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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH

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PUBLIC MEETING REGARDING
NIOSH DRAFT DOCUMENT:
CRITERIA FOR A RECOMMENDED STANDARD
OCCUPATIONAL EXPOSURE TO DIACETYL
AND 2,3-PENTANEDIONE

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FRIDAY
AUGUST 26, 2011

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The Public Meeting was held in
the Hampton Ballroom in the Omni Shoreham
Hotel, 2500 Calvert Street N.W., Washington,
D.C., at 8:00 a.m., T.J. Lentz, Moderator,
presiding.

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Education and Information Division, NIOSH

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ROBERT P. STREICHER, Ph.D., Chief, Chemical
Exposure and Monitoring Branch, Division of
Applied Research and Technology, NIOSH

JENNIFER TOPMILLER, M.S., Team Lead,
Engineering and Physical Hazards Branch,
Division of Applied Research and Technology

ALSO PRESENT:

JONATHAN BORAK, M.D., Yale University

PATRICK BURKE, Food Safety Inspection Service

HARVEY CHECKOWAY, M.P.H., Ph.D., University
of Washington

BRIAN CURWIN, Ph.D., Division of
Surveillance, Hazard Evaluations, and Field
Studies, NIOSH

DAVID EGILMAN, M.D., M.P.H., Brown University

JEFFREY FEDAN, Ph.D., Health Effects
Laboratory Division, NIOSH

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DANA HOLLINS, M.P.H., ChemRisk, LLC

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WARREN MYERS, M.S., M.P.H., Ph.D., West
Virginia University

JACQUELINE NOWELL, UFCW International Union

ED SARGENT, The Redstone Group

HANK SCHILLING

MARY TOWNSEND, DrPh, MC Townsend Associates
LLC

LES UNGERS, Ungers and Associates

C-O-N-T-E-N-T-S

	<u>Page</u>
Welcome	
T.J. Lentz, Ph.D.	6
Executive Summary of the Criteria Document/Exposure Assessment Summary	
Lauralynn Taylor McKernan, Sc.D.	11
Sampling and Analytical Methods for Diacetyl and 2,3-Pentanedione	
Robert P. Streicher, Ph.D.	37
Health Effects of Exposure in Workers	
Kathleen Kreiss, M.D.	51
Toxicology of Diacetyl and 2,3 Pentanedione	
Ann F. Hubbs, D.V.M., Ph.D., DACVP	80
Quantitative Risk Assessment Based on Worker Data	
Robert Park, M.S.	95
Quantitative Risk Assessment Based on Animal Data	
David A. Dankovic, Ph.D.	143
GUIDANCE SECTIONS:	
Hazard Prevention - Engineering Controls	
Jennifer Topmiller, M.S.	157
Hazard Prevention-Personal Protective Equipment	
Jay A. Parker, M.S., C.I.H.	172
Exposure Monitoring	
Lauralynn Taylor McKernan, Sc.D., CIH .	190
Medical Monitoring and Surveillance	
Kathleen Kreiss, M.D.	198

C-O-N-T-E-N-T-S (Cont'd.)

	<u>Page</u>
PRESENTATIONS BY INTERESTED PARTIES: (in alphabetical order)	
David Egilman, M.D., M.P.H., Private Person	218
Peter Harnett, M.S., M.P.H., C.I.H., C.S.P., Counsel in Occupational and Environmental Health, Inc	228
Dana Hollins, M.P.H., ChemRisk, LLC	247
Azita Mashayekhi, M.H.S., International Brotherhood of Teamsters ...	267
Adjournment	289

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

(8:05 a.m.)

DR. LENTZ: Well, good morning and welcome to this public meeting to present and discuss the NIOSH draft document entitled "Criteria for a Recommended Standard Occupational Exposure to diacetyl and 2,3 Pentanedione."

My name is T.J. Lentz. I am the Chief of the Document Development Branch in the Education and Information Division at the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention, NIOSH CDC. I will be chairing this morning's meeting and you will be hearing presentations from a number of my NIOSH colleagues who were on the team that developed this document.

Our Division Director in the Education and Information Division, Dr. Paul Schulte, extends his regrets that he could not attend this morning.

First as a matter of housekeeping, I would ask you to please note the location of the exit near the back on the right-hand side, especially given the seismic events and extreme weather that we are facing later on this weekend, too. I think it is important to note that. But also the restrooms, if you go out through the back where you came in, are located near the elevator.

The purpose of this meeting is to provide a public forum to present summaries of the most salient scientific and technical issues of the document and to provide an opportunity for clarification of issues or to raise issues for NIOSH to consider.

When NIOSH announced the availability of the document, it also announced the public comment period to last through October 14th. Written comments are requested to be submitted to the NