosis suggesting that they were

probably screen-detected. But we don't know for certain.

Eighty-two percent of the cases were localized at diagnosis, an unusually high percentage. The increased incidence of prostate cancer was concentrated in the company employees who were actively working. And these men were more likely to have worked for the company longer and, therefore, had more opportunities for PSA testing.

The medical surveillance of these workers may have been greater than that of contract workers and that of the general population. We certainly know it's greater than the contract workers. The authors addressed the issue of screening the general population. Their conclusion was that the screening at the plant was considerably higher than the general population, but there was no specific data for Louisiana. They looked at some other states like Texas where I believe the rate was 37 percent. They then looked at the incidence rate over time in Louisiana and concluded that Louisiana probably as a state probably had a lower screening rate than other parts of the country based on the pattern of incidence in the state.

And, lastly, they did have a companion mortality study with three observed deaths. And I believe it was 3.1 expected, so there was no excess of prostate cancer mortality in the facilities.

So that's it. And I'd like to invite Drs. Adami and Trichopoulos to comment in the microphone.

DR. ADAMI: Thank you, Jack.

My comments will be brief. But nevertheless, I have written them down in order to make sure that they adequately reflect, not only my own scientific evaluation, but also that of Dr. Trichopoulos who has read this and approved it.

The approach to screening healthy populations in order to detect important chronic diseases already in their asymptomatic phase is a very complex undertaking. This complexity is often underestimated even within the health professions. With regard to prostate cancer, PSA testing of asymptomatic men and the clinical management of the disease in its early stages has been described as the most controversial area in contemporary oncology or indeed in contemporary medicine.

Fortunately, however, there seems to be consensus within the scientific community with regard to three issues that are of key importance to our discussion today. Let me address these issues briefly.

Firstly, the existence of latent cancer is a unique feature of prostate cancer. Although different terminologies are used to describe this phenomenon, there is agreement concerning its fundamental

properties. As men grow older, an increasing proportion of them, ultimate 50 percent or more, will harbor lesions in their prostate gland that appear malignant in the microscope but never grow and progress to produce symptoms during their lifetime.

Existence of this type of lesion was documented in autopsy studies during the last 50 years. Needless to say, these lesions provide an enormous reservoir of tumors that may be potentially detectable by screening tests.

Secondly, there is complete consensus concerning the overall objective of PSA testing among asymptomatic men. The goal is to detect aggressive, potentially lethal cancers at an early stage when the cancer is still confined to the prostate gland and the patient can be cured by local treatment, surgical or radiotheraputical.

Thirdly, although we don't know yet whether PSA testing can effectively reduce prostate cancer mortality, it is increasingly well documented that the PSA test can advance the time of diagnosis. Indeed it seems that PSA testing advances the time of diagnosis more than most other screening tests for early diagnosis of cancer in, for example, the breast or the large bowel. Available estimates indicate that during different circumstances PSA testing may detect the cancer five to ten years, sometimes even longer, before the disease would

have surfaced clinically.

The issues just briefly introduced have an important corollary. Introduction of PSA testing entails an increased number of detected prostate cancers. Indeed if no such excess occurs, the screening program cannot serve its purpose to reduce mortality. An increased number of detected cancers is a necessary but not sufficient condition for a reduction in mortality.

In the context of prostate cancer, this excess number of diagnosed cases should be larger than for other available screening tools. And there are two reasons for this. Firstly, as we have heard, the advancement of diagnosis, the so-called "lead time," is longer. In other words, PSA testing preempts cases that would otherwise have been diagnosed in the population clinically within the next five to ten years or perhaps even more.

Second, it is increasingly well documented that PSA testing entails detection also of latent cancers. This over detection of clinically irrelevant cancers maybe substantial.

The question is how we can best quantify the excess number of prostate cancers that should be expected following introduction of PSA testing. The ideal source of such information is a randomized trial. Because in such a trial, the randomization process guarantees

that the two groups compared are identical in all relevant aspects. Hence any difference in prostate cancer incidence between the two groups, the screened and the unscreened, can be uniquely attributed to the PSA testing in only one of them.

Globally, two large scale PSA screening trials are ongoing. One in the United States run by the National Cancer Institute and the other in Europe. One month ago on June 18 the Journal of the National Cancer Institute in this country published an important paper from the Dutch component of the European trial. This paper provides a large amount of important information relevant to our interpretation of prostate cancer incidence at the St. Gabriel plant.

The duration of follow-up is similar in the European screening trial because it began in 1994 and follow-up is complete through June 2000. During this period, altogether 1,241 prostate cancers were detected among the 21,000 men who received PSA testing. 1,241. In contrast, only 221 prostate cancers were diagnosed among the 21,000 who were randomized to receive no screening with PSA. Hence, PSA testing increased the number of cancers almost six-fold or to be exact by a factor of 5.62. So this finding emphasized why so much debate focused on the potential for over diagnosis of prostate cancer following PSA testing. And it emphasized that we shouldn't be

surprised to find early excesses of up to six-fold when PSA testing is introduced.

Another aspect that may shed light on this is the age structure of the cases compared to that in a situation without screening. And that's something that Dr. Trichopoulos will expand on now.

DR. TRICHOPOULOS: Thank you, Mr. Chairman. Thank you, Professor Adami.

The data that Dr. Adami presented are actually most valuable because they rely on randomized setting. Then I'm going to show you one interesting thought because they show what has actually happened to the United States population with respect to prostate cancer incidents after the gradual introduction of screening. And these data come from SER program, the surveillance, epidemiology, and then the results program. And these are 1975 down to 2000. These are all ethnic groups together. These are whites and these are blacks. And, of course, you can see that in every year, the blacks have almost twice as high incidence of prostate cancer.

You can see that before screening was introduced with PSA, the incidence of whites, say, was hovering around 15. After the introduction of screening, these are young men, less than 65 years old. And I like this cut off point, 65. These are young men. But this is

relevant in this incidence because that's the group where the whole phenomenon appears in the St. Gabriel plant. It was hovering around 15. And then PSA screening was introduced, and then the incidence sky-rocketed to 58. That is to say at least four times higher. And among blacks it was hovering around 30. It went up to 110. And remember, these are data on total population that cannot possibly have achieved the circulation with PSA testing that existed in the St. Gabriel plant. So probably by the time it reaches that circulation, these 58 will become 70 or 80, five, six times higher than it used to be before PSA. And these will become probably over 150, again, five, six times higher than they used to be which that would indicate the order of magnitude of the increase you see at the plant indicate -- what I try to say is that the increase we have seen at St. Gabriel and Dr. Blondell and Dr. Mandel represented so well, the two and a half time, it's nothing really that surprises me at all. Even if I had an excess of four-fourth, four times higher, it would still not surprise me. That does mean to say that I expect that atrazine has a protective effect against prostate cancer. I mean to say that even if the effect was closer to the upper confidence limit, because you remember these are point estimates and there is a confidence interval. If it were even four times higher, it would still be quite compatible with an effect of

PSA screening. It has tremendous profound effects which are evident, and it's an evident observation in the United States population.

Thank you very much.

DR. MANDEL: Thank you, Dr. Trichopoulos. We'd now like to present to you the results of the nested case-control study. The conclusion of the authors in the St. Gabriel plant study was that the excess, their estimation was, likely due to the PSA testing; but they suggested this study be done. And we embarked on it a number of months ago. And Dr. Hessel and Dr. Smith will now present the results of that study. Thank you.

DR. HESSEL: Thanks, Jack. Mr. Chairman, committee members. Can I have the next slide?

The objective of the study, of course, was to examine the relationship between prostate cancer and occupational exposure to atrazine among the workers at the Syngenta plant.

This was a case-control study that was nested in the cohort that we heard described a couple of times this morning at the Syngenta plant.

We heard earlier about the three different groups of workers at the plant. I want to give you a little bit of context. The Syngenta workers included those who were virtually all of them management,

administrative people at the plant, supervisors. A lot of them were highly trained technical people were Syngenta workers, although there were some that were involved in the production activities.

The contract maintenance workers were generally not full-time continuing employees. They were often brought in during plant shutdown to do routine maintenance or other maintenance activities as they arose in the plant although some did work at the plant year round.

The contract production workers were more likely to work year round, more likely to work full time. Importantly, most of the people involved in the packaging of atrazine were the contract production workers. And this is where the exposures were highest.

We heard previously that the prostate cancer excess was limited to the Syngenta workers. Among the Syngenta workers, there were 14 prostate cancer cases through 1999. The PSA screening was available almost exclusively to Syngenta workers as parts of the health benefit package. There were only a few of the contract workers eligible for that program.

And as Dr. Bove pointed out, and I agree with you, the large scale, widespread screening program really begin in earnest in 1993.

12 of the 14 prostate cancer cases among the Syngenta workers were known to the plant medical department. The other two had been

identified by the Louisiana Tumor Registry. They were not known to the plant, nor were they known to us. So it was the 12 that were known to the plant medical department who were the cases for this case-control study.

The controls were also drawn at random from the Syngenta workers. They were part of the original cohort, and they individually matched by year of birth and race. By year of birth as closely as possible not to exceed five years. And the prostate cancer cases were eligible as controls until their date of the diagnosis.

The work histories were obtained from the plant personnel department. The data were abstracted, blinded to case-control status. For each job in the work history, the start and end dates were abstracted, the job title, and department information.

Exposure estimates were based on an extensive tour of the facility. A review of all existing air and monitoring data, the policies on personal protective equipment, documentation on process changes, and modifications in ventilation equipment.

To give you an idea of the magnitude of the industrial hygiene sampling at the plant, we see here in this slide, there were three time periods that were defined. Within each of these time periods, the exposures were relatively homogenous. So we see the first time

period, '70 to '78, '79 to '88, and '89 to '99.

We notice is it in the first time period, the sampling was focused exclusively on the packaging department, PKG standing for packaging, and total dust sampling. In the next time period, again a heavy emphasis on the packaging department where, of course, exposures were the highest with also some sampling being done in the formulations unit, Form, the formulation unit. This was where atrazine was actually being produced.

In the most recent time period, there was a shift in focus from the monitoring of total dust to monitoring atrazine in the total dust again with an emphasis on packaging but also with testing being done in the formulations unit.

In the 1980s, there was a urine monitoring program introduced focused on the packaging workers. The metabolite that was being examined there was not specific to atrazine. And so they would get people, for example, who had swimming pools or spent a lot of time in swimming pools who had come up positive. So that program was abandoned. And later they identified a different metabolite, and that testing was begun in the 1990s. So these data were available to us.

On the basis of the way the plant works and the way people move throughout the plant, we identified five exposure categories.

We looked at those with no exposure during their normal work activities. We looked as those with occasional exposure but whose normal activities did not involve exposure. These could have been, for example, engineers who worked in an office most of the time but occasionally had to go down into the production areas, perhaps once a week, perhaps a couple of times a month.

There were then those with regular exposure to lower levels to intermediate levels and to higher levels. Among those with exposure to higher levels, these were almost exclusively in the packaging department.

What we did then was to take those people in the highest exposure category in the earliest time periods and give them a relative exposure intensity, a relative exposure intensity, of 10. All of the remaining exposure categories and time periods were then calculated relative to this value of 10. And you can see them here in this slide.

While this slide is up, I'd ask Dr. Smith to speak about the exposure assessment.

DR. SMITH: One of the things I'd like to point out, and I'm sure you're aware, is that the exposure assessment is a very important aspect of this study and in many ways the reason it was conducted. To put this exposure assessment in context for those of you who aren't

familiar with this type of activity, this was a state-of-the-art exposure evaluation. It involved a very extensive effort to gather descriptive data on job tasks, on work locations, so that we could identify the exposure opportunities. This meant that we spent hundreds of hours -- not me personally but the group involved with this -- collecting and analyzing the data including meeting with retirees and long-term employees, so that we could really understand the nature of the jobs, where the exposures were coming from, and identify the exposure opportunities which covered the range which you can see up there.

The second point I want to make is that the exposure assignments were semi-quantitative categorical estimates. These numbers are arbitrary. They're really intended to indicate the rough relative difference among the groups. There is no -- there are no units on them. They are just relative.

The data that we used to sort of calibrate how big these relative differences were, were the industrial hygiene data. And as was noted earlier by Dr. Symanski, those data are not the basis normally for an epidemiologic study. They're the hazard control and surveillance program for the company. And as a result of that, most of the measurements were made in the highest exposure categories and there were none in the places where there wasn't any expectation

overexposure.

Because of those limitations, we used the data where it was available to essentially make a relative estimate of this exposure opportunity. How much intensity difference there might be across these categories. There were no data for the lowest categories as I mentioned, so those are based on the lowest levels that we saw anywhere in the plant.

Finally, we found these results to be a very robust exposure matrix. There are large differences across the exposure classification groups. There is a clear downward trend over time with the improvements made in the industrial hygiene control program. They improved the personnel protective equipment to reduce inhalation exposures and skin contact; they installed a decontamination facility to make sure that the atrazine and other materials were not carried out of the plant; and they did a lot of work with ventilation controls and engineering improvements to the process.

So I think we can conclude that we have a fair degree of confidence in the differences that you see within the table. And so with that comment, I'll turn it back to you, Pat.

DR. HESSEL: Thanks, Tom.

The review of the occupational histories gave us 341 unique job

title, department combinations. These 341 combinations were classified independently by our industrial hygienist, by the plant manager, and by two long-term employees. Again, these were blinded to case-control status.

Of the 341 initial combinations, agreement was reached, consensus was reached, on all but 86. So for 75 percent of the titles, we were able to -- three out of the four people rating it agreed on which of those five categories of exposure this job fell into. We had a meeting, myself and the four raters to discuss this. On the basis of this meeting we were able to resolve all but 38 of those.

It was felt that if the time period were available for some of these combinations of job title and department, they would be able to confidently classify them according to the exposure category. So those dates were provided for the jobs and an additional 13 could be resolved in that way.

The remaining 25 were reviewed by our industrial hygienist, again, blinded to case-control status but in this case looking at the entire work history, particularly focusing on the previous and subsequent job. And on the basis of that, all 25 could be resolved.

However, there were 20 workers for whom packaging was mentioned on the work history without an indication of whether this

was powder packaging or liquid packaging. And it was an important distinction because the exposures are very different.

These names were sent to two long-term employees who consulted as necessary with other long-term employees at the plant. The names and time periods were sent. On the basis of this, 15 of those could be resolved with confidence. And the remaining 5, that time was split between liquid and powder packaging.

Three exposure indicators were calculated for each of the people in the study. One was length of exposure, simply the number of days of exposure from the time that they began working at the plant until the day they left or until the date of diagnosis of the case or a similar date for their matched controls.

Time-weighted average exposure, again, throughout the entire duration of employment, and then cumulative exposure. Cumulative exposure being the intensity of exposure, the intensity being that relative intensity score that we saw for each job times the amount of time spent in that job summed over all jobs. So that was the cumulative exposure.

Again, these were calculated to the date of diagnosis of the case and to that same date for each of the cases matched controls.

When we calculated, we calculated using all of the cases and

controls; and we also, to evaluate the confounding effect of the PSA screening test, evaluated the subgroup that was eligible for the PSA screening, those being the people who were employed in or after 1993 and who had achieved at least age 45.

If we look at the logic behind viewing PSA screening as a potential confounder, what we were trying to look at is a relationship between atrazine exposure and prostate cancer. Now if atrazine exposure was related to the PSA testing, and we believe that in this case it was, because people had to have been at the plant in 1993 and to have achieved age 45 to be involved in the atrazine screening program. Therefore, we felt that there was the possibility of a relationship between atrazine exposure and PSA testing.

We heard earlier by Drs. Adami and Trichopoulos that there certainly is a relationship between PSA testing and the identification of prostate cancer. So given this, it appeared that certainly PSA testing could have been a confounder in this group.

We did two different kinds of analysis in this group. One was conditional logistic regression. This accounts for the matching of cases to controls. And we calculated odds ratios in those analyses. We also used a general lineal models program to look at the differences in the means between the cases and the controls

accounting again for the matching.

We had then 12 cases and 130 controls. The number of controls per case ranged from 3 to 14. There was only one case that had three controls. This was somebody with a very early year of birth and it was only possible to match three people to that person within five years. The remainder had between 10 and 14 controls per case.

When we looked at group that was eligible for screening, 11 of those 12 cases were eligible for screening, that is, they worked in 1993 or later and had achieved at least age 45 and 60 controls. Notable that 11 of the 12 cases had worked during the period of screening was available and only 60 of the 130 controls. The average age of the cases and the controls, right around 51 years.

The results then of the general linear models analysis, this represents the mean difference for days of exposure for cases minus controls. So the positive number here means that the cases had a longer duration of exposure, significantly longer duration of exposure, compared to the controls. Again, this is all subjects included.

When we focused on those who were eligible for the screening program, the mean difference reduced to a minus 312 days, meaning that the controls actually worked slightly longer than the cases

although this difference was not anywhere near statistically significant.

When we look at exposure intensity, again, this is at relative exposure intensity measure averaged over the working life, when we looked at the difference using all subjects, bearing in mind that exposure intensity is more or less time independent, we found another negative coefficient suggesting that the controls had higher levels of average intensity compared to the cases, although, again not significantly so. And we focused on the group that was eligible for screening, similar results.

When we looked at cumulative exposure, again this is exposure intensity times duration summed over all jobs, we saw, as you would have expected given the previous results, an excess among the cases. Not a statistically significant excess, but an excess among the cases when all subjects were used. When only those eligible for screening were used, we saw a minus 642 days again suggesting that the controls had slightly higher cumulative exposure, although, again, nowhere statistical significance.

When we did the logistic regression analysis, this only deals with those people who were eligible for the screening program, we see with duration -- and I just divided duration by a hundred so that the

odds ratios were more easily interpretable. However, we do have an odds ratio here very close to 1 confidence interval including 1, quite a high P value.

When we looked at average intensity of exposure, again, this is the actual number. You recall the mean value was about 1 for this. So the odds ratio associated with an increment of 1 in exposure intensity, 1.054, again not significantly different from the null value.

Cumulative exposure, again, divided by a hundred, an odds ratio virtually identical to 1, not significantly different from 1.

The study had several strengths that I think are very important. It was a relatively new facility. They began operation in 1970. As a result, the work histories were very detailed and very complete. In addition, there was industrial hygiene sampling from the start. This often isn't found when you're dealing with older facilities. And there were many samples to base our exposure estimates on.

The basic production process also had not changed very much over time. The people at the plant were kind of excited that, when they put the plant in place, it actually worked and they didn't have to modify the process very much over time.

The PSA screening program instituted at the plant gave us, I think, a unique opportunity to look at the potential confounding effect

of the PSA screening.

In terms of limitations, I think although the industrial hygiene data were very good, there was very little sampling in non-production and non-packaging areas and a number of the people worked in those areas.

The nature of the sampling did change over time. You recall that in the early years, they were dealing primarily with total dust sampling and the later years atrazine sampling. And there was very little overlap between. However, as you saw from the fact that consensus was reached by at least three out of the four raters in 75 percent of the job titles, we felt that we were able to capture jobs and assign exposure estimates quite successfully. The small size of the study is of course an issue.

To conclude, after we controlled for age, race, and PSA screening, there's no evidence that atrazine exposure was related to risk of prostate cancer in these workers. Further, the excess prostate cancer incidence that was found in the study by Delzell, et al., was confounded by the PSA testing.

Thank you.

DR. MANDEL: Dr. Pastides.

DR. PASTIDES: Good morning to the Panel. We are at the end

of our formal presentation. I am here as chair of the scientific advisory committee that provided oversight to Dr. Hessel and his colleagues at Exponent who conducted the nested case-control study. Our committee members had two roles; first to provide technical advice to the investigators, especially in the design of the study; and, second, to ensure independence of the scientists from the Syngenta study sponsors. And, indeed, there was no involvement by company officials in the design, analysis, or interpretation of this study. In fact, the company did not receive results of the study until two days ago.

I think as many of you know, the study was scheduled to be reported in September. And indeed a final report will be made available in September and plans for a manuscript to be submitted to a peer review journal will ensure as well. Nevertheless, Dr. Hessel and his colleagues did accelerate the rate of the analysis and the interpretation; and we do stand by these results. They are indeed official and will not change in the final report.

I wish to highlight briefly some of the results presented by Dr. Blondell very quickly from the Ag Health Study earlier today. I think this is a particularly important adjunct to the nested case-control study in helping the Scientific Advisory Panel render its conclusion,

in that as we know again, it is indeed the largest study of its kind. It had over 55,000 males who were followed. And the recent report by Alavanja and colleagues demonstrate, in fact in this slide right here, that there was absolutely no evidence for any dose-effect relationship between atrazine exposure and the risk of prostate cancer.

While the nature of the exposure was significantly different, obviously in the farm setting relative to the manufacturing setting, I think a major reason why we are concerned from a public health perspective about any potential risk of atrazine is because of its widespread use of applicators in the farm setting.

And, therefore, as a summary to the Agricultural Health Study, the largest prospective, study of prostate cancer conducted among farm applicators, again, there was no evidence of dose response and also there was no significant effect modification by whether the applicators did or did not have a family history of prostate cancer.

In conclusion, therefore, the St. Gabriel study, the original study by Delzell and colleagues, reported an excess finding in the incidence of prostate cancer, 11 observed cases relative to 6.3 expected. But the excess, indeed, the cases were confined to younger men who were active company employees and who had extensive participation in a PSA screening program. This was underscored by

the very early stage of cancer among the men diagnosed for whom medical information was known.

An extensive nested case-control study was, therefore, commissioned by Syngenta. It was conducted by Exponent scientists with oversight from a university based advisory committee. The study by Hessel and colleagues incorporated an extensive exposure assessment and found no evidence for dose effect. We believe, therefore, that the findings by Delzell and colleagues were likely due to a surveillance effect and that there is no substantive evidence to date for a causal relationship between atrazine exposure and risk for prostate cancer.

DR. BRECKENRIDGE: If you wish to address the questions that you may have to the individual speakers, you may do so. If you don't know who the question might be appropriate for, just address it to Dr. Mandel or myself depending on the whether it's in the area of the epidemiology or a more general question for me. Thank you.

DR. PORTIER: Thank you very much, Dr. Breckenridge. And I want to thank your panel for remaining on time, the time allotted. Before we go to any questions from this Panel, I wanted to know if there was going to be any additional written material on the case-control study given to the Panel to our discussion this afternoon,

or is this the material we are supposed to work with?

DR. BRECKENRIDGE: Mr. Chairman, the slide sets that you have will be all the material that you have on the nested case-control study. There was one handout that the epidemiologic panel prepared on the other cancers in anticipation that there could be some questions about that. And they might be able to entertain any questions about those studies. But that has not been the focus of our preparation. Thank you.

DR. PORTIER: Thank you very much. Dr. Bove.

DR. BOVE: I am just wondering if you also did analysis where you looked at the exposure categories you have in one of the slides and looked at the odds ratios for each one of those categories or did we just do an looking --

DR. PORTIER: Dr. Bove, could you use the microphone, please.

DR. BOVE: I'm sorry.

DR. PORTIER: And start over.

DR. BOVE: You did an analysis looking at exposure as a continuous variable. I was wondering if you also computed odds ratios for the exposure categories listed on one of the slides so that we can get a handle on what's going on in these different categories of

exposure.

DR. HESSEL: If I understand your suggestion -- and I would like to do it -- would be to look at the people who had high exposure. For example, to look at those people who were ever or never in the highest exposure category or perhaps length of duration in the highest exposure category versus others. And then do the same for the intermediate and --

DR. BOVE: Well, you did it before in the previous material submitted.

DR. HESSEL: Yes.

DR. BOVE: Right. So I was wondering why it's not here, too.

DR. HESSEL: Well, a number of the people varied from one exposure category to another. To do that we could either categorize cumulative exposure. Or alternatively, look at the amount of either ever-never exposure in one of those categories or somehow look at the amount of time in the high-exposure category which might be the most formative.

DR. BOVE: Right. Because as you said, these weights were pretty arbitrary.

One other question about that table. I thought I heard it said

that these periods, these three time periods, are relatively homogenous in terms of exposure. But I understand that in 1975, for example, they had a change in the packaging; they introduced automatic bagging according to the article that was published. And in the early 80s, they had more extensive ventilation control. So that it would seem that these periods aren't exactly homogenous at all. Maybe there is some split in between.

So can you go over why you considered these to be homogenous periods?

DR. SMITH: I think that homogenous in the sense that within the time period within a category they tended to have a consistent exposure. When you do this process of dividing up the time periods, inevitably there are -- these are really not sharp boundaries. That, in fact, you would observe that they would -- the trend is right. But it's not, in fact, a nice sharp step. So what we tried to do is identify those factors that would most affect exposure and then set the steps there. It just gets too complicated to reasonably do.

DR. PORTIER: Dr. Knobeloch.

DR. KNOBELOCH: Yes, I have two questions. My first question is: You've testified, and I think over the years have maintained, that atrazine, if it is a carcinogen, it is not a carcinogen

as an initiator but rather as a promoter via a hormonal mechanism. I'm wondering whether or not in any of your animal studies whether you have tested atrazine as a classical promoter, i.e., via chronic exposure following exposure of the animals to an initiator?

DR. BRECKENRIDGE: We have not conducted classical promotion study in the sense of promotion in regard to the female mammary tumor response. We believe the promoter was estrogen, the androgenous estrogen that was attributed to the disruption of the cycle.

In the case of the males, in fact, I would say androgens would be reduced if anything and certainly testosterone is a promoter as is DHT for prostate cancer. So we're not thinking of atrazine as a promoter directly, but through its mediation of hormone milieu within the animal and in the female Sprague-Dawley rat that that eventuality will occur, that there was more androgenous estrogen exposure. But we would not have anticipated that in the male. And, in fact, our data showed that testosterone at high doses is reduced.

DR. KNOBELOCH: I'll ask my second question. And that is I'm wondering why the men at St. Gabriel plant were so intensively screened for PSA. I would suspect that simply by offering it as a free test, you would not get 100 percent of the men to come in for

screening, especially not in men under the age of 50 who presumably would not be very concerned about prostate cancer. And I'm also wondering whether Novartis does this extent of screening in other plants of other employees who not are exposed to triazines; and if so, whether or not those men could be used as a control group.

DR. BRECKENRIDGE: I'll answer the first part of the question, and I'll defer the second part to Dr. Mandel.

In regard to the policy about offering PSA screening, this is a company-wide policy at least in the United States. So that there are other sites. Our Greensboro corporate site is screened in the same manner as part of the same benefit program. Why individuals chose to have that screening is obviously up to the individual. And obviously they perceive that there is some benefit in knowing than not knowing.

I'll defer the second question relative to using that site as an alternate control site for this.

DR. HESSEL: I would also like to add, if you knew the nurse at the plant, you would understand why the program is so successful. She's just recently retired. And she's awesome. And I think it was largely through her efforts that the program was as successful as it was.

DR. PORTIER: Is that the end of the answer?

DR. MANDEL: Your other part of the question was could another facility be used as a control. There was actually one of the studies the Alabama group did where it included two facilities, I think Alabama facility as I recall, and there was no excess of prostate cancer in that study.

Whether or not you could compare another facility would largely depend on the comparability of the two places. Might you have less comparability if you go to a population in another state outside of Louisiana than you would in a population within Louisiana? I think it gets very difficult to decide what might be an appropriate comparison group. Perhaps another way to look at it was might you do a study at another facility to see if you see the same effect.

DR. PORTIER: That was Dr. Hessel, and then Dr. Mandel. Dr. Reif.

DR. REIF: This question is for Dr. Adami and his colleagues that reviewed the PSA screening data.

I wonder whether your group considered the cumulative incidence or the time course of the detection of new cases in your review. Screening at the plant was virtually complete for men age 45 by the years 1994 and 1995 according to Table 4 of the McClennan paper. And yet there are new cases being detected, six in 1999 and

two in 1997. And the question, when you did your evaluation, it was under the general idea of could you account for a doubling or tripling in the expected incidence rates. But I don't recall that you considered the time of development of these new cases in that analysis. And wonder whether you discussed it and what your interpretation of these large numbers, relative large numbers, of incident cases in the very recent time period might be with respect to initiation of PSA screening around 1993, 1994.

DR. ADAMI: We did not discuss that in any detail. Actually, the paper from which the data were derived provides an enormous amount of information. We thought, however -- and it's based also on a modeling exercise. We thought, however, that the most informative data in the paper were the real empirical evidence from the trial itself about the cumulative number of diagnosed cases in the control group and in the PSA screening group. And we considered that particularly informative since the time period of follow-up following the initiation of the screening program was virtually identical. It was from about '93 through '99 in the St. Gabriel plant, and it was from 1994 through 2000 in the Dutch screening trial.

But if we try to look at this more deeply, it's obvious that there are a number of factors that influence the excess of diagnosed prostate

cancer, including the sensitivity of the process which in itself has several different components such as the cut-off level for PSA, the diagnostic work-up of positive findings, the way you take biopsies, et cetera. It depends on the prior screening history. It depends on contamination of the control group, which was clearly existent in the Dutch screening trial. It depends on the interval. And it depends also on the age range of your target population.

And, if anything, the Dutch trial indicates that the lead time is higher in younger ages than in older ages. So that might at least in part be an explanation why the SIR, standardized incidence rates, were if anything higher in the younger age groups.

So the dynamics here are extraordinary complex, but we believe that the cumulative number within six years might be after all the most informative measure.

DR. PORTIER: Dr. Reif.

DR. REIF: Can I ask a follow-up question then of Dr. Breckenridge since you summarized those 17 cases in the supplementary data that you provided. For those recently diagnosed persons, diagnosed in 1998, 1999, in particular, were these the result of second screenings or third screenings of individuals who had been screened earlier in 1993; or were these the initial screenings of those

patients in that latter time period?

DR. BRECKENRIDGE: I'll be going from memory here. But some of these cases were detected by a combination. And we had records, I believe, for nine individuals where we actually had the PSA values over time. And some of those individuals had multiple years of PSA values where at some point they exceeded the criteria of, I believe, 4. And at that point, then, they went through a biopsy procedure.

Other cases, it might have been on their first instance. So it's a mixed group of results there. But I don't have the exact memory.

DR. MANDEL: Hopefully to clarify and not confuse. And I have no particular knowledge of those six. The program was offered annually to people. People may have gone through a series of screening tests, been negative three or four or five times, and then finally had a cancer detected. PSA is not a perfect test.

And also the trigger for a diagnostic work-up was largely based on a criterion that was set. But as I understand it, sometimes for whatever reason, a physician might decide to do a work-up when it was 3.5 and not 4.

So the PSA test simply brings a person into a diagnostic procedure. It's not diagnostic in and of itself. Without the biopsy, it

won't identify the prostate cancer. So it was a trigger point for the physician to subsequently do the follow-up examination which would lead to the biopsy. So people had multiple testing in this facility. And I expect as we continue to track them, as the screening program continues and the cohort is ageing -- you must keep that in mind, too. This is an ageing cohort. They're moving into the higher incidence rate -- we'll see more and more cases of prostate cancer evolve as has been seen in the United States.

DR. PORTIER: I'm sorry. I'm going to make sure we're very pointed in our answers. So I'm going to try to paraphrase Dr. Reif's question here and see if you can give me a good answer for it because I think it's a key question.

I believe Dr. Reif's question pertains to the issue of: In the very last two years the potential increase in prostate cancers due to the PSA screening should have been strongly attenuated into the 1999, 2000, 2001 time frame. And yet you're seeing in 1999 a fairly large number of prostate cancers coming in. Can we have a direct answer to that question? Do you know of anything pertinent to that issue, and is that point important or not? John, that was your implication, wasn't it?

DR. REIF: In part, yes.

DR. TRICHOPOULOS: From when you have latent cancers, which exist and they will never become clinical cancers, you may hope that in the original one or two rounds of screening you may capture them. This may be relevant when you have the 80 or 85 years old when you have an excess incidence which declines later on.

However, in the younger age group, this does not happen. There you have really several cancers that tend to be projectory that may become parallel and never become clinical. And several cancers that will become clinical and aggressive. This is a continuous process. We capture really the origins of these cancers.

So as soon as you continue the screening, you'll be capturing the excess, let's say, 50 percent, 60 percent cancers that you would be capturing. This is not really a phenomenon where we'll harvest everything (inaudible) and you capture them all.

So you have a continuous process whereupon you capture a few cases that will never become; or a slowly progression, and you capture them earlier. And this generates the excess incidence you can see there.

The second process is that occasionally you may need two screenings in order to detect cancer because it's the rate of increase in the concentration of PSA that becomes diagnostic. You have to take

into account how sharply they increase.

DR. PORTIER: Dr. Reif, did that cover your points well enough?

DR. REIF: I'll accept the answers. Thank you.

DR. MANDEL: Dr. Reif, there's one more fact in the paper that all the six cases came through the medical department of the facility. It may suggest that if they're known to the medical department, they might have been part of the screening program.

DR. PORTIER: Dr. Hopenhayn.

DR. HOPENHAYN: I'm going to follow up a little also on the issue that Dr. Reif brought up because I was intrigued particularly. I don't know if that's what you were looking at. But one of the graphs in the supplementary information that was sent to us authored by Dr. Breckenridge. And I don't know if you have that with you. But I would like a little bit of clarification on the fact that there were the six additional cases in the last two years and the relation to what here is labeled as percent of cases with first PSA screening.

My first interpretation of this graph was that those cases had a first, were having a first screening. But perhaps I misread the graph in here. But I also wondered whether what the age of these new cases were and what the length of exposure or the time since starting at the

company was to see if there were any issues of latency that might start to reveal as we progress in time.

DR. BRECKENRIDGE: I believe you're discussing Figure 8 of the October 31 report. And there's two sets of data being depicted on that table or graph. The continuous line in blue represents the proportion or percent of cases at different points in time relative to their first screen. So that eventually by late 1997, they had all participated to the extent of at least having one screen accomplished.

And the red bars on that chart refer to the left axis which is a cumulative -- or sorry -- to the cumulative incidence. And we're just counting the cases out of the total 12 in terms of when they were detected. So we have two appearing in '89, two additional in '92, and so on until all 12 cases are detected.

Now I believe the second part of your question had to do with job profiling and cumulative exposure information. Obviously, this particular report was a first attempt at doing that quantification. And it would be more prudent to use the matrix that was subsequently developed by this panel to look at the question about the individual job profiles relative to their duration of employment and their cumulative exposure index as it builds up over time.

Obviously, that information is available and could be made

available. I think I'll defer that question to Dr. Hessel.

DR. HESSEL: Yeah. I think if I can clarify two issues. First, the people at the plant are abstracting the information on all of the PSA and digital rectal examinations for each of the 142 people in the study. So that's ongoing. Unfortunately, we couldn't incorporate that and analyze that at this point; but that will happen.

I think another point necessary to make is that we don't know -- we will know, but we don't know now how many PSA tests each of these people had and what the timing of those tests was. So they may have had a test when they were 45 years of age and then skipped a couple of years and had another one. With such a small number of cases, it's almost looking at it anecdotally to try to look at what those patterns might be. But we can certainly look at that.

And another thing that I think is important and is related to the issue of the timing of the testing is that although the criterion for some kind of follow-up was a PSA value of 4, if there was a change -- and this was not objective. But if the person looking at the test results felt that there was a change from one time to the next, even if it was nowhere near 4, but if from one year to the next or one test to the next there was a marked increase, then that person would have been referred for testing.

So I think there are a lot of dynamics that have to be discerned and can only be discerned once we get the additional data.

DR. PORTIER: Did that cover all your questions, Dr. Hopenhayn?

DR. HOPENHAYN: Yes.

DR. PORTIER: Dr. Gold. Excuse me, Dr. Gold. I'm not being fair to Dr. Isom. He had asked earlier to comment. I'll come back that way.

DR. ISOM: Actually, the question I had was partly related to the point you just made but with regards to some of the dynamics or the clinical aspects of PSA testing. PSA testing obviously suggests that you may have something going on with the gland or the organ but not necessarily a cancer malignancy. And that has to be diagnosed definitively with a biopsy.

From your knowledge, any of your knowledge, of going back, looking at the records, is there an increase of positive testing and at what level is it considered positive? And you've mentioned follow-up. But what I'm getting at is: Is there an increase in perhaps other types of prostatic diseases, prostatitis, in this population which wouldn't be diagnosed and put into this set of data?

DR. HESSEL: We just don't know. We haven't abstracted that

information. And even with the information that we are abstracting, we're not going to have necessarily a resolution of every -- we won't know the resolution of every test that went forward for follow-up for clinical follow-up. So we don't have that now. And I don't think we're going to be getting it unless we went back into the data.

DR. PORTIER: Dr. Gold.

DR. GOLD: I have two questions. One has to do the industrial hygiene sampling. You said that the sort of weights that you came up with for the various time periods and the different exposure categories was somewhat arbitrary. But there was some sampling data, error sampling and so forth. Was there any attempt to look at whether there was any kind of correlation between these arbitrary weights that you came up with and your actual measurements?

DR. SMITH: Maybe I can clarify a bit how this was done. The relative ranking is a two-part process. The first part is really an exposure opportunity evaluation. If you looked at those five or six categories, that's really what that was about.

Then we went -- the second step was to say, okay, given that and that a, for example, the packaging technician was the highest exposure category and that's where we also happened to have the most data, we looked at that data and said, how has that changed across

time and in an admittedly course way because of the limitation of the data. And that's where the relative change came from.

The packaging technician had data for all three of the time periods and showed the kind of decline across time which you saw in that matrix. The most recent time period, we had the urine data which would reflect all routes of entry for the exposed people. And it was covering more of the job categories. So we could, again, look to see how these exposure assignments differed.

And then as always, we were forced to make some assumptions about how we go now from those most recent backwards in time to fill out the matrix.

Does that help?

DR. GOLD: It does sound like you used some of the measurement data to help you come up with these weights. Is that correct?

DR. SMITH: Yes, we did.

DR. GOLD: May I ask my second question which is unrelated to this.

All through this and for a couple of years now it sounds like people have been aware that the real problem is the small number of cases. And I heard mentioned here today and I read it somewhere in

all the material where we see that there is another plant in Alabama that was manufacturing atrazine. And so I'm wondering why there was not an attempt to get cases from that plant to bolster the numbers in terms of numbers of cases. And then there's the whole other issue of having a comparison plant somewhere.

DR. BRECKENRIDGE: I believe the initial parts of Elizabeth Delzell's work actually involved investigations in the plant in Alabama. But since at least five years now that plant is no longer a Syngenta plant and is no longer engaged in triazine manufacture. I believe that's correct. If I'm misstating that, someone from Syngenta, please correct that. But it's no longer actively -- it's not our company plant anymore, and it's not producing triazines.

DR. PORTIER: Okay. Dr. Sandy.

DR. SANDY: I have a couple different questions. One going back to the six cases that were diagnosed in that last two-year period. Do you have data on the age at diagnoses for those cases as well as the others, the 17 total?

DR. BRECKENRIDGE: We have the age of diagnoses for every case except the two that are unknown to us at this point in time that came from the Louisiana registry.

DR. SANDY: And are those presented anywhere in the material

you've sent us?

DR. MANDEL: They're in the published paper. The age range was 48 to 56 for the six cases. Five of the six were localized tumors at time of diagnosis. And all six were identified by the medical department. Those are all from the published the paper, those facts.

DR. MANDEL: I don't have any additional data other than what's in the report or the published paper.

DR. SANDY: Going back to the exposure assessment, you've mentioned you've used the urine metabolite data to check your exposure matrix. Is that written up anywhere? Oftentimes when you have biomarker data, you find out that folks you thought were highly exposed may not be so highly exposed. And folks you thought were exposed at a much lower level actually have surprisingly more exposure than you thought.

DR. SMITH: Yes, that's quite true. Well, a comment about the urine methodology. As far as I know, that's not been published. Is that correct? The DAPT method?

DR. BRECKENRIDGE: The urine monitoring method hasn't been formally published. It's certainly being submitted in documents to the EPA. And I'll just briefly mention that if that's what you wish to know about.

There are three principal cholorotriazine metabolites. Atrazine is rapidly transformed into these metabolites. Shortly after administration, you won't detect atrazine in plasma or urine. But you will detect the mono and di-dealcholated metabolites. And in this particular method that was applied early, it was the diaminochlorotriazine metabolite. It is the di-dealcholated chlorotriazine. It accounts for the single greatest percent.

DR. PORTIER: I think the question pertained to whether it's published anywhere, especially the actual monitoring data that was done in the population, not necessarily about the method per se.

DR. BRECKENRIDGE: Sorry. I misunderstood. It's not published. It's available in documents to the EPA.

DR. PORTIER: And the actual exposure measurements in the urine in the workers from the factory, is that available at all?

DR. SMITH: Again, I would have to defer to the company.

DR. BRECKENRIDGE: It's in documents submitted to the Agency not publicly available unless for discovery. Thank you.

DR. PORTIER: Does that answer your question, Dr. Sandy?

DR. SANDY: It answers that one. But I have another one. But if you have a follow-up.

DR. SMITH: Actually there was one point you made that the

biological monitoring data can show different relationships among the exposure groups than you see with, say, air monitoring. We definitely saw that. For the most recent time period, the people who are not in the high powder exposure areas showed a much higher relative amount of the metabolites in their urine than you would expect just from the air monitoring, which we interpreted as being either ingestion or skin absorption.

DR. SANDY: And that was taken into account. Did you adjust the --

DR. SMITH: Yes.

DR. SANDY: -- assignment of exposure, relative exposure levels for those individuals --

DR. SMITH: That's right.

DR. SANDY: -- in those categories?

DR. SMITH: Yep.

DR. SANDY: Okay. Then I had a series of questions on the modes of action presentation at the beginning.

DR. PORTIER: Dr. Sandy, can we hold a minute? Dr. Handwerger, you have a follow-up on the exposure issue?

DR. HANDWERGER: No.

DR. PORTIER: Okay. Go on.

DR. SANDY: You mentioned the mode of action involving the hypothalamic pituitary axis. But we also know that atrazine induces aromatase. And I wondered, can you comment on -- have you measured estrogen levels in animals? In males exposed to atrazine, do you see a change? You've mentioned that testosterone goes down and you have an explanation for that. But might there also be an aromatase role in that.

DR. SIMPKINS: The only documented induction of aromatase is an adrenal cromathin tumor in vitro model. No one has to date shown that atrazine induces aromatase in any animal model, certainly not in rodents. We did not in that study, as I recall -- Charles you can correct me -- assay estrogens. Dr. Cooper in some high-dose treatment studies assayed both androgens and estrogens, saw an increase in estrone and no change in estradiol in his studies.

DR. BRECKENRIDGE: In regard to the question of aromatase induction or the hypothesis of aromatase induction, with collaboration with Dr. Zirkin we have a study underway and planned to, in fact, replicate the testosterone reduction experiment but measure estrone and estradiol and measure the expression of message for aromatase and measure aromatase. So that data is not yet available. We're trying to attempt to test the hypothesis about aromatase induction

which has been observed as Dr. Simpkins indicated in the ex vivo model.

DR. SANDY: That model, I thought, was an in vitro human cell line where they did see an induction in aromatase.

DR. SIMPKINS: Yes, that is correct. It's adrenal cromathin tumor cell line. The extent of increase in enzyme activity, aromatase activity, was about two-fold. Frankly, those are the only data on aromatase induction that are out there.

DR. SANDY: I think I recall seeing some data submitted to us suggesting that there's an increase also in alligators.

DR. BRECKENRIDGE: I guess we can talk alligators if we wish. There was a study by Lou Gillette that exposed alligator eggs to atrazine. He also exposed those eggs to estradiol. This was a subject of a SAP meeting just three or four weeks ago. And in that experiment, he observed a marginal increase in aromatase inside the eggs, or inside hatchling alligators, after they had hatched.

In regard to the effect of that elevation that he reported, there was no biologic consequence because had he a model whereby alligators were sex reversed by means of temperature. And I'm sure this is outside the areas of expertise here. But you can make alligators all female or all male and they become sensitive then to

estradiol in terms of reversing that sex.

And in the case of this particular study, the positive control, estradiol, did, in fact, reverse the sex of these males back to females. Whereas in this particular study where he claimed there as an aromatase induction, there was no effect on the sex reversal with respect to the atrazine exposure.

And I should also mention that this was conducted at 14,000 part per billion applied to the surface of the egg with an ethynol vehicle to carry it into the egg. If we wanted to get a total itinerary of all of the work that's being conducted with the term aromatase and atrazine in, we could do that. But we hardly thought it was relevant to this discussion. Thank you.

DR. PORTIER: If I might follow up with a question, again. We're getting close to lunchtime, so I'm really looking for short answers to some of these questions. In the clinical chemistry that is done on the blood of the workers at the plant, you may or may not have done hormonal measurement. If yes or no, has that been looked at and has any of that been presented; and is there any change whatsoever in observed clinical chemistry in the workers in terms of testosterone or any other hormone level in the blood?

DR. BRECKENRIDGE: To my knowledge, hormones are not

routinely screened as part of the medical wellness program for individual cases. Individual persons with medical disease, they may well have. And we have no knowledge of that or the association with atrazine.

DR. PORTIER: Thank you. Dr. Young, you're next.

DR. YOUNG: I wanted to go back to the nested case-control study. And you stated that you had the subgroup of 11 cases who were eligible for screening. I was curious. How may of those were actually identified before 1993 when widespread screening was implemented?

DR. MANDEL: I don't have the answer to that question. I'm sorry.

DR. SMITH: There were three cases diagnosed prior to '93 in the entire study.

DR. HESSEL: But that's not necessarily three out of the same 11 that you're talking about.

DR. YOUNG: But then at least 2 of those would be since there were 12 cases. Okay. Thanks. There were 12 medically identified cases. And you had 11 that you said were eligible for screening. Is that --

DR. HESSEL: Well, we were dealing with 12. But there were actually 14 prostate cancers in the Syngenta workers. Two of them we

didn't know about, so we won't have a date of the diagnosis for them.

DR. YOUNG: So you're saying that some of those three could be in that group as well then.

DR. HESSEL: It's possible, yes.

DR. PORTIER: Dr. Symanski. I'm sorry. I've got a whole list of people, and I've got to give everybody an opportunity. So I'm going to walk my way back around the table.

DR. SYMANSKI: I had a couple of exposure assessment questions. One, in the reading of the draft protocol that we received for the case-control study, I noted that the data were going to be used to determine the unique job categories. And I just want to confirm that that was not done.

DR. SMITH: As far as I know, it wasn't.

DR. SYMANSKI: Second question, it's a follow-up to Dr. Gold's question. Given the biases inherent in the industrial hygiene data, what's the basis for assuming that the rates of decline were the same across the three exposure categories: Regular high or regular intermediate and regular lower?

DR. SMITH: We basically assumed that the things that were being changed were affecting most of the exposures within the plant. That's an assumption. And there may be some inconsistencies with

that in particular areas. Because, clearly, if you install a ventilation system on a bagger, just the people working at the bagger will have the major effect. But there were much changes going on throughout the plant as was noted in some of the earlier discussion. So the simplest assumption we could make given what data we had was that they would be approximately parallel.

DR. SYMANSKI: The second question, in estimating cumulative exposure, if I understood you correctly, that you estimated exposure up to the time that a prostate cancer presented or up to the time at the end of the study for the noncases.

DR. SMITH: The exposures were calculated up to the date of diagnosis of the case for the cases. And for the controls that were matched to that case, exposures were calculated up to that same date of diagnosis.

DR. SYMANSKI: Okay. Follow-up question: Was there any attempt to estimate cumulative exposures excluding the most recent exposures? Because if that shifted the distribution of cumulative exposures, that might have had an effect on the results that you're presenting today.

DR. SMITH: We did calculate all of the exposure measures up to a period six months prior to diagnosis of the case.

DR. SYMANSKI: Just six months.

DR. SMITH: And that had no effect on the results.

DR. SYMANSKI: And my last question, if I may.

DR. PORTIER: Dr. Symanski, I just want to remind you that the material that was presented here today, since we're going to have very limited additional information on it, we may have some difficulty in using that in some of discussion interpretation. So we may not need a lot of clarification on that. It depends on how much you're actually going to use that in your further discussion in the issues to come. I just wanted to remind you of that question.

DR. SYMANSKI: Okay. Keeping that in mind, I'll have one last question.

As you know, Dr. Smith, there's growing evidence in the occupational hygiene literature of significant interindividual variation in exposure for workers who are classified by job title or location or works or other important determinants of exposure. And in the absence of monitoring data, you're not able to actually evaluate homogeneity within these exposure categories. And I'm just wondering if you could comment on what effects significant interindividual variation might have had on the results that were presented?

DR. SMITH: I agree that that certainly is a factor and has been the source of investigations by a number of people including myself. We tried -- since we couldn't directly deal with that, we tried to deal with it by looking for big differences. And so the smallest difference we used in our calculations was two-fold. But we also had three-fold and five-fold differences as well. I guess our underlying assumption is that the variability between individuals doing the same task in the same area would be smaller than the variability between areas and between tasks.

DR. SYMANSKI: Thank you.

DR. PORTIER: Dr. Reif.

DR. REIF: This nested case-control study is, I think, very important to the interpretation of the data. And I think Dr. Blair in his comments pointed out the need for it. So I'm going to ask you a couple of questions about the study design and the analysis.

In the early protocol, you talked about matching on PSA status. And I take it you abandoned the idea of matching on PSA status in the selection of controls.

DR. HESSEL: Yes. Is that short enough?

DR. PORTIER: Yeah.

DR. REIF: With respect to the analysis, could you summarize

the ways in which you attempted to look at the relationship between PSA and atrazine exposure. The only thing that you presented was an analysis in which you do the analysis with all subjects and then you subdivide it or stratify it with respect for the subjects eligible for screening. But there are clearly other ways that you could have explored either effect modification or confounding the relationship between PSA and atrazine. And I wonder what else you did or what you did or what you didn't do with respect to that very critical question.

DR. HESSEL: The focus of the analysis was really on the relationship between prostate cancer and atrazine. Our focus really was not PSA. We have the PSA data that have been extracted now, have not been incorporated into the data set yet. So we may be able to look in more detail at the relationship between PSA and atrazine once we get those data.

But for now, the criterion of 1995, age 45, was based on the data in the report that indicated that that's when pretty much everybody was tested. On the basis of the data that we get, we will be able to do an even better job of zeroing in on people who did or did not.

DR. REIF: I recall in the presentation you showed the classical

triangle that defines confounding with respect to atrazine PSA and prostate cancer. So I take it from your answer, however, that the only exploration of that relationship that you summarized, in fact, you said it in your conclusion, is the analysis that you've shown us with respect to the proportion eligible for screening and the total number of subjects.

And that's what I'm asking. How else did you evaluate the role of PSA as a confounder other than the analysis that --

DR. HESSEL: Yes, yes. No, I understand. That conclusion was based not just on the results of our study but on the basis of the information that was presented by Drs. Adami and Trichopoulos that we know about. And, in fact, the information that was presented by Dr. Delzell and her colleagues.

DR. REIF: Thank you for that clarification.

DR. PORTIER: Is that it, Dr. REIF? Dr. Handwerger.

DR. HANDWERGER: I'd like to get back to the point raised initially by Dr. Portier. And it's to whether or not atrazine is a hormone disruptor in humans. I think you presented evidence that it clearly is in animal models by disrupting GnRH. And then you concluded that you didn't have any mechanism really that could possibly explain how it could be involved in prostate cancer. And you

haven't measured testosterone levels. And I would agree that's not the best thing to measure. If you think it is through a GnRH mechanism, it would be LH and FSH. And you would expect that if you were lowering LH and FSH and you were essentially having some effects on androgen or even on aromatase activity, you might lead to an increase in infertility and a decrease in sperm count.

Do we know anything about the fertility of the people who have been exposed to atrazine? What about the number of children they have? What about the abortion rates? What about those kinds of things? Because I'm really concerned not about prostate cancer alone, but is this drug -- is it a drug? Is it a compound that is a hormone disruptor? Could it play a role if disrupting the hormone systems in humans? And that's what I want to get to.

DR. BRECKENRIDGE: The first point relative to the GnRH mode of action elaborated in rodents. The EPA has adopted a strategy for the regulation of this product to use those endpoints for setting doses of safe exposure. Syngenta does not disagree with that, that strategy. Therefore, we're implicitly acknowledging the potential for atrazine to have an effect on the GnRH system in humans at some dose.

In regard to the expression of that affect in terms of fertility

reduction, we note that 100 milligrams per kg. in the rodent mode generates an effect but 50 per kg. does not. We also note that the exposure levels of humans are orders of magnitude below that.

In regard to the question of whether or not we have any evidence that atrazine causes fertility impairment in the plant, we do not have any evidence.

DR. HANDWERGER: Have you looked?

DR. BRECKENRIDGE: One does not look. It probably would get reported through consequence rather than an explicit study. So that, no, we have not looked explicitly in this study.

DR. HANDWERGER: I think it's hard to know about infertility unless you ask the question.

DR. PORTIER: Dr. Roberts.

DR. ROBERTS: I just wanted to go back to bio-monitoring just very quickly. There are bio-monitoring data, I guess, techniques that were worked out in the '90s for this plant. I wondered if you are aware of any similar bio-monitoring data from end users of the product such that it would help us get perspective on the differences in atrazine exposure in terms of the magnitude that might exist in this plant versus other individuals, for example, those that might make up the bulk of the Ag Health Study subjects?

DR. BRECKENRIDGE: Again, there are a few published literatures on this technique for bio-monitoring small numbers of subjects. CDC last year reported a larger bioassay survey. I think there was in the order of several hundred, maybe 1,800 individuals that were randomly drawn or drawn from across the country. I don't think it was randomly. The were measuring mercapturic acid of atrazine. Their sensitivity of detection, I believe, was 73 parts per trillion in the urine. They found no detects in the general population.

The only other study that we have relative to bio-monitoring is the agricultural study that we conducted in two states with about 122 workers. And there were three-day total void samples collected from these individuals at a time when they were -- and these were generally custom applicators that were handling large amounts of atrazine during the season. And those were the values or the ranges of values that you saw on our dose continuum was from that set of data. So those are reasonable estimates about what an agricultural worker might receive using an analytic method to quantify that exposure with no information about hygiene practices of those individuals, but presuming they are following label and protective clothing. Thank you.

DR. PORTIER: Dr. Knobeloch.

DR. KNOBELOCH: I think I know the answer to this question, but I just want a clarification. One of you, I've forgotten which, alluded to the positive urine tests that were apparently related to swimming and the use of simazine as a swimming pool chemical. And I wonder to what extent you were able to consider nonoccupational or preemployment exposures of your cohort to triazines.

DR. BRECKENRIDGE: I'll just answer one question relative to the confounding with swimming pool chemicals. It's not simazine. It's cyanuric acid. And if fact, that agent was used as a disinfectant in swimming pools for many years. I think it subsequently has been no longer been employed for that purpose. It is a three-chlorine-substituted triazine ring. And it is making chlorine available for disinfectant purposes. And I believe that was the molecule they measuring early. So realizing that there was that potential confounding, they went to something that was more specific to atrazine.

The second part of your question relative to other confounders of exposure, simazine or other triazines relative to this plant, I'll pass over to these gentlemen.

DR. HESSEL: We didn't get any information about nonoccupational exposure.

DR. PORTIER: Dr. Bove.

DR. BOVE: I want to go back to the screening program. And looking at the data, it appears that African Americans and white employees were screened about the same although African Americans slightly more in the age groups 45 and over. But in the age 40 to 44, there's a huge difference in the percentage of African Americans, nearly a hundred percent being tested as opposed to about 20 to 25 percent among whites. Yet the difference in observed and expected for African Americans is not that great. It seems to be bigger among whites. So you have more intensive screening being done in the African American populations, yet you don't see much excess. How does that jive with the hypothesis that PSA screening can explain the excess?

DR. MANDEL: First, let me point out that in the published paper the SIR for white men was 183. The SIR for nonwhite men was 146 with overlapping confidence intervals. It was very hard to interpret the numbers when the numbers get very small. What we don't know is the follow-up of the PSA tests because they were not done by the facility. And that would ultimately determine the detection of the cancers. And individuals were referred out to physicians in the community for follow-up exams, and we don't have

any information how the extent, whether it varied by race.

DR. BOVE: Even so, wouldn't you expect to see at least as high if not higher excess among African Americans?

DR. MANDEL: As I mentioned the data that was published was 146 versus 183 with overlapping intervals suggesting there's no difference at least between the two race roles. I mean, it's very hard to interpret these numbers because they're so small. But there was an excess in black men as well as white men almost of the same order of magnitude.

DR. PORTIER: Unless there's additional pressing questions for clarification -- I'll get you, Dr. Young. Dr. Young.

DR. YOUNG: I want to go back to the cohort study and the question I asked earlier this morning to Dr. Blondell about analyzing the data separately for prior to 1993 and after 1993.

It looks like you kind of got a rough cut at it when you look at the previous study that was unpublished but is cited in the documents that we have that looked at that data from 1985 to 1993. And you weren't seeing an excess risk overall. But when you did look at that subgroup for age groups less than 55, there was a significant risk. And it was about seven and a half time higher. Given that PSA screening wasn't widely implemented during that time period, how do

you explain those results?

DR. MANDEL: I think the screening rate prior to that period was about 20 percent. And I don't know the screening histories of those few cases. I think there were a total of five.

DR. YOUNG: About four.

DR. MANDEL: Four. I don't know the screening histories of those four cases.

DR. YOUNG: Well, your document says that one in four had a PSA test before diagnosis.

DR. TRICHOPOULOS: There are two distinct issues there. When you compare the plant, the population of the plant, the Syngenta employees to the outside community to the baseline, their PSAs are confounded because you have a resident exposure and you have PSA. When you look within the plant as in the case-control study, the studies are confounded only with respect to duration of employment because you have to be employed long enough in order to be captured by the PSA screening. But it won't be a confounder for levels of exposure.

So as you have seen the analysis when you make the remark very early, which is a very astute one, when you look there, you will see an effect which is confounded only with duration because,

obviously, you have to be there. For the actual levels intensity of exposure, you don't see an effect. It's whether you control or don't control for the PSA.

So it's really this duel role. PSA is a confounder when you're already testing, the Delzell study, with the outside population. You go to the case-control study, it's only a confounder to the extent that's associated with long employment so you would be able to be captured by the PSA.

DR. PORTIER: Other questions of clarification?

DR. HOPENHAYN: I just need a clarification. In the nested case control study, were both the cases -- and you probably already said that, but I just need it clear. Were both the cases and the controls only employees of Syngenta and none of the contract workers?

DR. HESSEL: Yes.

DR. HOPENHAYN: And of the controls, of the 130 controls, only 60 were eligible for the screening. Does that reflect, even though the mean ages of the cases in the controls were similar, does that just reflect a very different age distribution so that half of the controls were ineligible for testing even though they were employees? Were they just younger or why weren't they eligible for screening?

DR. HESSEL: I'm not sure I'm following the question entirely.

The age was calculated up to the date of diagnosis of the case, and the controls were matched by year of birth. So the ages would be fairly similar.

DR. HOPENHAYN: I'm just trying to understand why just about half of the controls were eligible for screening.

DR. PORTIER: Dr. Trichopoulos, were you going to add something?

DR. TRICHOPOULOS: Yes. Essentially you have to match for age, you match for ethnic group race, and then you have whether they have been long enough to be captured by the screening that started in 1995. If they were not there long enough there to be captured, then you were out.

DR. HOPENHAYN: Okay.

DR. MANDEL: If I could just add one statement to this. The cases, because they were largely screen-detected, had to be there during the screening program.

DR. TRICHOPOULOS: Others don't.

DR. MANDEL: So there was in a sense a built-in bias and why we didn't follow through on the matching for PSA screening as originally proposed because we were concerned about creating an even a bigger problem.

DR. PORTIER: Dr. Merrill.

DR. MERRILL: He answered my question.

DR. PORTIER: All right. Dr. Sandy.

DR. SANDY: Can you again explain what the definition of eligible for screening was?

DR. HESSEL: These were people who were employed in 1993 or later, and who achieved at least age 45 during that time period.

DR. SANDY: Was that a criterion for the original cohort study?

DR. HESSEL: No, no, not at all.

DR. SANDY: No. Okay.

DR. HESSEL: Not at all.

DR. PORTIER: Any other questions or for clarification before we break for lunch? We've had this Panel here for two hours. Okay. I want to -- Dr. Bove.

DR. BOVE: Just real quick. One more time on the controls. Are they restricted to company employees or to the whole cohort?

DR. HESSEL: No. They were only Syngenta employees.

DR. BOVE: Syngenta employees. Okay.

DR. MANDEL: As were the cases.

DR. PORTIER: Dr. Breckenridge, I want to thank you and your panel for the time and effort to explain this to the SAP and your

patience with our questions. We had one more public comment before lunch. I'm going to push that public comment until after lunch. We're going to break now for -- let's try to eat lunch in 45 minutes and be back in 1:30. Otherwise, we're going to be very late into the afternoon. We will try to be back at 1:30, please.

[Lunch recess taken at 12:45 p.m.;

session reconvened at 1:35 p.m.]

DR. PORTIER: We are just getting all the electronics, starting in about a minute. If you could sit down and get prepared to begin. Is Scott Slaughter here? Our first public commentor after lunch will be Jennifer Sass and Carol Strobel. I hope you're prepared. Yes.

DR. SASS: Carol is going to go first for time issues.

DR. PORTIER: Okay. We'll be starting in about a minute.

Welcome back to the July 17 FIFRA Science Advisory Panel meeting. I'm Chris Portier from the National Institute of Environmental Health Sciences, and I'm chairing the meeting this afternoon.

We've finished with EPA's presentations this morning. We've done the first of the public commenters, and now we're continuing on the public comment period. I would like it noted to all the public commenters to please identify yourself, the organization you're

representing, and then go on with your public statement.

In addition, would all the Panel members, please, remember to use the microphones, speak clearly. And if I don't introduce you, please introduce yourself when you make your comments. And if the Panel members could look to notify me in advance of wanting to make their comments, I'll keep a list of who wants to comment. And with that, we'll begin with Dr. Strobel.

DR. STROBEL: Thank you, Dr. Portier. Actually, I want to make clear. I'm not Dr. Strobel. My name is Carol Strobel. And I do policy work for the Children's Environment Health Network. I'm here today on behalf of the network and Physicians for Social Responsibility and the America Public Health Association. And I just have some very brief comments.

My purpose for speaking today is to highlight for you the comments recently submitted by these three organizations. I believe it's a letter in your packet. And I just want to focus on two points.

We believe that at this point atrazine should be classified as a likely human carcinogen. Evidence continues to accumulate suggestive of an association in humans between atrazine and cancer. And we think it's important for you to consider the widest perspective on the questions before you rather than limiting your consideration

narrowly, particularly when we're talking about very important human health questions. The letter provides additional information supportive of our conclusion.

And our second point is that we think that it's important to use the best available information to make our decisions. And we believe that the new cancer risk assessment guidelines should be used to evaluate the cancer effects of atrazine. These guidelines have been extensively reviewed. They've been approved by the SAB. And the SAB has recommended that they be implemented as soon as possible. And we strongly agree with that. If these guidelines are not used, we would be deeply concerned about how many more years will pass before these approved guidelines will be used on this pesticide.

That's the extent of my comments. Thank you.

DR. PORTIER: Thank you. Are there any questions for Ms. Strobel? You're welcome to stay during Dr. Sass's if there are any follow-up questions and you're still available. Dr. Sass.

DR. SASS: Thank you for the opportunity to present comment to the Scientific Advisory Panel and thank you also to the Panel members for coming together and giving your time to this very important issue.

Atrazine has been in special review for about eight years I think

now, and --

DR. PORTIER: Introduce yourself.

DR. SASS: I'm Jennifer Sass. I'm a scientist, a senior scientist with the Natural Resources Defense Council. It's an environmental non-profit group. I'm based here in Washington, D.C. My own background is in some molecular biology. My degrees are in anatomy and cell biology. My post-doc was in neurotoxicology. And I did actually take only about five epidemiology classes during that time, so I'm not really an epidemiologist. But that's some of what I'm going to be commenting on today.

Atrazine has been in special review for a while, or what we jokingly call really, really special review. And at this point, once a decision is made on this chemical, it really won't come up again in the cycle for about 14 years. So what I would like to suggest to the Scientific Advisory Panel today is that we really review all the data that's available on the carcinogenicity of atrazine, there's some human, some animal data, in order to make a really full and informed decision about this chemical.

It was reviewed by the Scientific Advisory Panel in the year 2000. But since then, new evidence has come to light. And I think that the body of the evidence as a whole deserves to be reviewed.

The comments I'm presenting today are supported by the following cosigners, the Northwest Coalition for Alternatives to Pesticides, Consumer Union, Beyond Pesticides, the American Bird Conservancy, Defenders of Wildlife, Sierra Club, and the Environmental Working Group. Together we represent millions and millions of people in this country, and many of them are affected by atrazine exposure which, as you know, is widespread pollutant in waterways throughout the U.S.

The EPA called this Scientific Advisory Panel together and also one last month to review the effects if atrazine on amphibians in a consent degree with the Natural Resources Defense Council. And we asked them at the time to please rereview the available amphibian data, a few other things, and also to reconsider the cancer classification of atrazine.

The EPA chose to stick to not only the letter of the law but actually what we consider an erroneous interpretation, and they did not provide any data submitted after February 20, 2003, to this Scientific Advisory Panel although there was new data, published data, that was available pertaining to this issue directly. As well, they believe that because the Scientific Advisory Panel did meet on this issue in June 2000, three years ago, that that data didn't have to be

looked at again. So what I would like to ask the Scientific Advisory Panel today is, if they could provide a full and informed review of the carcinogenicity of atrazine using the 2003 Draft Final Cancer Guidelines. Currently, the EPA is using the 1999 Draft Cancer Guidelines. And we're suggesting that we use the new way of thinking about this issue.

Under those new draft final guidelines, we believe that atrazine would be classified as a likely human carcinogen. So what I'm going to present to you today is the data that I believe supports this kind of classification under these guidelines. I don't think I'm going to read these here because I'm going to go through them one at a time with the data that I believe supports each criteria. But I would just like to say that these are all five of the criteria directly taken from those draft final guidelines. So I haven't changed a word; I haven't left or added any criteria or anything. And then I'm just going to go through them one at a time and show you the data I believe supports this kind of classification.

Number one, "an agent with some evidence of an association between human exposure and cancer, with or without evidence of carcinogenicity in animals." This is some of the epidemiology data. This study was published in 2003, this spring in fact, Paul Mills.

Actually, it's not et al. This was just a Paul Mills. And it's on Hispanic farm workers. This is a follow-up to an epidemiology study that he had published a few years ago. And this one continued looking at that same cohort.

And what he found was that there was an increase in prostate cancer associated with high triazine exposure. This came out after the February 28, 2003, EPA set deadline. And that's why it wasn't provided to you. But you think I provided desk copies in consultation with EPA with their permission to you.

He had a number of cases of prostate cancer. And he divided them into different exposure levels, four exposure categories. And this is the number of cases in each category and then the odds ratio associated with triazine exposure. He looked at other chemical exposure, too. These farm workers were exposed to a number of different chemicals.

And what he found was that there was at the high level, where there was 29 cases, an odds ratio of 1.81; and at Level 3, there was 44 cases with an odds ratio of 1.56. The confidence intervals do span one. But, in fact, the tail here goes quite high. And they're fairly close to the one. So although this was considered nonsignificant technically, there was a positive trend. There's somewhat of a dose

trend increasing here with increasing odds ratios.

As well he found the relationship was statistically significant in men with more advanced disease at diagnosis. And for here he had an N of 94 cases. And the odds ratio was 2.16. It did not span one in this case.

The author concluded the Hispanic farm workers with relatively high levels of exposure to triazine herbicides, in this case, simazine was the associated exposure, experience elevated levels of prostate cancer compared to workers with lower levels of exposure. And simazine, as you know, is a triazine. It's related to atrazine. And the EPA considers them to be have the same mechanism of toxicity. They are reviewing them under the same mechanism of toxicity group.

There was a study published in 1999 by Donna, et al., an Italian study I'm sure you're aware of. But very briefly, it found an association between triazine exposures associated with ovarian cancer in exposed previously exposed women. They report that women previously exposed to triazines, this was looking backwards, a retrospective study, showed a significant relative risk of 2.7 for ovarian neoplasms. And the doses could not be quantified for the study subjects. It was done by questionnaire. But the authors suggest that risk trends for duration and probability of exposure to triazines

both favor the plausibility of the association.

I also included this in your desk copy. There's a reply and a subject issue of the Scandinavian Journal this was published in and then the authors' reply to that. But the study stands.

You've heard a little bit about the Ag Health Study. The National Cancer Institute is doing a study, the Agricultural Health Study. And this study, although they did not find an association between prostate cancer and atrazine, they have not yet looked for an association between atrazine and overall cancer incidents. They are going to do this. They meant to do this, and they ran into some road blocks along the way. Technically, it actually had to do with the war. Some of the people who were reservists who were working on this project and got pulled away. But that data will be out.

And meanwhile, they've let me know that there's an association between female pesticide applicators in the Midwest and ovarian cancer; although they have not broken this down yet to what kinds of chemicals they were exposed to. But the researchers do point out to me that in the Midwest there's a lot of atrazine that's applied. In fact, in the states where this was significantly elevated, when the two-state data were pooled, Iowa applied 7 to 8 million pounds of atrazine annually; and North Carolina applied approximately half a million

pounds of atrazine in 2001. This is the most recent data I could get. And it fluctuates year by year. Although Iowa was pretty steady at 7 to 8 million.

And this when these two states were pooled, they found an elevated ovarian cancer in female applicators that was statistically significant. There was only eight observed cases, but versus 1.9 expected. So they're looking at this further. And this data is being submitted for publication in the Scandinavian Journal of Work and Environmental Health.

There is, of course, the industry sponsored study that is the narrow topic of today's meeting. I won't go into it. I know that you have a far deeper understanding of this study than I do.

But I will point out that they did find that workers had elevated prostate and other cancers and the confounding issue was never clarified. So there is no data one way or the other to dismiss these cancer findings or, in fact, to dismiss the PSA confounding.

The authors themselves believe that a four to five to six times elevation may be explained by PSA confounding based on other published reports. But I've pointed out in a letter written in response to this publication which is published in a subsequent issue of the Journal, and which I've attached to the publication in your desk

copies, that if you divide up the workers, the real problem with confounding is real, which is that active company workers, which is this group right here with the asterisk, this was the group that had the PSA testing and it was the group with the longest duration of exposure. So it is a confounder. This is a problem.

But it doesn't go away. There's no data that have been provided. They did not do a matching reference group that was also PSA screened or some other technique that could be done to make these confounders nonconfounding. If a confounder applies to both groups, then it's nonconfounding anymore of course.

So in this group, you have 11 cases. It's not a lot of cases. This study did not have the power to make much of a statement one way or the other. And all of the reviewers agreed to that. However, with 11 cases versus 1.8 expected, this is not the four or five times that the PSA seems to explain. I'm not reading into this anymore than what can be said from an underpowered, statistically weak study with few cases. Except that I don't think it's been explained. And I think that it deserves further follow up and can't be dismissed.

Criteria No. 2 for a classification of likely under the 2003 draft final guidelines is: "An agent that has tested positive in more than one species, sex, strain, site, or exposure route with or without

evidence of carcinogenicity in humans." So we have three studies that suggest carcinogenicity in humans. But what about some of the other species?

There's a paper published also by the same Donna in Italy showing tumors in male mice. These were Swiss mice, males, following interperitoneal injections of atrazine. And the interesting thing about this study is that they did take it to a full year. And they found 6 lymphomas in 30 treated animals. And in the controls, they a hundred controls, and they found only one. So it's highly statistically significant. And that's a male mouse study.

In female Sprague-Dawley rats, this one is actually published by a group of authors that include some authors that list their affiliations as Novartis. Although in the publication under the acknowledgement, it's not stated who fund the study. I'm assuming that Novartis at least knows about this study. Novartis being the former Ciba-Geigy. After Ciba-Geigy and before Syngenta, let's say.

They found tumors in female Sprague-Dawley rats. The interesting thing is they actually did three, two-year studies. And then this particular publication I've cited here is the review that compares all -- I'm sorry. They did five two-year studies, and they found significant results in three out of five of the two-year oral

dosing studies. So this is rats, Sprague-Dawley, oral dosing. The one I just did was mice, Swiss, male, IP injection.

And they found quote, "A mammary tumor response," and this was fibroadenomas adenocarcinomas, "has been consistently observed in Sprague-Dawley female rats following chronic oral dosing of atrazine and simazine" -- these are separately done -- "at or above the maximum tolerated dose."

Now the tolerated dose is 400 part per million. But actually if you look at the table, the data tables in the study, what I have found was there are significant effects. They identify them as significant with as asterisks using a P value of .05. At 50 part per million, that was one out of five of the studies; 70 part per million in two out of five of the studies; and at 400 part per million, in one study but both fibroadenomas and adenocarcinomas; and at 500 part per million, also in one study, both cancer types; and at a thousand part per million in two studies.

Now, when I say one or two studies, they're not all the same studies. The authors correctly identified that there was three studies that showed positive results. But what I'm telling you here is that some of them showed it all the way down to 50. So that's two strains, and male and female.

Some evidence in humans based on three different studies, the ag field study from California, the Italian study, and the workers study.

And a positive study that indicates a highly significant result. For example, an uncommon tumor. We don't have that obviously with prostate cancer, a high degree of malignancy, or an early age at onset. What's interesting, and one of the Panel members raised already this morning, is a highly significant result that was published recently by Drs. Birnbaum and Fenton and also shown at an abstracted SOT by Fenton and Davis in 2002. The publication was in 2003, and was not deemed important enough to give the Scientific Advisory Panel.

But they did something very interesting. They tested atrazine the way I think it really should be tested. They looked at whether exposures during development, in utero exposures, predisposes an animal to cancers later in life following exposures with other carcinogens. And this was a different strain, Long-Evans rats. They were exposed in utero to atrazine followed by a challenge with a known carcinogen. And what they found was atrazine-exposed pups demonstrated delayed mammary bud outgrowth followed by an increase, in multiplicity and volume of tumors, after exposure to the carcinogen compared to the non-atrazine treated controls.

So controls were not exposed. Atrazine was during in utero. And then both groups with challenged with a known carcinogen. Those that were exposed in utero to atrazine had much higher levels, multiplicity and volume of tumors. In addition, those exposed pups also showed an increase in organ pathology. This included adrenal nodules, pituitary foci, large ovarian cysts -- large is greater 2 millimeters in this case -- lymph node and spleen enlargements compared to controls.

Criteria 4, last criteria that I'll do, is a positive study that is strengthen by other lines of evidence. For example, some evidence of an association between human exposure and cancer but not enough to infer a causal association -- I think that's what we have here with the human exposures -- or evidence that the agent or important metabolite causes events generally known to be associated with tumor formation.

Here I want to draw your attention to the endocrine disruption activity of atrazine. The Scientific Advisory Board in its meeting last month while reviewing the Draft Final Cancer Guidelines said in the report that it is likely that early life stages have windows of susceptibility to carcinogens acting through endocrine disruption. And they provided some examples in there report. And they stated in summary that there is reason to believe that hormonal agents can be

more potent carcinogens when exposures occur early in early life stages rather than later life stages alone.

This to me is a criteria that's filled clearly by the experiments by Birnbaum and Fenton where they showed that exposures during in utero to the Long-Evans rats predisposed to cancer when they were confronted later with a known carcinogen.

So I think that atrazine at least with some data, let's say the time where atrazine has actually been looked at in this manner, what's been found, I think, is that atrazine has a mechanism of action, endocrine disruption, which may predispose when an animal when exposed in utero or during early life stages to cancers later in life.

There's some animal data here. I actually don't want to go over this because you've seen it all. Actually, the public commenters went over this. It's some of the data that I picked. There's a number of other studies, but I picked that the larger studies, just showing that atrazine does act as an endocrine disruptor in a number of different animal studies, in a number of different strains by a number of different labs. But since the public commenters earlier did acknowledge that atrazine is an endocrine disruptor and does reduce testosterone levels and disrupts luteinizing hormones and gonadaltrophic releasing hormone levels, I don't want to go into this.

I'll just point out that there's some prostate gland inflammation when nurse rats were exposed. I think what's most interesting about this study for me is that the atrazine did not travel through the milk. They actually measured in the milk. And in fact what it did was alter hormone levels in the dam, the nursing mother. And then those altered hormone levels were passed through to alter the hormone levels in the pups that were drinking.

This one was in Wistar rats. This study was also in Wistar rats, and it showed delayed puberty in both male and female Wistar rats when they were exposed early in life. And what was interesting I think to this was that males were more sensitive to this. Males had affects down at 12 and a half milligrams per kilogram atrazine; whereas the females didn't have affects until up to 50 milligrams per kilogram atrazine. And these were atrazine administered post-natally.

And atrazine reduced sperm motility in Fischer rats. That was IP injections. This was a study published in the year 2000.

The frog data I really don't want to go into. But it's just the recent publications by Tyrone Hayes. It's been also confirmed in some other labs. The Mendosa paper, two Mendosa papers, have been published from Canada that basically showed that Xenopus laevis exposed in the laboratory had various different gonadal disturbances

in their developments. And some of that was as low as .1 part per billion. Although the Mendosa tried 25 part per billion and found similar affects and included hermaphrodites.

And the Hayes also found that at 25 parts per billion, males displayed a decrease of testosterone levels which we've also seen in the rat data.

In 2003, Hayes published showing retarded gonadal development in exposed animals. And he associated some of this with Rana pipians in the wild.

And this is a study that has not been given much air time. And the reason why is it's not published. It's a Syngenta-sponsored study. And they consider the results preliminary. And they did talk about it at the meeting last month, but dismissed it as preliminary.

And it is preliminary. They're right. It's a Syngenta-sponsored. But it's very interesting. They looked at Bufo marinus which is a toad in sugarcane fields in Florida. The sugarcane fields are treated with atrazine. And what they found was that the frogs closer to the fields or within the treated fields were the males, the genetic males actually showed female skin colorations. And some of them had eggs or were hermaphrodites. And the farther you got from the treated fields, the less you observed this.

So they consider it preliminary because they don't have dose type data. And EPA considered also that these studies didn't have good dose response relationships in the frog data. But I consider it interesting because I think it's got a built-in dose response gradient, although it is a preliminary study.

They presented this at the Society of Toxicology meeting. And it was written up in a small report. Not by them, but by an earth science reporter there, who quoted the authors as saying that the work, quote, "lends credence to University of Berkeley endocrinologist Tyrone Hayes' hypothesis that atrazine is affecting sexual development of amphibians."

And that another of the Syngenta-sponsored researchers, Jim Carr finds an effect at atrazine concentrations that are similar to what we see in the field and to what we think toads are exposed to. So one more species which is affected.

In summary, I think there is evidence of cancer in laboratory animals in two species, rats and mice. There is demonstrated endocrine in multiple strains. There is demonstrated endocrine disruption in Aventis-exposed laboratory animals. I think with endocrine disruption, we can safely say it's a multi-species endpoint which may predispose an atrazine-exposed fetus or neonate to cancer

later in life. This is coming from a rat study.

There is evidence that exposure to atrazine during development predisposes laboratory animals to developing cancer later in life, the Birnbaum and Fenton work.

And there are reports of endocrine and cancer effects in atrazine-exposed humans. I cited the two studies that are published, Donna and Mills. But I also bring up the study that you're discussing today as I think interesting and worthy of follow-up.

So we suggest that the Scientific Advisory Panel recommend that atrazine be classified as a likely human carcinogen based on the 2003 draft final guidelines. And in the event that the SAP feels that it needs more opportunity to comprehensively review the available data, we recommend that the SAP request that EPA promptly reconvene to review all available data using the 2003 draft final cancer guidelines to make a determination of cancer classification. Thank you.

DR. PORTIER: Thank you. Are there any questions from the SAP?

Dr. Sass, if you could join us over here instead of to the back of the Panel it would be better at this point. Questions for clarification? None. Thank you very much.

Our next public commentor is Alan Roberson, the American

Water Works Association.

MR. ROBERSON: Good afternoon. I'm Alan Roberson. I'm director of regulatory affairs for the American Water Works Association. You're probably not very familiar with our association. There are a couple familiar faces here. But we're the largest scientific and technical association representing drinking water. Our members kind of cover the range of water utilities to consulting engineers, manufacturers, academic, state regulators. We've got 57,000 members and represent 4,200 utilities that serve about 82 percent of the water in the United States.

So you may be asking why are we here today. Atrazine is a pretty significant problem for many of our member utilities in the Midwest. The atrazine standard was established in 1991 at three parts per billion. Compliance is based on an annual average of four quarterly samples, a rolling annual average. During the '90s, many of our member utilities in the Midwest had to install additional treatment to comply with the standard. It continues to be an ongoing problem.

Utilities continually have to bear a financial burden for this additional treatment. This financial burden has been shifted to the water utilities from the manufacturers and the growers, and we think that's unfair.

We've been pretty actively involved in following the special review since it started, as Jennifer said, the last eight years. We've commented on many different pieces of, submitted some extensive comments on the IRED that came out earlier this year.

We generally support the IRED, particularly on the concept of environmental monitoring, that is, monitoring F source waters as part of the registration process. We do have one significant problem with the IRED with the mitigation trigger. We think the mitigation trigger should be 12 parts per billion. Because if a utility gets a single sample at 12 in their source water, without any additional treatment, that is a violation of the Safe Drinking Water Act standard. In other words, if you take that 12, divide it by 4 you get three; and that's a violation of the standard.

Because of our ongoing concerns, we've started an extensive monitoring project in the Midwest this year. We're monitoring 40 sources on a weekly basis, doing both a paired and a finished water sample. At 15 of these sources, we're also doing weekly, Monday through Friday sampling. We're also taking 10 percent of these samples and doing further analysis through GCMS to look at triazines and some of the metabolites to better under the relationships between those. We're also looking at some treatability studies to try and

understand the efficacy of different kinds of carbon treatment.

This is a significant investment for our association, for the member utilities to do this. And we feel like we're doing it because it's important to our members.

So I want to summarize. I tried to keep this short and on one piece of paper. We really have two recommendations. First, we think it's important that the financial burden for an ongoing treatment get shifted away from the water utilities and back to the manufacturers and the grower.

Secondly, we'd implore that the SAP and EPA complete the special review as soon as possible and then to appropriately revise the drinking water standard as soon as possible. Our member utilities have been wrestling with this health effects debate for the last eight years. We're not toxicologists. We're not epidemiologists. I'm a civil engineer by training. Most of our members are either engineers or chemists. You start having this debate about these kind of studies, and we can't really actively participate. But yet our member utilities are feeling pressure from the public because of these media stories about endocrine disruptors and hermaphroditic frogs. I had to put in that frog reference because I missed the June meeting and I just like saying that word in public.

But it is a real problem. We have our member utilities in the Midwest, a large utility on the Missouri River, that's had to lower their internal treatment goal a few times over the past decade because of this uncertainty in health effects study. We'd like for this uncertainty to get resolved so our utilities would know where they need go with treatment and can go ahead and put that in.

So I appreciate the opportunity to make these comments to the SAP. And if there are any questions, I'll take them.

DR. PORTIER: Are there any questions for Mr. Roberson? No. Thank you very much.

Mr. Leonard Geonessi. He will be followed by Dr. Dan Bird.

MR. GEONESSI: I believe you have copies of my remarks. My name is Leonard Geonessi. I'm with National Center for Food and Agricultural Policy. We're a private non-profit group here in Washington, D.C. And for the past 10 years, my organization has maintained a unique national data base on pesticide use for the United States. We track the use of 200 different pesticides as they're used on 87 crops in the 48 continental states.

In terms of volume, atrazine currently ranks number two in the United States in use amounts among herbicides used in agriculture. For many years, atrazine was the number one volume herbicide used in

the United States. But recently it's been eclipsed by the tremendous increase in glyphosates usage.

Now there's been much discussion about the risks and the benefits of atrazines use. And what I'd like to talk about today is some of the benefits of atrazines continued use particularly to the nations corn and sorghum growers. Basically, atrazine is a very inexpensive herbicide. It costs four to five dollars per acre to be used. It's usually applied at planting. It provides residual control of germinating weeds throughout the growing season. It kills a broad spectrum of weeds, both grasses and broad leaves. But it's typically applied with other herbicides to extend its spectrum of control.

Between 1986 and 1994, there were nine studies that estimated the potential economic impacts on U.S. corn and sorghum growers if atrazine were to be removed from the marketplace. And the estimated economic impacts range from $460 million a year to $3.3 billion a year.

In 1996, Novartis submitted a comprehensive economic analysis of a potential ban on atrazine's use for the nations corn and sorghum growers based on a study done by David Bridges at the University of Georgia. And that study estimated that the lose of atrazine would result in an economic cost of $1.2 billion to the nation's corn and

sorghum growers. And most of this increase costs or loss would be associated with the potential loss consists of higher costs due to more expensive alternatives that would have to be used.

Now, the alternative herbicides are more costly for several reasons. Many of the alternatives are newer. They're still on patent; and, thereafter, they are more expensive. Secondly, the alternatives do not provide a broad a spectrum of weed control in comparison to atrazine; thus, you have to use several herbicides. And, third, many of the alternatives do not have a sufficient residual control period in the soil. And as a result, multiple applications have to be made.

Well, it's been seven years since the last comprehensive economic assessment was conducted. So what I thought I would do would be to collect some information currently to informally provide you with a current view of what the loss of atrazine would cost if it went into effect today. After all, there have been some new herbicides that have been registered in the past seven years, including Isoxiflutal, nesitrione for use with conventional corn, and glyphosate which now can be used with genetically engineered corn.

Some of these new alternatives have quite a broad spectrum of control. For example, glyphosate has very few weaknesses, misses very few weed species. So we conducted an informal poll of 15 weed

scientists around the country who are responsible for developing weed control recommendations for corn farmers. We asked them which alternatives would likely be used if atrazine were no longer available. It's still true that no single alternative could substitute for atrazine.

As broad spectrum as glyphosate is, it has no residual activity; and as a result, it would have to be sprayed multiple times as well as be paired with some early residual herbicides. Thus, the unanimous response that we got from the weed scientists was that multiple applications of multiple herbicides would still have to be made for to substitute for atrazine.

In addition, the experts agree that without atrazine, weed control costs in corn fields would go up by $20 dollars per acre. We have about 50 million acres of corn treated with atrazine at this time. The increased costs of alternatives if atrazine would not be available would total about $1 billion a year in extra costs for our corn growers.

Now, this simulation assumes that all corn growers would continue to grow corn without atrazine and simply switch to the use of these alternative. However, several of the weed scientists that we talked with expressed the opinion that corn growers in their states would stop growing corn completely without atrazine. This concern was raised particularly by scientists in southern states where

corn-yield potential and economic returns are lower than they are in the Midwest. States such as Georgia and Oklahoma would likely see a reduction in corn acreage because corn growers could not afford the extra $20 dollars an acre for weed control.

Some weed scientists have strong concerns that managing herbicide-resistant weeds will be significantly more difficult without atrazine. For example, there are states where mare's tail populations resistant to glyphosate have evolved in soy beans, a crop which is typically rotated with corn. Atrazine use in corn is critical in controlling the populations of these glyphosate-resistant mare's tail. Without atrazine's use in corn, mare's tail populations in soy beans will be greater the next year. And this problem will grow then if glyphosate is substituted for atrazine in corn. And it's also being used in soy beans.

A recent program in Iowa was designed to encourage corn farmers in a reservoir watershed to stop using atrazine. Farmers would be paid $20 per acre not to use atrazine. About one-third of the growers signed up, while two-thirds of the growers felt that $20 an acre was not enough compensation to stop using this product.

There are intangible benefits that are not directly captured in a straight comparison of costs. For example, it's extremely complicated

to choose these sequential applications of separate, expensive herbicides to replace a single application of inexpensive atrazine.

So as you can see, growers have elected to use atrazine for a reason. It's a low-cost way of controlling serious weed problems faced by growers around the country. With limited and more expensive alternatives, a loss of atrazine would force growers to make difficult choices and, in some cases, to stop growing corn.

I am not aware of an effort to measure the economic damages associated with atrazine's use. The economic benefit, on the other hand, of using atrazine is at least a billion dollars a year.

Thank you very much.

DR. PORTIER: Thank you, Mr. Geonessi. Are there any other questions? None. Thank you very much.

Dr. Bird. After Dr. Bird will be Jerry White and Donald Ridley.

DR. BIRD: I would like to thank the Chair, the Science Advisory Panel, and the members of the Panel for the opportunity to testify. I've sent you all I believe twice, once in paper and once by e-mail, my written comments which are brief. I really have just two points to make.

The first is that I think EPA has done a very credible job going through the epidemiology data and I think that you can make a

decision about the epidemiology data based solely on the epidemiology data itself. It's not necessary to go outside of those data to come to a conclusion.

The second is, if you do want to go outside of those data and you want to look at the mechanism or the mode of action in rodents, which I think is very strongly validated at this point through many publications in the scientific literature, we call it the "neuroendocrine hypothesis," you have to look at biological plausibility which is a heavy element in the mode of action in the new cancer guidelines. That takes you in a direction of figuring out why the predicted direction of the effects of atrazine would be the opposite of those seen in the St. Gabriel work force.

So those are my two comments. I have nothing further to say. I think, Chair, you wanted me to announce my name and where I'm from. I apologize. My name is Daniel Bird. I'm a toxicologist professionally. I'm representing myself today. The firm on the letterhead is one I used to work in. They were kind enough to let me use their secretarial workforce in return for putting it on their letterhead. I used to be the president of the company. I no longer work there.

DR. PORTIER: Thank you. Are there any questions? No.

Thank you very much, Dr. Bird. Dr. Ridley. This presentation will be followed by Mr. Hedberg. You'll be after them.

MR. WHITE: Mr. Chairman, I will start off the comments. My name is Jerry White. I'm the executive director of the Kansas Corn Growers Association and also the Kansas Grain and Sorghum Producers. I live in east central Kansas. I'm not a scientist, but I brought one with me today. I also serve as a chairman of a coalition known as the "Triazine Network." This is a grower coalition that was formed in 1995 by producers of over 30 commodities to provide a vehicle for participation in the EPA's special review of triazine herbicides.

Our objective is to ensure that EPA has and utilizes the best available science to conduct the special review. Our membership encompasses producer groups from sea to sea and border to border. And certainly the producers of over 30 commodities.

Atrazine has been used as a foundation of most of our weed control programs since the 1950s. And as talked about earlier, our sister organizations that don't necessarily have the same issues with atrazine directly that corn, sorghum, and sugarcane might have, certainly have similar issues that are tied to it through simazine use. We know the product well. It's been used for a long time if we know

how to use a product in a way that provides safety for ourselves in the environment that we farm and live in. And we have confidence in the product because of this long history.

While we have not always agreed with past EPA assessments relative to atrazine, in general, the process has moved forward in a positive way for the product; although, certainly, it seems like at a snail's pace from time to time.

We have observed that increasingly in recent years nonstandard studies and even reports based on such studies many times fielded by the activists, move quickly through the popular press only to at some point in the future be widely dismissed by the scientific community with minimal reporting. But we are pleased, however, with this process today to appear before the Panel and commend EPA for their position paper relative to this SAP.

Years of extensive work dedicated to atrazine, cancer issues by EPA, by Syngenta and its predecessor organizations, and most recently by the June 2000 SAP, have already determined that atrazine is not likely to cause cancer in humans. That is not to say that the issue is not subject to further deliberation. Obviously, this SAP is an example. But I think there is a reason. I think it's been explained fairly well why the charge to this Panel is a somewhat simple one.

EPA is correct in not charging the panel with issues thoroughly reviewed by previous SAPs. And, actually, we're here today because of a consent decree that at the time last summer was justified by the Agency as being based on workload issues. I don't think anyone's told you that today. But it was not really issues of concern with prostate cancer that drove this SAP in terms of the Agency.

Obviously, the consent decree was entered into with a plaintiff that did have those issues. I don't think anyone said it. But I would like to make sure it's in the record.

In spite of anything that you might have heard to the contrary, farmers and consumers really do want the same outcomes. If there is an issue relative to the safety in using a herbicide, it's much more profound to those of us that directly use the materials. We live and raise our children and grandchildren in the same area that we grow our crops. And, of course, if there are real issues concerning safe use of any product, we need and want to know about it.

While EPA concluded available data do not support a likely relationship between atrazine exposure and prostate cancer, they do stop short of saying it's an absolute term. They made their best assessment using all the available data and balance, and we believe this to be appropriate.

And I would offer a little food for thought on this issue. If atrazine were to be banded an action called for by the NRDC, the loss of income for Kansas farmers -- I'm only speaking about Kansas alone -- will total some $120 mill at the farm gate. Mr. Geonessi actually just alluded to this. This is based on $20 an acre in increased costs, really not taking into account yield differences and the fact that we have some 6 million acres of corn and sorghum in the State of Kansas.

And when you measure that loss at the farm gate of $120 million, you have to really consider the impact to the Kansas rural communities. This is because when a farmer gets a dollar, they tend to reinvest in goods and services in local community. The people that they invest it in tend to reinvest it as well. And the economic multiplier that typically is used in Kansas is some four to five times. So a farm-gate value of $120 million also become a rural community value that probably comes close to equaling or exceeding a half a billion dollars. This is economic activity that in turn supports other very critical services including emergency medical services, prescription drugs, schools. The list goes on and on. But there are some very dynamic health-related services that are support by this type of economic activity.

And the fact is that if you are chasing a precautionary principle

that would be going to the extreme and going after something that maybe is not addressed in a negative to the absolute, in your quest to do that you could actually place real people at greater risk in their human health.

And I can tell you from experience in working with my members, that when things get tight economically on the farm, one of the first things to fall off the plate is adequate health care and health insurance. That is a fact. My real point is this would be an ironic and hopefully unintended outcome of that type of pursuit.

We also have concerns that activist groups and class action attorneys have misused data generated by an industry wellness program in an attempt to further their political and monetary agendas. If allowed to do this, in our opinion, they place such programs at risk in the future and in reality place human lives in peril. There has been a lack of respect for the privacy of the participants and disregard for the value of the programs. Not so much in the discussion today, but if you go back to some of the earlier correspondence, there were real attempts to get beyond some of the confidentiality provisions of the wellness program at the manufacturing facility.

And I've had this decision with some of the strongest supporters of early screening, PSA screening, and wellness programs in general.

And, in fact, they would be concerned if a wellness program was twisted into some sort of liability for an industry that was willing to initiate it. And I think it bears some consideration. Fortunately, I think in this case the general facts will lead you to a similar conclusion that the EPA has already determined.

And we believe that these programs are good programs. Employers and employees alike should benefit from them. They detect more illnesses by saving more lives, and this is the way it should be.

Joining me today in our comments is Dr. Donald Ridley, CANTOX Health Sciences, International, who we have used in the past with some of our assessments of scientific issues and certainly used in the June 2000 SAP. Don.

DR. RIDLEY: Thank you, Jerry.

Mr. Chairman, panel members, my name is Don Ridley. I'm with CANTOX Health Sciences, International. It's a consulting firm, toxicology and regulatory. We've been in business for 20 years. And as Jerry has said, we've spoken and presented previously at other SAPs on atrazine.

We've been requested by the Triazine Network to review the epidemiology data on atrazine with respect to prostrate cancer. And

as a second request, they wanted us to formulate an opinion on the impact of the data on the pending interim reregistration eligibility decision or the IRED.

The epidemiology studies in the 1980s and early 1990s initially focused on the potential association between atrazine use and developmental of ovarian, breast, and other cancers, including non-Hodgkin's lymphoma. Both a comprehensive review by Zahm in 1993, and as we heard this morning with Dr. Blondell, the EPA has concluded that the epidemiology studies to this point in time do not show evidence of a causal effect of atrazine exposure on the incidence cancer.

The recent focus of EPA and the subject matter for this SAP are the two epidemiology studies that evaluate the incidence of prostate cancer in relation to potential atrazine exposure or use. The first study, or the St. Gabriel study, that's been mentioned previously, was a study of 2,045 workers at the atrazine production plant in Louisiana. And the second study was the Agricultural Health Study that has been mentioned previously by Alavanja, and that included 55,332 male pesticide applicators.

CANTOX agrees with the EPA's conclusions with respect to the findings of the two epidemiology studies. Namely in the St. Gabriel

study, the increased incidents the prostate cancer in works was largely explained by the intensive PSA screening program leading to early detection of cancers in place at plant. And, secondly, we agree with the conclusion of the Agricultural Health Study, at least to this point in time, that they did not find an association between atrazine use among pesticide applicators and the incidence prostate cancer.

Therefore, CANTOX agrees with the EPA's overall conclusion that, and I quote, "the available epidemiology data do not support a likely relationship between atrazine exposure and prostate cancer."

In terms of some of the comments to enable me to talk or give an opinion on the IRED process, we went through several things that have already occurred. First, the EPA has evaluated the animal toxicology data and concluded that the mammary tumors occurring in female Sprague-Dawley rats administered atrazine are of no relevance to humans. Secondly, there are no substantive animal or human data or plausible mechanistic data to indicate that early life exposure to atrazine presents a carcinogenic risk. Third, EPA has concluded that the available data support a classification of, and again I quote, "not likely to be carcinogenic to humans."

It is our opinion that the potential carcinogenicity of atrazine has been well characterized and that the data are sufficient to continue

support of the current classification of not likely to be carcinogenic to humans. We also feel that future analysis of St. Gabriel and Agricultural Health Study are unlikely to change the overall conclusions about the carcinogenic potential of atrazine.

Therefore, our opinion in terms of the IRED is that, given the weight of data to support a not likely to be carcinogenic to humans classification, there is no justification for the EPA not to proceed with that classification in establishment of an Interim Reregistration Eligibility Decision scheduled for October of 2003.

Thank you very much for your time.

DR. PORTIER: Thank you very much. Are there any questions from the Panel? I have a question for EPA on the slides we were given. Third to last slide, "EPA has concluded that the available data support a classification of not likely to be a carcinogenic to humans," is that a correct quote and a correct classification?

DR. STASIKOWSKI: Yes.

DR. PORTIER: Thanks. The next public commentor, Mr. Robert Hedberg. Mr. Hedberg is delayed a bit. James Stevens. And he'll be followed by Ed Gray.

DR. STEVENS: Good afternoon. My name is Jim Stevens. And I'm speaking today on behalf of Crop Life America.

Crop Life America is a trade association which represents the common interest of manufactures, formulators, and distributors for virtually all of the active ingredients used in crop protection products in the United States. As a general policy, Crop Life does not defend specific products. However, in the course of making regulatory evaluations and decisions on individual products, the potential exists to set new policies and alter existing ones which will affect subsequent decisions. In those cases, we are obliged to monitor actions on specific products and to comment where appropriate.

The EPA initiated the special reviews on triazine herbicides in November of 1994. There are six manufactures and more than 30 companies that sell products containing atrazine. Over the past nine years, industry has provided the EPA with over 200 additional studies that support the previously conducted study. We welcome the transparency of the process and the opportunity to provide information to the EPA to assist its scientists in making the most informed discussions.

The EPA has had an opportunity to review an overwhelming body of research, more than 800 scientific papers in the last four decades. And their review support the safety of atrazine to humans and in the environment.

In this particular case, Crop Life is concerned that the EPA has had more than enough information to make a regulatory decision to issue atrazine's IRED. The EPA has made a determination that the perceived increase in prostate cancer, as previously discussed, incidence at the St. Gabriel plant in Louisiana is likely a product of the state of the art, PSA screening component of the wellness program.

The results of the Agricultural Health Study also show the lack of association between atrazine use and prostate cancer. This study, a perspective cohort study, is one of the largest and strongest studies conducted to address the question of prostate cancer and farmers; and no link was established with atrazine.

Crop Life agrees with the EPA's determination that the best available data do not support a relationship between atrazine and prostate cancer. It is worth noting that the other studies suggesting possible associations with other cancers have been comprehensively reviewed by qualified EPA scientists and those within the science advisory panel membership. No association with these cancers or other cancers has been established.

To support an open and transparent regulatory process which gives all interested parties an opportunity to comment and provide

information for the consideration in EPA's risk assessment procedures, we support that. However, it's become a greater concern that when the potential for a decision-making process can be compromised by unwarranted delays for atrazine and other crop protection chemicals.

Last year's extension of the atrazine IRED timetable is troublesome to us; particularly because it's accompanied by a revision in the consent decree between the Agency and the NRDC when a well established transparent process for risk assessment decisions is already in place. The revised consent decree contains not only a new timetable but a baseless requirement for the Agency to conduct additional SAPs on issues which have already been thoroughly considered by the Agency.

We submit that the October 3 -- October 2003, excuse me -- deadline for the IRED should not be compromised or renegotiated based on anything other than sound scientific reasoning. To do anything other than this would be to call into question the integrity of the science-based regulatory process at the EPA.

Thank you for your time and attention.

DR. PORTIER: Thank you very much. Are there any questions? Dr. Gold?

DR. GOLD: Can I just clarify. Did you say that there were six manufactures of atrazine?

DR. STEVENS: That is correct.

DR. GOLD: Thank you.

DR. STEVENS: Only one in the U.S., the others are offshore.

DR. PORTIER: No other questions. Thank you very much. Ed Gray. Dr. Gray will be followed by Stephanie Whalen.

MR. GRAY: Thank you, Mr. Chairman, and good afternoon members of the Panel. Thank you, Dr. Portier, for conferring the doctorship on me.

DR. PORTIER: When in doubt, I always put the doctor in front.

MR. GRAY: I'm appearing today on behalf of the National Grain Sorghum Producers. And what I want to do is talk briefly about the various Mills studies that have been discussed at some point earlier today.

You'll be given a copy of my paper. And I'm going to skip over parts of it because I think it's already been covered pretty well by some of the things that Dr. Blondell and others have talked about this morning. I seem to have a frog in my throat.

But I would like to speak about the conclusions that he reached, not from the standpoint of the cancer incidents, because I don't

purport to know anything about that; I want to talk about how he calculated exposure in these two studies.

I think there are serious flaws with the studies and the methodology, and I think you ought to look very carefully at that methodology, as I discuss more in detail in my paper, before you give any credence to the associations that he's derived.

Both atrazine association from the 1998 study and the simazine association from the 2003 study suffer from the same basic flaws, I believe. I discussed the problems with the plausibility of finding a connection between the ways these products are used in the field and exposure to farm workers and others. I'm not going to get into that any more. Jerry Blondell already dealt with that. But I think it's important to look at because it's a serious plausibility issue.

But what I really want to talk about is how he calculated the exposure numbers. And I think there's two or three things wrong with it, especially with the 2003 study. In the first place, he used as an index the county poundage applied. And what he seems to have not thought about, although he's been very careful in adjusting for other things, is some counties are a lot bigger than others and have a lot more agricultural acreage than others, and, therefore, a lot more treatment than others.

Back in the middle of this paper, I've got a table that you can see, for instance, the difference between Kern County and Kings County which are adjacent in the San Joaquin Valley. And one of them has 10 times the acreage of the other. And from what I can tell, what that means is, if a fellow worked in Kern County, he was regarded as having ten times higher exposure than if he had worked across the county line.

Another problem is that the study doesn't seem to take into account when a person worked in a county in a year. Simazine is almost entirely applied in the late fall or the winter. It's a time when not very many people are around these farms. There's not a lot of work to be done in orchards or vineyards in the middle of the winter. Some pruning and what not, but it's sporadic. And so there's not likely to be the kind of traditional farm worker exposure with foliage and residues and things like that are concerned. And I think a lot of the farm workers won't be working in the winter. But it looks to me like they get credit for a year's worth the application whether they were working anywhere near the time when that exposure could occur or not.

And I also think that it looks like they happen to be working in two counties in the same year, they're going to get counted for both

counties. I'm not sure of any of this stuff. I think that's what the report says. I've had some preliminary communications with Dr. Mills, and I believe that I'm right. But I didn't get a response to my last set of questions, so I'm not sure.

I think these things are fixable in the sense that you could go back and recalculate everything. But I think that until you do, what you have is a set of numbers that are based on completely wrong exposure information.

The only other thing I'd like to say is something not discussed in my paper, but it is a response to the NRDC presentation seeking basically to have you use the 2003 cancer guidelines as your model, the criteria that are set out in this draft guidelines.

Point of fact, the guidelines that are in effect are those that were issued in 1999. EPA has expressly said that until the new ones are made final, the 1999 will stay in effect. Those are the ones that were used, of course, in the exercise that led to the 2000 SAP review. And the new ones that are being debated right now have been the subject of intense public comment. A lot of people don't like what they say including NRDC. They are by no means the last word on anything, and they are not in operation at this time. So I think that you can consult with the Agency to see if I'm wrong about that, but I

don't think I am.

Thank you.

DR. PORTIER: Thank you very much. Are there any questions? No. Thank you. Stephanie Whalen.

DR. WHALEN: Well, aloha, and you do have some decent weather here today I must say. When I went out there at lunch, it was really nice.

My name is Stephanie Whalen. I am the president and director of the Hawaii Agriculture Research Center. And essentially we are the research arm for the sugar industry in Hawaii which has had this association and technology transfer development group for over 100 years. So we've been very active in the development of herbicides for the industry. We don't have to use insecticides because we have those insects under biological control.

So my point is that we've been involved with the triazines early on. We are a minor crop as considered by the chemical companies in that we're small volume; and so we've always done most of the work to get compounds registered ourself, including metabolism studies and soil work. That's kind of our been our involvement here all along.

Atrazine is one of our primary, has been, since the compound came out and we were able to get it registered for sugarcane. It's been

one of our primary weed control components. And Ken also addressed some of these exposure issues. And just to give you a better feel for, I think, how our organization and our industry is a lot different than others, we are a large corporate farming in Hawaii. That was the only way were able to survive in the middle of nowhere in a commodity situation. So our workers, they are unionized. And so we have very highly specialized labor. So we control people. And that's what they do. And we operate 12 months of the year because of our year-round climate. We don't have this on and off again kind of operation.

And because of industry has been good -- actually, it was employees and the environment, we've had a health care program in place, a private-run system, since the 1930s. And then as HMOs became the thing, then of our employees are covered by HMOs. And we still carry the cost of that for them.

So I just want you to understand that because some of my comments. And then also in terms of environment stewardship, I think we've been a leader in being concerned about only because we had our own research institute which was doing a lot of registration work and capable of doing our own analysis. We set up a groundwater monitoring program because our operations on all the major islands were sitting over the drinking water which in our state is ground

water. And so we were very concerned for our selves. Basically, the rural communities was our employees, ourselves. And so we started a groundwater monitoring program way back in the early '80s when it first starting coming to the attention that there might be some concerns.

And so what I want to point out is that the growers are concerned. We do put in stewardship programs; and, likewise, that same practice now is practiced by most of the growers in the Midwest and everyone now who had stewardship programs in reducing use and trying to control and keeping the compound where it's supposed to be on your own land and in the area where it's doing some good for weed control.

And since those stewardship programs have been in effect, there is a decrease in the amount of atrazine being found in the systems. And we agree with what was said by the American Water Works Association, that we would like EPA to revisit the MCL. Because we think if the did, based on the last Scientific Advisory Panel, in saying that this is a threshold effect and not modeled the same way they do if they consider it a likely carcinogen, then they would be revising the MCL and then there wouldn't be a concern because it never would go up and so many things have falling off.

Irrespective of that, we still want to make sure that we put in practice and keep the compound where it belongs in the top three or four inches where it does the good and the reason that we're applying it.

I just want to Panel to recognize that as producers, as Jerry White has said, we're on the front line and we do have concerns. And that's why we're part of this process.

The other thing I wanted to say was that, although there has been a few epidemiological studies -- I want to tell you a little bit of my background. I am a scientist. My background is in chemistry and pharmacology. And so I've followed a lot of the information. It's always been my responsibility before I became the president and director to follow the environmental issues and the health issues for our workers.

So although there's been a few epidemiological studies showing some association of some pesticides with various health effects, I want to remind the Panel, since many of your background is in epidemiology, about the premature weight given to some epidemiological studies and the dilemma in stress that this science has caused for women of my age over the hormone replacement therapy where for decades the epi studies led the medical community to

prescribe what is now considered a wrong treatment. And I think we really need to put some of these things in perspective.

And I just wanted to remind people about that because a lot of times these epi studies on pesticides don't go to much further than first studies that raise a lot of concern. And then, you know, because these other types of studies cost so much, that's why they weren't done in the hormone-replacement-therapy work before either.

I'm glad to see the major study that's going on is a more prospective study because at least that's a better type of study. And then, of course, the case-control studies where you can get ones or even better than that but recognize they're very expensive.

I'm not aware of any human health incidence, and we've looked at that as acute or chronic, that have been demonstrated to be the results of exposures, accidental or intentional. Intentional is people do try to poison themselves a lot with pesticides. And those come to the attention of the poison control groups thought the United States. We have one also in Hawaii. And we've never seen one that's been based on exposure to atrazine in our farming community.

We agree that the EPA's overall conclusion that the available epidemiological data do not support a likely relationship between atrazine exposure and prostate cancer. There's been no suspicious

health problems associated with the use of atrazine or, for that matter, the mix of herbicides in use by the Hawaiian sugar industry over the past four decades.

Hawaii's sugar employees may enjoy, as I said, full medical and Worker's Compensation benefits in labeling health problems to be readily identified. They have no problem in saying that they're sick and going off on sick leave. And so, you know, to our knowledge, we feel that that would be an early warning because our medical community, which focuses a lot on the real community, not just on sugar workers, would bring that to our attention.

Also the insurance companies's data bases have been reviewed for diseases for different purposes and nothing has come out when we've looked at them for other issues that have come up that were non-pesticide-related.

In addition, in 1993, Dr. DeWolf Miller of the University of Hawaii Public School of Health reported on sugarcane workers' morbidity and mortality. And the abstract of this paper he states, "That after 18 years of follow-up, and this is a quote, those men who indicated one or more years work on sugarcane plantations had no significant difference in age adjusted mortality nor incidence of CHD, cardio problems, stroke, cancer, or lung cancer and there were no

differences in risk factors compared to participants who were never employed on sugarcane plantations nor were there differences in lung function as measured by FEV1. These findings were unchanged after adjusting for general potential confounding variables. These findings were not due to healthy worker bias and indicated that employment on a sugarcane plantation in Hawaii is not associated with elevated rates of chronic diseases."

This study was conducted using the Honolulu Heart Program Cohort that was established in 1965. This cohort has been used for many epi studies because of the uniqueness of its data base. And just like any other study, we take pot shots; and there's problems with it. But at least that was one that was done in our area.

Mr. White, that second paragraph on the second page there, he pretty much covered it. I think that we, the farmers, are really here to make sure that the Agency gets it right regarding health concerns. Obviously, we're in the front line and also economics. This has both been very important to the rural communities in which we operate.

Just to gripe a little bit. The process began in November 1994, and this Panel is but one of many in that continuum. And you, I believe, are the fourth of such prominent groups to look at the atrazine cancer risk including groups in the other countries. Several of us

from the grower community have been involved from the onset, whereas many of the other participants have changed regularly.

We have been through rumors, information leaks, illusive draft documents; scientific advisory panels and boards; interim documents; administrative changes; numerous new studies; new laws, the Food Quality Protection Act, which totally upended the transparent process set out in the special review which we never quite knew what was the next step in this process; the Data Quality Act, which hopefully enables sound science to prevail in these processes; proposed new cancers guidelines, which are caught up and have been talked about here already; (inaudible) which has been the single party to dictate the process; possible adverse health effects.

And we've more recently listened to speculation on ecological effects in frog feminization problem. And this frog problem is not a new problem. And I think those that went to the SAP Panel last month realized that this has been an issue out there for a long, long time and that many scientists are working on it, trying to figure out what the cause is. And it goes from chemicals to women, drugs, and sun spots, and everything else.

For all of us, the growers, this has been an interesting experience, one which we would continue to anticipate that, in the

end, sound science will prevail due to the efforts of impartial experts like yourselves.

However, the speculation on human and/or environmental effects and the timing of their public releases have not ceased to amaze us and is beginning to appear endless. While there seems to be a couple of additional studies which precipitated your Panel's establishment, the EPA reviews indicate that further evaluation of the studies are unlikely to support a relationship between atrazine exposure and prostate cancer.

From the grower's perspective, the science developed over the last decade now since this thing started, and to which we have been exposed during the review process, has validated our original experience and belief that this product is safe. The concerns of the original EPA document have been addressed. It's time for the Agency to move ahead with the IRED for atrazine. We do believe investigations on potential health effects of pesticides should continue in the scientific community.

Basically, again, we're the frontline people. We understand the scientific process is an ongoing one. And it's especially difficult for the general population. You know, doing studies in the general population and the environment is getting more difficult. But it is a

study -- we expect the studies are not based on preliminary ones or reports but on the weight of evidence and, most importantly, on a plausible mechanism.

If in the future more robust epidemiological studies implicate atrazine to some adverse health effect, then a reevaluation can be made. And a little bit contrary to what was said earlier, this won't take 14 years. If there's a serious adverse effect, EPA can act on it just like they did in the special review process. So the process is different now, and you can check with EPA if that's not true.

Now it's time for the Agency to move ahead with the IRED for atrazine. And I appreciate this opportunity to provide you with my comments.

DR. PORTIER: Thank you very much. Are there any questions? Thank you.

I'm now going to go back to two of the public commentors on my list who were not here earlier. Mr. Scott Slaughter.

MR. SLAUGHTER: Thank you for the opportunity to comment here today. My name is Scott Slaughter, and I represent the Center for Regulatory Effectiveness. I do not have any written comments, but I will be happy to prepare some and give them to you if you don't already have too much to read already.

CRE's interest in this proceeding is the Data Quality Act. The Data Quality Act is a new statute that imposes new standards on information disseminated by EPA and most other federal agencies. Those new standards include a requirement that information based on tests be based on tests that have been demonstrated to be reliable and reproducible among other laboratories. I note that the Food Quality Protection Act which this review is being conducted partially under imposes a similar validation requirement for endocrine disruptor tests.

Setting aside the issue, at least for now, as to whether or not the SAP's report itself is subject to the new Data Quality Act standards, it is at least clearly included within the category of outside information solicited by or submitted to EPA. As such, EPA cannot use the SAP report or rely on it in any way unless the report itself meets the Data Quality Act standards.

Now this is relevant to an issue that's been discussed here today already. NRDC and some others have argued that atrazine is an endocrine disruptor. One of the problems with this argument is that there are no relevant tests for endocrine disruption that have been demonstrated to be reliable and reproducible among laboratories.

For example, one postulated mode of action that has been discussed here today is aromatase induction. To the best of my

knowledge, neither EPA nor any other agency nor anyone has validated a test for aromatase induction in accordance with the New Data Quality Act standards.

There are some other examples of some of the other tests that have been used to supposedly support an endocrine disruptor argument here that also have never been demonstrated to be reliable or reproducible. For example, I believe NRDC mentioned the amphibian effects test. That was the subject of an SAP last month. The problem with the amphibian effects test is that no one has been able to reproduce the same test and the same result among different laboratories.

And I believe that the NRDC person who testified here mentioned a Syngenta test by a Dr. Carr which allegedly showed atrazine showing some amphibian effects at 25 parts per billion. The problem with that argument is that another scientist tried to reproduce that test -- I believe it was Dr. Geise from Michigan State -- and he was unable to reproduce those effects.

There's some other examples of tests that have been cited here for endocrine disruption which do not meet Data Quality Act standards. And the Data Quality Act standards are basically sound science standards. It's just now it's a law.

For example, NRDC, I believe, cited a study by Donna, et al., as demonstrating a link between atrazine exposure and ovarian cancer. I do not believe that that is the case. Because, among other reasons, there were confounder factors of poor or no recall of pesticide exposures in the test.

And I also believe that, to follow-up on a line that you've already heard here before, this is not the first SAP for atrazine. When I was coming here, a line from that great environment scientist, Yogi Berra, came to mind: It's deja vu all over again.

A prior SAP, as I understand it, looked at the Donna, et al., test -- prior SAPs looked at the Donna test and, you know, evaluated and decided it did not support a link between atrazine and ovarian cancer.

Another example of a bad test, or at least one that hasn't been proven to be reliable, is that I understand that NRDC has cited some tests by Birnbaum and Fenton in 2003 as demonstrating a relationship to an increased susceptibility to cancer from early life exposure. This experiment has never been proven to be reproducible among other laboratories. And the Data Quality Act for influential scientific information, which your report certainly is, and this review certainly is, requires validation of tests. That means the ability to reproduce it among different laboratories.

I'll give you another example to that. Not a bad test, but one that cannot be relied on at this point in time, the Stoker, et al., test in 1999. No one has ever been able to reproduce that test. And to the best of my knowledge, the test protocol itself has never been validated.

I have one other comment I'd like to make. NRDC cited a June 20 SAP report on -- basically, the title is as elegant as most of these titles are -- "Supplemental Guidance for assessing cancer Susceptibility From Early Life Exposure to Carcinogenesis, (SGACS), Review Panel." NRDC discussed it at some length and quoted it. The front page of the report -- and I'm quoting -- says, quote, "Draft. Do not cite or quote," closed quote. And then if you go down to the bottom of it, it says once again, quote, "Do not quote, cite or use," closed quote.

I also I believe Mr. Gray raised some concerns about NRDC's reliance on the draft final cancer guidelines, and I concur with him entirely. Those are not the final. They are not final. They are not the guidelines that EPA is using to assess cancer risk. And I believe the Agency has stated publicly that it will not use those new guidelines until and unless they are promulgated into final guidelines.

Thank you. I will try to answer any questions you have.

DR. PORTIER: Thank you very much. Before the Panel asks any questions, I'll ask EPA if they have any points of clarification on the Data Quality Act per se here. I will have some points of qualification from my perspective.

DR. STASIKOWSKI: I heard Dr. Slaughter discuss the Data Quality Guidelines. And I personally do not know this: How do they apply to Science Advisory Panel deliberations. I know that they do apply to the way we conduct our assessments. And the two comments that I wanted to make is I wanted to make sure that you understand that we are relying on the 1999 cancer guidelines. That's the Agency policy. And the paper by Dr. Birnbaum and Dr. Fenton has not been peer-reviewed as of yet, and we are not relying on it for the same reason that we will not rely on nonpeer-reviewed studies.

DR. ROBERTS: So I will point out for the SAP that the Data Quality Protection Act does not pertain to our discussions per se. We are a science advisory panel, and we have considerable lenience in terms of what we consider in making an opinion to the Agency. The only thing that does pertain is, in fact, that our minutes do reflect what we said accurately and precisely correctly. That is my interpretation.

The Agency does, in fact, have an official policy on the Data

Quality Protection Act. Every federal agency does. And if any of the Panel members are interested in that issue, we can certainly try to get the Agency to get you a clarification on the issue. Thank you very much.

MR. SLAUGHTER: Thank you. And I appreciate the honorary doctorate like Mr. Gray did, too.

DR. PORTIER: Mr. Robert Hedberg, has he arrived yet?

VOICE: He will be here in a few minutes.

DR. PORTIER: Not yet. Then we will do one other comment. Dr. Mandel, you have exactly one minute to clarify. Please reintroduce yourself.

DR. MANDEL: Thank you. Jack Mandel, Emory University. Dr. Young, in response to your question about the cases, the four cases pre '93, as was mentioned, we're in the process of trying to collect the screening data. Two of the cases were diagnosed in 1989. Two were diagnosed in 1992. Two were definitely PSA-detected of the four. The other two were listed as digital rectal. One was an individual under treatment for prostatitis.

DR. YOUNG: Thank you.

DR. MANDEL: That's all the information I have. And all six post-'97 were PSA-detected. Thank you.

DR. PORTIER: PSA-detected meaning the PSA test was first then further diagnosis not PSA confirmed.

DR. MANDEL: Yes, PSA-detected.

DR. PORTIER: One last check. Mr. Hedberg. Okay. While waiting for Mr. Hedberg, I'll ask, are there any other public comments, people who have not put their name on the list who would like to make a brief public comment at this time?

Bearing that then, I will close the public comments session except to allow Mr. Hedberg to make a public comment at the beginning of the session after our break. That will be the last public comment. If he is not here at that time, that public comment will not be done.

At this point, we're going to break for 15 minutes. We will come back then with one public comment, and we will start the deliberations of the Panel. Thank you very much.

[Break taken.]

DR. PORTIER: If we could reconvene, I would appreciate it. Welcome back to the July 17 EPA FIFRA Science Advisory Panel meeting. We have one last public comment. After which I will close the public comments completely, permanently.

That would be Mr. Robert Hedberg. Please introduce yourself.

Thank you very much.

MR. HEDBERG: Thank you. My name is Robert Hedberg. I am the Director of Science Policy for the Weed Science Society of America. I appreciate the opportunity to speak after the break because I'm doing double duty at a meeting that is just down the street between EPA and USDA today; so I was doing a lot of running back and forth.

I understand it's late in the day. And I also understand that many of the points that I wanted to make today have already been made, so I'll keep this as brief as possible.

The point I do want to make is that our society and our affiliate societies represent about 4,000 members around the country, scientists working in academia, regulatory, and industry. And as a scientific society, we've been very concerned about the whole process of review of this triazine family of herbicides.

The reason for that is because they are very critical weed-management tools that we have been recommending for many years. In a nutshell, atrazine is used on approximately 60 million acres of corn a year and has been done so for approximately 40 years. It just shows the enormous utility. And we have an interest in making sure that the safety is fully reviewed and that we have the opportunity

to continue using this as it's proven safe.

We also want to point out that we were really glad that the Agency has taken on large-scale epidemiology. We thing that that is an appropriate tool to be using to look for the risks, and we're glad that the results have been as positive as they are.

The final thing -- I think I have passed out written comments. I know you've got a lot of things that you want to cover today, so I'm not going to belabor it anymore. But just to stress the utility of this product in terms of the many benefits to society: Cost to production, conservation, tillage, where we're able to finally start reducing the tillage that's used on the land. And in so doing, we're able to keep nutrients and soil out of the waterways. It's been a major conservation accomplishment. And this is one of the herbicides that has made that possible. So I just wanted to stress that kind of benefit.

And then I'll close and ask if there are any comments or any questions for me.

DR. PORTIER: Thank you, Mr. Hedberg. Are there any questions? Thank you.

DR. PORTIER: Thank you very much. I think that was a perfect introduction into the discussions we have to have now on the important role of scientific review and making sure that a highly used

product like this is public-health safe. Thank you very much.

MR. HEDBERG: Thank you.

DR. PORTIER: We will now close the public comment session and move into the overall discussion by the Panel. Prior to the reading of the questions by EPA, I will clarify a couple of points that many members of the Panel asked me about. There were several questions concerning material that was presented today that may not have already been peer-reviewed for which we may not have full details and whether or not that material can be used in our discussions and in our deliberations.

Yes, the material can be used. You are all scientists. You have to judge that material and its value and weight in your deliberations based upon what you hear and what you know about it. But there is nothing that should restrict this Panel from using the material presented by the public and any of the commentors and the Agency in reaching our overall conclusions and discussions on the questions that the Agency has asked us.

If we use any of the material, we should cite it and note it. And if you feel that the material needs to be followed up for clarity, that's something also we would note. But there is no restriction on the type of material we would use in reaching our opinion. Just the request

that the opinion be clear and concise to the Agency and the basis for the opinion be presented as precisely as we possibly can.

Any questions from the Panel before we proceed?

So we'll now go into the questions. And, Dr. Stasikowski, are you going to read the question; or will it be Dr. Blondell?

DR. STASIKOWSKI: Dr. Blondell will go ahead and read it.

DR. BLONDELL: The first question, EPA has concluded that the increase in prostate cancer observed at the St. Gabriel manufacturing plant workers could be explained in the PSA screening for these workers. Due to the lack of detailed exposure analysis based on job history and the limited statistical power due to small sample size, atrazine could not be ruled out as a potential cause; but a role for atrazine seems unlikely. Please comment on EPA's conclusion. Please identify any additional data or analyses.

DR. PORTIER: I believe, Dr. Bove, you are going first on this issue, on this question. You are the second question. So it's this side. Dr. Merrill.

DR. MERRILL: I agree with EPA's assessment. The study was insufficiently large. There's lack of careful assessment of exposures in cases and comparison populations. The main issue is the PSA screening. And we've known for several years that PSA screening has

had profound effects on the incidence of prostate cancer.

An autopsy study performed by Carter, et al., in 1990 -- it was published in 1990, but it involved data in the pre-PSA era -- showed that, even for men that were 65 years of age and younger, there was a pretty high level of prostate cancer found in these autopsy studies. For men ages 40 to 44, there was 3 percent; for men 45 to 49, 8 percent; for men ages 50 to 54, 10 percent; and for men ages 55 to 59, 15 percent; and then 60 to 64, 20 percent.

In some studies when we've done some cross sectional studies looking at the amount of PSA screening for men in this age range in Utah, we found that about 35 to 50 percent had a PSA screen. And the Louisiana -- the comment was made earlier that PSA screening was probably lower in Louisiana than in many places in the country. And so to compare that with the nearly a hundred percent or hundred percent PSA screening, you'd expect that there would be a profound effect on the incidence due to the PSA screening.

Dr. Adami this morning referred to the JNCI article in which the incidence among those people that were screened was six times higher. And that was overall. For the younger age groups, you'd expect it would be even higher. And so I guess my feeling is this is a very complex situation and probably impossible to disentangle the

effect that PSA screening has had on these incidences, these cases, at the St. Gabriel plant. But we know that it has had a profound effect on the incidence there.

An issue that I have with the nested case-control study is I think it's a good idea. It's going in the right direction, except it's severely under powered, 12 cases. I wonder if it's reasonable to expect that any positive effect could be found with that sample size. And I'm also concerned that they elected not to adjust for PSA screening or have not done that so far. And the recommendation that I would have would be that they, in their future analysis, adjust for PSA screening.

DR. PORTIER: Is that it? Dr. Gold.

DR. GOLD: I basically saw three parts to what the EPA's statement contained. The first part had to do with whether the PSA screening could explain the excess, the second part that atrazine could not be ruled out as a potential cause, and the last, that atrazine is unlikely, does not seem to have been supported. So I'd like to talk about each of those three elements. And if it's all right with you, I'll read from what I had drafted before I came. And I've also made some modifications that I'll read as well.

It seems to me the strongest argument supporting the importance of PSA screening and explaining at least part of the excess

of prostate cancer in the Novartis St. Gabriel Louisiana plant were -- there are several of them -- one, the excess was entirely in men under the age of 60, which is the age group that would be overall at lower risk of prostate cancer and would be likely to have detected cases revealed by screening; two, most of the cases were asymptomatic, and 82 percent were localized, which is higher than the general population rate and which are the characteristics that are indicative of early detection by screening; three, most of the excess prostate cancer was among active Novartis employees who were the ones who were most likely to have received the screening; and, four, the excess of prostate cancer occurred mostly in the mid to late 1990s when PSA screening of younger active workers was nearly complete.

Arguments were presented by Syngenta against atrazine exposure explaining the increased prostate cancer in their workers; but these were less persuasive for a number of reasons. First, the argument that no biologic or epidemiologic evidence shows that atrazine is a human carcinogen would not appear to be correct since both biologic and epidemiologic data were cited in the materials that the SAP received that suggest a possible relation of atrazine to cancer and/or to biologic effects that might be related to cancer.

Second, while, quote, "no established environmental risk

factor," end quote, has been shown to double the incidence of prostate cancer, this may just mean that the scientific investigation has not yet unveiled such an agent. It does not mean that such a factor does not exist.

Third, no explanation is provided, and the validity is doubtful, of the statement that environmental factors are likely to quote, "operate early in life since the change incidence requires the passage of at least a generation," end quote. While it is true the changes in incidents of the magnitude of those seen for prostate cancer in such a short period of time are usually indicative of a non-genetic and sometimes artifactual cause, such as a new screening test, environmental carcinogens do not necessarily require generations to show increases.

Examples can be found in cancer epidemiology research of environmental factors whose exposures occur only or largely in adult life. And yet changes in incidence are observed in less than a generation.

Fourth, even though no known or suspected non-genetic risk factor for prostate cancer differentially affects incidence by age, we cannot rule out the possibility that this a limitation in our knowledge. That one day may be overcome with the discovery of such a factor.

Examples in other cancer epidemiology suggests that different factors have different strengths for association at different times of life. So we can't rule that out as a possibility.

Fifth, while environmental factors have shown an influence on promoting rather than initiating cancer, this observation also does not rule out the possibility of discovering such agents that might be related to early rather than advanced stages of disease.

And, finally, the fact that no excess incidence was noted for other forms of cancer other than prostate cancer among the St. Gabriel workers does not negate the possibility that atrazine may be organ specific in its effects in addition to the fact that the expected number of other specific cancers was so small that the lack of excesses is not surprising; that is, the number of cases were too small to detect significant excess of other cancer types which have been observed in some other studies.

So the last conclusion that atrazine is unlikely to have a role in the excess of prostate cancer at the St. Gabriel plant is not adequately supported by the materials provided for a number of reasons.

First, while it is true that the overall excess of prostate cancer in the Novartis workers was in the two- to four-fold range of increase in incidence of prostate cancer that is expected to be due to PSA

screening based on a variety of studies, a few of the subgroups in the tables have excesses well beyond the magnitude of this range. Now, while subgroups have smaller sample sizes and have greater variability, this means that these greater excesses are suggestive and not definitive. But they suggest that factors in addition to screening may be partially responsible for the excesses.

Second, Syngenta's original data show that 77 percent of all employees had low proximity to atrazine, but only 50 percent of prostate cancer cases were classified as low proximity in contrast to 23 percent of all employees with moderate or high proximity, but more than double that, 49 percent, of prostate cancer cases had moderate or high proximity.

The more recent data that they gave us showed an even lower percent of time spent by cases with low proximity and a higher time spent in moderate or high proximity. Not statistically significant due to the small numbers but, nonetheless, noteworthy. So these findings are suggestive of a possible role for atrazine that could be explored further.

Third, while no relation of prostate cancer to duration was found, the numbers were just too small to perform a meaningful assessment of dose response with duration, and inadequate exposure

information was available for the workers. We saw some today. But we've had some difficulty evaluating it.

Fourth, it's interesting to note that, although the numbers are small and we pointed this out earlier, that in the five-years periods, '89 to '92 and '93 to '97, five prostate cancer cases each were identified. While in the two-year period, 1998 to '99, another six cases were identified. So we need denominators to assess this adequately. But these data may indicate that the excesses continuing or even growing after screening has been in place with nearly complete screening coverage for the workers for a number of years which would further suggest that some factor in addition to screening may be contributing to the excess.

Finally, the present SAP reviewers were provided with, in addition to the variety of commentaries that we've seen today, an additional follow-up of cases through 1999 and a few published papers of epidemiologic studies of the relationship of atrazine to prostate cancer. One of these papers reported on an ecologic analysis that showed borderline statistically significant positive association by county with prostate cancer incidence rates in black males. And the second paper reported a cohort analysis of pesticide applicators which showed no association of self-reported atrazine with prostate cancer.

These materials were inadequate to determine if the role for atrazine on prostate cancer is unlikely. A more thorough and systematic review of the biologic and epidemiologic literature on the topic of the effects of atrazine exposure on the prostate would need to be undertaken before determination could be made that atrazine was an unlikely explanation for the excess of prostate cancer in the Novartis workers.

And I think I'll stop there.

DR. PORTIER: Thank you. Dr. Hopenhayn.

DR. HOPENHAYN: Well, I want to thank Dr. Gold for a very thorough review. I pretty much agree with much of what she says, and I probably don't have much new to add to what the previous two Panel members said.

I do want to stress the fact that I do agree that it's likely that there is at least a partial explanation probably due to the increased screening that we see in this population, but I do not think that that's necessarily sufficient to rule out a role for atrazine or for something else causing the increase in prostate cancer.

I also want to express my concern for the very small sample size of the study in the St. Gabriel plant in how much weight seems to be given to that study given the sample size. The fact that we have

nonsignificant associations in most of the analyses, I think it's to be pretty much expected with such a small sample size. So I'm not sure that I agree with being able to make any conclusions regarding the negative associations that have been presented in relation to exposure and other subgroups.

DR. PORTIER: Thank you. Dr. Sandy.

DR. SANDY: I agree with what's been said by Dr. Gold and Dr. Hopenhayn about the St. Gabriel plant study, the small numbers and the limited power of that study, to make any causal associations with atrazine exposure. I don't think the role of PSA screening has been explored or explained effectively. I think a follow-up study might be to look at another population of workers that underwent the same intensity of PSA screening over the same time period and that where not exposed to atrazine but were perhaps exposed to something else, or perhaps in the headquarters building of Syngenta or something, and look and see if you also see a similar increase. Can you attribute that increase solely to PSA screening, or could there be something else going on in the St. Gabriel plant?

I don't think I agree with the conclusion that it's unlikely for atrazine to have a role based on what we know about biologic mechanisms. Because atrazine is an endocrine disruptor and it seems

to be one in multiple species, it seems to act at multiple levels. There is evidence, I believe, of aromatase induction. There's evidence of lowering of LH surge and testosterone levels. I think there could be multiple mechanisms going on. And as we know with other endocrine disruptors, for example DES and Tamoxifin, the effects are often age-specific, organ-specific, and species-specific.

I think it's very hard for us right now to be able to predict an effect that atrazine might have in humans and say that something that's seen in a rodent species would not occur in humans, looking at DES, looking at Tamoxifin, where you have in utero or neonatal exposures resulting in greatly increased cancers risk for reproductive organs. Adult exposures, you often see an increase cancer risk at a different site. So the chemical's working, operating differently in different organs because of expression of different hormonally related proteins or genes or pathways.

DR. PORTIER: Dr. Young.

DR. YOUNG: I think I pretty much concur with what everyone else has already said. I'll just summarize a few key points.

While it seems that the increase in the PSA screening certainly accounts for a large portion of the excess prostate cancer cases, I don't believe that it definitely accounts for the significant subgroup risk

that we were seeing, four to six times greater, among those less than 50 years old and six to nine times greater among the active Novartis employees. The elevated risk in these subgroups may, in fact, be significant and shouldn't be completely dismissed or explained by increased PSA screening.

I also want to point out that, when you look at the data from the 1985 to 1993 cohort, within a subgroup of men under 55 years of age, they do note a standardized incidence ratio which is significant of 757. And if you look at the rate of screening in employees under 50 years of age, it was only 5 percent in 1992; and it didn't increase to 50 percent until 1993. So it seems unlikely to me that the excess in the early time period could be accounted for by the PSA screening when, in fact, the program was virtually not in effect for the younger age groups.

Secondly, I think, given the conflicting evidence from the industry and then some of the epidemiological studies that we've seen, including the data from the Mills and Yang study which looked at the simazine risk, although that study does have some methodological problems, I think it's premature to reject atrazine's potential role in the increased risk of prostate cancer. It is certainly still a possibility that it's a potential factor.

And I just want to restate that I think we do need additional analyses, like Dr. Sandy suggested, looking at another population with no exposures but the same or close to the same levels of PSA screening.

DR. PORTIER: Any other comments by the Panel?

DR. HANDWERGER: May I ask a question?

DR. PORTIER: Certainly, Dr. Handwerger.

DR. HANDWERGER: We learned just a few minutes ago that there are six sites that make atrazine thought the world. Do we know anything at all from the other five sites? Is there any data at all that we can use that's even very preliminary?

DR. PORTIER: Dr. Blondell.

DR. BLONDELL: No, I do not believe there are. Well, there was one report, and I'd have to go back and look at it. And, again, it's small sample size. I think it was a plant in Germany that there was some -- and there I'd have to go back and find it. There may be one additional report. But it was -- there is one other study in another plant, and I'll have to go back and get that.

DR. HANDWERGER: I think that's really important to know that.

DR. PORTIER: Any other comments by the Panel or questions?

Dr. Reif.

DR. REIF: I had a few isolated points that I wanted to make, although I wasn't a part of the group that addressed Question 1.

First, I'd like to make a recommendation to EPA. Thought this discussion, many persons have commented on the small numbers of available cases for analyses in the incidence study as well as in the nested case-control study. It is not a difficult undertaking to prepare power tables so that we can really evaluate the question of power for various levels of risk. It's a fairly straight-forward process that is almost required of people who submit grants these days to agencies like NIH to provide such data. And it's my recommendation that, to supplement your materials and to give people an idea of what the power was, that you calculate and produce those tables.

With the existing data, there are certainly unanswered questions. However, I believe that there are some additional analyses that could be performed in a straight-forward manner to at least approach some of them. For example, I believe it would be useful to calculate the SIRs in a temporal manner, for example, to calculate the SIR among Novartis employees in the year, let's say, '92, '95, and '98, to try to see what effect PSA screening has had.

As came up earlier this morning, the six new cases identified

most recently are somewhat concerning since one might have hypothesized that the advent of a hundred percent surveillance in this population should had uncovered the majority of latent cancers that existed at the time that screening was initiated in approximately 1993. And it may be that additional evaluation of temporal sequence related to the SIR can be elucidating.

Further, I would suggest that, given the recent increase, that further follow-up of this cohort is really essential. Whatever the outcome of these deliberations are, it would be my personal recommendation that EPA ask Syngenta to continue to provide ongoing surveillance and update the data base appropriately.

I find the lack of information about family history in this population a bit distressing in view of the possibility that new information may become available regarding genetic susceptibility for prostate cancer. And, therefore, one would like to know about a specific member's family history. And, in fact, of course, one would like to have DNA from those people to anticipate the availability of exploration of genetic polymorphisms that might increase susceptibility.

It would be a plausible hypothesis to test that exposure to a compound like atrazine that may have weak or no effects in the

general population that may have an effect in a genetically susceptible subset of the population. And, of course, the availability of DNA and the availability of specific hypotheses to test susceptibility factors could be very important in the future. And so perhaps some thought could be given to incorporating DNA collection in this cohort.

There are some analyses in the data that were provided that I think could be strengthened. For example, in the submission by Dr. Breckinridge, he has a Figure 3 in which he explores the relationship between proximity as a surrogate for exposure and age. I think there are more useful comparisons that could be made with those data specifically to look at something like time since hire and specific age strata, using time since hire as a potential surrogate for induction time if, in fact, there were an environmental trigger. So that could be explored. I think there are analyses like that that could have been explored in the data that were provided that are still potentially doable given the existing data base.

Similarly, I believe that the analytic efforts in this cohort should focus very strongly on the regular company employees and avoid the temptation to achieve larger sample size by including contract employees at the obvious expense of including people with very short median durations of employment, and, therefore, probably

very, at least in terms of cumulative exposure, lower levels of exposure.

So my recommendation would be, as Dr. Delzell did in her report, to look very carefully at company employees specifically. And in the nested case-control study, of course, it's the company employees that are the focus of that. And that's a very appropriate group. Whether it happened by serendipity or it happened deliberately, it's a very appropriate group to do the nested case-control study and for the reasons that I've indicated.

That's all I have at this point.

DR. PORTIER: Thank you, Dr. Reif. Dr. Knobeloch.

DR. KNOBELOCH: Thank you. I'd also like to just add to what many of my colleagues have already said.

I find it very problematic, when I saw the statistical analysis that pooled moderate and low exposure people because of the disproportionate sizes of those to exposure cohorts, to take the moderate exposure group which consisted of only 20 men, four of which had prostate cancer, and add that group to a much larger low exposure group that had a much lower cancer incidence really loses the effect, you know, really seriously dilutes that moderate exposure group. You know, the effect of atrazine, if there is one in that group,

is lost in that sort of analysis. I'm not sure why you would not have pooled instead the moderate and the high exposure groups which give you a statistically significant increase of cancer in those two groups.

I think also when the effect is only seen in the moderate and high exposure groups and only seen in long-term workers, it's very difficult to continue to believe that it's an artifact of screening. If it is an artifact of screening, it should have been equally evident among the whole exposure group. And it was not. And I think we can't just ignore that fact.

I think this is obviously a very underpowered study. The failure to control in any way for secondary risk factors, such as smoking status, family history, vasectomy status, makes the analysis that much more difficult. I think there could have been an attempt to do that, and it was not done.

The argument that this is not a true effect because there's not a strong dose response, I think, is a ridiculous argument because of the very small sizes of moderate and the high exposure groups. When you only have 83 men in those two exposure groups, you can hardly expect to see a clear dose response. You just don't have the numbers.

And I also would have to take exception to the idea that there is not biologic plausibility. We've know for a very long time that

atrazine is an endocrine disruptor and that it's seems to act by a promoting mechanism. And to me, there's good reason to think that it might have an effect on an endocrine gland such as the prostate gland.

DR. PORTIER: Dr. Bove.

DR. BOVE: I just want to follow up on the last comments about the comparison of the high, moderate, and low proximity. If you do combine the high and moderate group, you have a relative risk of 3.4. You'd expect to see a situation like we see here. With extreme exposure misclassification, which I'm sure is going on here, you get these kinds of responses where the middle group has a high relative risk and then it drops off in the high group. And that's exactly what you see here.

It makes no sense to combine the low and moderate group. It's never done unless and only if the incidences in those two groups, the rates of those two groups, are similar. But they're so dissimilar here it makes absolutely no sense to combine the low and moderate. And the reason to do it is to try to hide something in my opinion. But regardless, you'd expect a distorted dose response with exposure misclassification. And that's exactly what you have here.

So I would suggest that you change your analysis or evaluation of at least that part of the material submitted by Syngenta, because as

I said, you expect no dose response. And there is an effect. It's pretty obvious there and cannot be explained by PSA screening whatsoever.

DR. PORTIER: Dr. Gold.

DR. GOLD: I didn't include my comments about extra analyses. And I want to support the idea of extending the cohort to get beyond the problem or try to get beyond the problem of the small numbers. But in addition to extending the cohort forward beyond 1999, I have two other suggestions. One is for the company to consider doing a historical cohort study where they go back before 1985 and do a very systematic, thorough tracing of workers prior to that time for their prostate cancer risk. That obviously is a more expensive and intensive undertaking, but it's a possibility that would help with the numbers problem.

And the other suggestion, which has sort of been touched on, which is to examine other potential manufacturing settings for atrazine to see what their experience with prostate cancer is in those settings as well. And I think until we have substantial enough numbers, it's going to be hard to say with any certainty whether it's likely or not likely carcinogen.

DR. PORTIER: Dr. Reif.

DR. REIF: I wanted to make a couple of other comments about

the nested case-control study just to be sure that we can deal with it to the extent that we can. I think it was commendable to try and advance the time line for this very important data set. But at the same time, the lack of a text, and I think a somewhat preliminary analysis of the data, make it difficult to interpret, at least to me personally, at this point in time.

I think the relationship between PSA screening and the various exposure metrics is an extremely important component of this study that hasn't been fully elucidated so far and certainly needs to be. I also found it incomplete to the extent that the logistic regression analyses did not including risk estimates for two of the three exposure metrics that were defined by the industrial hygiene group.

So I think this is a good start. But I certainly would like to see a fully developed report and/or a peer-reviewed publication of this nested case-control study before I can personally make sense of it and try to determine to what extent the nested case-control study contributes to our understanding of the standardized incidents ratios for prostate cancer.

DR. PORTIER: Thanks, Dr. Reif. Dr. Symanski.

DR. SYMANSKI: Just a follow-up question on the comment on the nested case-control study that we saw presented today. I would

agree with Dr. Smith that state-of-the-art techniques were applied in their attempt to retrospectively assess exposures. Nonetheless, in constructing the job exposure matrix and in developing the exposure indices that were used in their analyses, several assumptions were made. And these assumptions revolve around the relative magnitude of average exposures for each of the exposure categories over time, the rates of decline and exposure over time, and the degree of heterogeneity in exposure within each exposure category.

However, it was not possible to evaluate the validity of the assumptions that they made based on the information that was presented. And it's certainly possible that, had different assumptions been, that the distribution of exposures could have been different. And we don't know what those affects might have had on the results that they presented.

DR. PORTIER: Thanks. Any members of the Panel who have not yet had a chance to comment? Otherwise, I'll try to do a quick summary. And you tell me if I've got at least some of the major points. I think I like the way Dr. Sandy broke the question down into three parts. And I'm going to start particular type of summary.

I think -- Dr. Gold. I'm sorry. Could PSA explain the excess? I think the Panel is pretty much unanimous on that is saying yes. I

think there's some degree of variation in that yes. My answer to that would be that it could explain all of it. I think Dr. Bove has less belief in terms that PSA could explain all of it. So I think you got some range on the Panel on that issue. But I think we all believe that PSA could explain some of what was seen.

Could atrazine be ruled out? Your comment about atrazine not being able to be ruled out in the comment, I think the Panel, again, is unanimous that, yes, that atrazine cannot be ruled out as a potential correlate in this case.

And is atrazine then unlikely to be the cause of the prostate cancer? And I think the Panel is uniformly agreeing that that statement is too strong. I think the words "unlikely" is the one we're most uncomfortable with.

I believe there were a number suggested analyses that would have helped. I think key to that would have been finding a population with similar PSA testing attributes. I think that probably would have carried a lot of weight in moving us more towards unlikely.

That's my interpretation of some of the things I heard from the Panel, although there were a number of other additional studies and additional analyses that could have been done, most notably, where's the cohort today, where was the cohort years and years ago, and what

about the other cohorts that are working in atrazine processing plant.

I think, hopefully, I've captured most of what we've said. And if I haven't, someone will correct me here. No. Any other comments that haven't been made pertaining to Question 1? If not, I think we'll move to Question 2. Dr. Knobeloch.

DR. KNOBELOCH: I'd just like to reiterate that you did ask -- I tried to get clarification on whether the rate observed in the low exposure cohort, which is a fairly large -- I mean, it's the largest cohort -- whether the rates seen in that group was higher than the rate seen in the industrial corridor. And I did not get an answer to that. Apparently, it's not clear that it is higher. If this is an effective screening, it should have been much higher. So I think that the question is answerable. I'm not sure why they didn't have to that. It's a fairly simple question.

DR. PORTIER: Dr. Sandy.

DR. SANDY: In your characterization of the first point, I think I heard that, as a group, the Panel agrees that PSA screening can account for some of the increase. But I thing there's sort of a range. Some people strongly feeling you can't explain all of it, and others saying maybe it doesn't.

DR. KNOBELOCH: It certainly doesn't explain the distribution

of rates that we see in these three exposure groups. It just can't explain that.

DR. PORTIER: Dr. Herringa.

DR. HERRINGA: I concur with Dr. Portier's summary. I think the one word that I get caught up on here is seems unlikely because that essentially sort of id denying even low probability events. I believe that the effect of the PSA screening could explain the size of the effect that we're seeing here. Just a simple calculation, taking the ratio of screened individuals in this plant to the sort of the average in male populations and statewide that Dr. Merrill referred to and then looking at the change in incidents occurred in terms of reported or detected incidence that's occurred, say, between the year 1998 and the year 1988, there's almost a doubling in reported incidents. And we'd have a doubling in reported screening between the individuals in the plant and sort of the average for males in the population. So a doubling of a doubling is about a four-fold.

So I think that it's realistic or plausible that the screening effect has, in fact, produced the increased and detection in incidence. But, again, it does not rule out other potential factors as well.

DR. PORTIER: Okay. With that, I think we will move on to the next question. And there's always a chance at the end to come back to

anything we've missed. So if you could read us the next question, Dr. Blondell.

DR. BLONDELL: Thank you. Other available studies may assist the assessments of the potential for association between atrazine exposure and prostate cancer. Agricultural workers generally have much shorter duration of exposure compared to workers at the manufacturing plant. In addition, agricultural workers are expected to have a different pattern of exposure compared to manufacturing workers, for example, intensity, seasonality, routes of exposure.

Please comment on comparing the results of the epidemiology study of prostate cancer conducted in the St. Gabriel plant to the results of the Agricultural Health Study considering that the participants in these two studies were likely to have experienced different exposures. Discuss what such a comparison indicates about a relationship between exposure to atrazine and prostate cancer.

DR. PORTIER: Thank you. Dr. Bove.

DR. BOVE: I'll talk about a couple of points and then maybe say some specific comments about both studies. First, the differences in exposure pattern and duration between the two cohorts, the workers in the Agricultural Health Study cohort likely experienced a different pattern of exposure than the workers at the St. Gabriel triazine plant.

They had differences in magnitude of exposure received, the pattern and duration of exposure, the potential for other exposure, such as drinking water exposure, to the agricultural workers exposed to atrazine in their drinking water.

There are also other kinds of things that occur in agricultural situations such as spills that could also happen in the manufacturing processes, too; but are probably more likely in agricultural. There may be some differences in what the primary routes of exposure are.

So in general, the company employees at St. Gabriel plant likely experienced a relatively constant, chronic exposure; whereas the agricultural cohort experienced a more intermittent, seasonal exposure with long intervals between exposures. So there are some drastic differences.

The problem, of course, of trying to figure all this out is that the information provided in the St. Gabriel study is very sketchy at best. So it remains unclear whether St. Gabriel company employees had higher peak exposures than agricultural workers. And I'll talk a little bit more about the problems of trying to figure out what kinds of exposures they actually did have.

But, in general, differences in the pattern of exposure may be important depending upon the etiology of the disease, the target

organs of injury, the specific mechanisms of the toxicant and so on. So differences in exposure profiles between the farm workers and manufacturing plant workers would and probably are important. If chronic, long term exposures are more important than intermittent exposures in the etiology of prostate cancer, then it certainly makes a difference. So if atrazine acts as a cancer promoter, then intermittent exposures may not be sufficient to cause an increase in tumor rate.

Let me talk now about differences in the exposure assessment between the two studies because those are drastic. There are essentially no exposure assessment for the St. Gabriel study. Subsequently, there was some aggregate information on job titles, and, you know, about that data, proximity to packaging areas. Nevertheless, at best, the information permits only very crude assessment of relative exposure among company employees. And you'd expect a lot of exposure misclassification as I said earlier.

In stark contrast, the Agriculture Health Study conducted an extensive exposure assessment, based on questionnaire information provided by the pesticide applicators. And so that was an extremely good exposure assessment.

Limitations of the two studies, both studies do have important limitations. The Agriculture Health Study had a short follow-up time,

less than five years, and involved a relatively young cohort. And that was also true of the St. Gabriel cohort. It could also have looked into induction periods. It didn't do that.

The St. Gabriel study, again, had no exposure assessment. And there are other problems that we've been talking about all day, so I won't go over them again.

The Agricultural Health Study conducted an extensive exposure assessment. But there may be two sources of inaccuracy in the exposure assessment, including the use of weightings; and the index algorithm may not reflect the actual situations in Iowa and North Carolina.

The situations in Iowa and North Carolina are very different in terms of crops, size of the farms. Probably a personal hygiene practice and personal protective use may be different in the two states so that there maybe some differences in exposure patterns within that study between the two states. So that needs to be taken into consideration. And, also, there probably is some inaccurate recall of pesticide use decades in the past that the applicators were to remember.

So in conclusion, given the striking differences between the two studies and the patterns of exposure and the quality of exposure

assessments, it maybe be useful to compare the two studies. And given the limitations in both studies, EPA should not base its conclusion about atrazine and prostate cancer solely on either study.

Let me say a few things about the Agricultural Health Study. Again, it was well conducted. A cohort was followed prospectively. The follow-up period, again, was short; but the study is ongoing. And a planned reanalysis will approximately, as we heard today, double the number of prostate cancer as were analyzed in the published study. Therefore, EPA should wait for the reanalysis and base its conclusion about the causal relationship between atrazine and prostate cancer on what's been done so far.

There is an interesting finding. It's not a totally negative study as people seem to make out that it is. There is an interaction effect that was there. It's not statistically significant. But in all these studies, we're having trouble with statistical power. So I don't focus on the lower tail of a 95 percent confidence interval. I try to focus on the effect estimate itself.

And the effect estimate is 1.5 when comparing those ever exposed. And remember, ever exposed being a very crude way of getting at exposure would introduce again exposure misclassification, biasing these effect measures towards the null, making it harding to

find a statistically significant finding anyway.

But anyway, the interaction of ever exposed and having a positive family history compared to never exposed and having no family history was 1.52. So I suggest that it may be possible for even these intermittent exposures to have an effect if atrazine works as a promoter in a highly susceptible population. So that goes back to what John was saying earlier, maybe trying to identify those susceptible populations is future studies.

The triazine study, the only point I want to make here that hasn't been made already is the exposure information is general and vague. But it appears that the contract production workers had the highest exposures, but they were the short-term employees. The company employees were employed long term, but only a small percentage either worked in production or worked in areas in proximity to the contaminated areas. And they also shifted from working in the package or production to managerial and supervisory jobs. So they may have been getting some exposure high in the beginning of their employment history and then switching to getting no exposure or very low exposure later in their work histories.

So it's going to be difficult to figure out just how much they were exposed to, what their peak levels or average exposure levels

were, over their work history. And, again, there were changes during the time period in the introduction of technology for bagging and ventilation controls; so the exposure are going down after 1975.

That's all I want to say now about that.

DR. PORTIER: Thank you, Dr. Bove. Dr. Knobeloch.

DR. KNOBELOCH: I basically concur with what Dr. Bove has said. Assuming that if atrazine does indeed contribute to prostate cancer, it would be doing it via a promotional mechanism. I wouldn't expect to see an effect in agricultural workers; and, indeed, none was seen.

I would think that you would want to look at production workers that have daily exposure over a period of five years or longer. That's where we are potentially seeing an effect. So I think that these two studies are consistent with what we would expect, given that atrazine may be working as an endocrine disruptor to promote prostate cancer developments.

DR. PORTIER: Dr. Reif.

DR. REIF: I'd like to make a couple points that Frank didn't address.

First, as evidence for a difference in exposure frequency between the Agricultural Health Study and the St. Gabriel study, I'll

refer to Sheila Horizom's initial 1986 publication from Kansas, which was a case-control study of non-Hodgkin's lymphoma and soft tissue sarcoma, in which she looked at exposure to a number of pesticides. The highest exposure group in that study had a frequency of exposure of more than 20 days per year. So it puts some quantitative comparison between 20 days a year is the highest exposure and a cohort like the St. Gabriel cohort to show that, in fact, the exposures are quite different.

That said, one recommendation I would have is I believe that the Agricultural Health Study has a subset sampling for bio-monitoring of specific pesticides. And I do not know whether atrazine and its metabolites are a target of those studies. But I would hope that they would be. If that's the case, then there may be data. In fact, there may already be data that I don't know about that would permit looking at urine biomonitoring data for the AHS cohort and the St. Gabriel cohort to attain quantify differences if the AHS protocol requires the use of the diaminochlorometabolite of atrazine as reported by Syngenta for some of their employees this morning. So there may be data that then would be useful in looking specifically at a biomarker to look at exposure across the two populations.

One problem with the Agricultural Health Study that I see that

hasn't been acknowledged by the authors yet is the possibility that the pervasive contamination of groundwater and surface water and private wells in areas where atrazine is used intensively may lead to comparison groups, that is, groups that claim they have never used atrazine but, in fact, had been exposed to atrazine chronically without their knowledge. It's a little bit like some other pervasive exposures that Dr. Portier is very familiar with. In other words, there is no unexposed group. That may be the case, at least to some extent, with the Agricultural Health Study cohort.

There are many published studies. One from our lab, from our group in 1986, from Colorado. Dr. Hopenhayn has a publication from Kentucky citing groundwater contamination in a large proportion of the county groups in her ecological study. And I had several other references that I provided to Dr. Bove for the document that also, of course, attest to the pervasive contamination of groundwater in areas where atrazine is used intensively on corn and other crops. So the problem of not seeing an effect when there is pervasive exposure to the persons who deny the use of atrazine is a methodological issue and results in some misclassification that's difficult to deal with.

Those are the only additional points I have.

DR. PORTIER: Thank you, Dr. Reif. Dr. Symanski.

DR. SYMANSKI: Dr. Bove very nicely summarized the points that I want to make, so I won't repeat them here. Thank you.

DR. PORTIER: Any other comments by the Panel? Additional comments, changes in different ideas about this particular question? None. I'm not going to attempt to summarize most of this because it was extraordinary detailed.

I think if I had to capture some of the salient points, the most important one is that one has to be very cautious in making a comparison between these to different studies because they're going to be remarkably different studies. And you might be able to do it, but you better be cautious in doing it.

Have I captured the basic idea there? I think Dr. Reif's last comment about potential water exposure and the problems that might pose for the Agricultural Health Study, I think, is something that's really a very serious concern for that particular study that we're going to have to look at carefully as well.

Any other comments on this question? Dr. Herringa.

DR. HERRINGA: I'd like to make a comment. There's a tendency to want to draw comparability between this sort of null results from the first round of the Agricultural Health Survey and the California work done by Dr. Mills. And I have some questions about

the California work, not only because of the ecological or aggregation implicit in them and then potentially some of the scaling measures. It's a tough situation working from a registry like this, or a farm worker's data base, matching against a cancer registry and then trying to assess exposure for these individuals because you don't get direct measurements on each individual.

I think that there is a lot of explanation statistically and otherwise why you wouldn't see consistency between this first round from the Agricultural Health Study and the Central Valley studies or the Fresno area studies by Dr. Mills. So I think that that inconsistency, I think, could be explained, in part, on an analytic basis. And I would prefer my own self to stay with the Agricultural Health Survey and what it's finding and then continue with the follow-up as we accumulate more data and more cases of prostate and other cancers.

DR. PORTIER: Okay. With that, then, I think we've covered EPA's questions. And I'll come back to you in a minute to see if we have done that. Before I go to that, I'm going to ask the Panel: Do you have any additional points you want to make beyond the two questions that we had on this topic for the EPA? Now is your opportunity to do it. Dr. Handwerger.

DR. HANDWERGER: I don't think this is the last time we're going to be visiting the St. Gabriel study. I think we're going to be looking at it again in two years or three years. And I would urge that we get more data. So that when we view it again, we don't have to ask about family histories and some of the potential other risk factors that may complicate interpretation. I think it's really vital that, in addition to seeing new cases, we see more data about existing cases so that we can make some sense out of this.

And I urge you to try to find information about the five other centers. I mean, we're just looking at a small percentage of a number of people who are working at production plants for atrazine. Why can't we at least see the other data before we discount it? There may be something of value in the other data that already exist. And I'm really disappointed that we don't have any of that data to evaluate.

DR. PORTIER: Dr. Symanski.

DR. SYMANSKI: I think one recommendation that I would have for the Agency would be if they could encourage Syngenta to collect some prospective monitoring data that would allow them at least to evaluate some of the assumptions that they're making about exposure about the present day period.

DR. PORTIER: Any other comments?

DR. SANDY: I'd like to follow up --

DR. PORTIER: Okay.

DR. SANDY: -- on Elaine's comment. I think you'd want biological monitoring data would be the best rather than personal air sampling.

DR. PORTIER: Dr. Bove.

DR. BOVE: Do we want to say anything more about that because I want to change the topic a little bit?

Earlier today, I asked you why we weren't also evaluating the studies, including the recent study of non-Hodgkin's lymphoma done by NCI. And I didn't feel I got a terrific response. But going back to that -- I mean, a lot of people today talked about the 2000 Scientific Advisory Panel's report. And I have it with me, and a lot of things were said about it that weren't actually accurate.

In that report, we were basically saying that the epi literature had not been evaluated pretty much at all and it needed to be. And that there was plenty of evidence, at least plenty of studies, that we could sink our teeth in and try to evaluate. And it wasn't done then, and it's still not done. And there was plenty of conflicting information in the literature just like there is with prostate cancer.

At some point, we need to revisit these studies that keep coming

up and have a full discussion because I have not been happy with the way EPA has discussed these studies. We weren't happy about it back in 2000 either. We need to have that discussion before a full Panel.

The other thing -- well, one other thing, we recommended this back in 2000, and I guess I'll recommend it again, that we do do this evaluation of other cancers in the epi literature.

And, you know, the conclusion of our Panel, sure, was that it wasn't likely that atrazine was a carcinogen at that point because of the problems with the animal data information, certainly not because of the epi data. The epi data didn't show that it was unlikely. We thought for the most part that there wasn't enough information because we didn't have enough time to actually evaluate the epi data in a full discussion. And I think that until we do that, you know, it's hard to make statements like the statement made in Question 1, that it's unlikely or seems unlikely.

DR. PORTIER: And I would like to concur with Dr. Bove on that issue as well. One of the things that we clearly asked from the 2000 meeting was, in fact, a full evaluation of the epi. And I still feel a little bit marginalized in what I've been able to comment on here at the SAP meeting today in terms of the epidemiology associated with atrazine.

I also recall that -- this is my comment from the 2000 review. And that was that if I'd seen any indication, if I saw any indication in the human literature of an endocrine-oriented cancer effect from exposure to atrazine, that would raise some flags with me. I'm still not sure we're there or not there with these particular studies whether it holds to the commonly believed mechanism involved in LH drop and decrease in testosterone and hints potentially at decrease in the risk of prostate cancer or doesn't hold to that.

If I was convinced there was an endocrine-mediated tumor in a cohort exposed to atrazine, it would raise my concern considerably. And I think it is something that has to be very seriously looked at by the Agency whether or not that mechanism is consistent with what's understood or not. And I think it's something that I would again encourage you to have a broader debate with the Panel on because I think it would be of benefit in the long run. Dr. Knobeloch.

DR. KNOBELOCH: Yes, I'd like to comment on one other thing that disturbs me. And that's the use of underpowered studies for which no power calculation has apparently been done to then draw the conclusion that a chemical does not cause cancer. I think if you're going to use a human study to determine whether or not a chemical is a human carcinogen, you have to do a power calculation and ensure

that you have a large enough population to see an effect if there is one.

I'm not convinced that any of these studies have the power to show an effect. Given what we know about the strength of atrazine as a carcinogen, if we go back and look at the old Q-Star that was developed for atrazine based on the mammary tumors, you wouldn't expect really to see an effect at St. Gabriel plant with these numbers.

DR. PORTIER: With that, I'm going to go back to Dr. Stasikowski and Dr. Blondell and ask you, have we addressed your questions? Were there parts of it that haven't been addressed for you that you would like to address or additional questions you want? We still have some time and I think this is an opportunity for you as well.

DR. BLONDELL: Well, I guess maybe starting at the end of that.

One question that I would have for the Panel is that, if you want me to revisit other cancers beside prostate cancer, please, provide me with a substantial reason to do so. Relooking at studies that are just ecological studies, which most epidemiologists agree are only a basis for hypothesis generating, is not a substantial, in my view. And I would certainly want to see some strong study.

And I could see for NHL, maybe you have a justification.

You've thrown it open. You've said, well, let's look at everything. I don't think -- you need to give me something substantial if you want me to revisit all of the cancers, a reason for doing that. Cite some strong study or something substantial about at least one of these studies if you're going to say that, please, in your final report. Because that's going to involve a lot of work, and I want a reason for why I'm doing that work.

DR. PORTIER: Any additional?

DR. BLONDELL: No. The only other thing we want to say is that we are going to be waiting to see the results of the additional studies from the completed report for the nested case-control study, the repeat of the Agricultural Health Study. We certainly will want to relay any advice that you have on the comments on different approaches to doing the analysis. I particularly like the idea of, if we can get bio-monitoring data, doing a comparison, seeing if there is an overlap between the Agriculture Health Study and also taking that look at the drinking water. So I think that's very helpful.

DR. PORTIER: To clarify my comments, to make sure it's clear, for the record, my comment was not that I felt the epi data had to be properly reviewed again. The comment I made was that I don't think the SAP has had an opportunity to comment on the full review of

the epidemiology data. And we still have not had an opportunity to comment on the full review of the epidemiology data.

The 2000 review had very marginal information on epidemiology in it to which we commented that it would have been nice to see the full picture. We still haven't seen the full picture, and that's my comment back to you. Whether you, then, believe it's not worth the time and effort is something the Agency has to decide. I'm not saying the epi data should or should not come before the SAP for review. I'm simply noting that we have not really had an opportunity to review it and in its entirety.

DR. STASIKOWSKI: At the beginning, when Dr. Blondell was make presentation, he identified a number of other epi studies that will be coming over the next six months to a year. And had we had an opportunity not to set up this meeting at this time, I think we would have felt a lot more comfortable with presenting the data when those studies were in our hands, were peer-reviewed, and then we could have brought entire data.

It is very possible that this is -- well, it is likely that this is just the first meeting during which we'll discuss with you the epi data as the other studies come in. So this really does not mean that this is the only time we will discuss epi data.

DR. PORTIER: Any other comments from the Panel? Dr. Sandy.

DR. SANDY: One other thought as I was reviewing the studies and noting other studies on the triazines. Because of the similar mechanism of action of simazine and other triazines to atrazine, I would recommend then, in looking at the epidemiological data, you look at studies including other triazines.

What we have before us today are limited power studies. I'm guessing it's going to continue to be that way for a while. But as Dr. Portier said, if there's an endocrine-related tumor that pops up, that's a flag to look at it a little more carefully.

DR. BOVE: I want to make one quick point. If you read the Science Advisory Panel's report in 2000, you'll see a pretty good discussion, although it was done very quickly, overnight practically, of the studies. And you'll notice that there were quite a number of studies, particularly with regards to non-Hodgkin's lymphoma, but also the ovarian cancer study. They're not ecological. There are limitations to the ovarian cancer studies, and they're mentioned in the report. So I suggest you reread that report. And, again, there are plenty of studies that we could have been discussing today.

That's true that there will be studies in the future as well, and

this could be an ongoing process. But I'm not sure what tripped this meeting. But there was, as I said, a recent study done looking at non-Hodgkin's lymphoma which was positive. And that's not being brought up here. And I'm not sure I understand why. And I didn't get, I thought, a good answer this morning.

DR. PORTIER: Last call for any possible comments from the Panel. Additional comments from the Agency?

Steve, any closing comments?

Then I want to thank the Agency for offering us this opportunity to look at this. I want to thank all the presenters for bringing the material forward as well as the Agency for our review. I want to thank the Panel for their time and effort. On behalf of the federal government, as a federal taxpayer, I think it's great that you would spend your time and effort looking into this important issue on behalf of the American public.

And I think with that, I'm going to close the meeting unless there's anything else. No. I would ask that the Panel meet very briefly in the Panel room after we close the meeting to briefly go over the logistics for our writing session tomorrow.

Thank you all for being here. Good evening.

[Session concluded at 4:48 p.m.]

CERTIFICATE OF STENOTYPE REPORTER

I, Jane F. Hoffman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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JANE F. HOFFMAN

**I-N-V-O-I-C-E**** ****I-N-V-O-I-C-E****

JANE F. HOFFMAN

TODAY'S DATE: 8/5/03

DATE TAKEN: 7/17/03

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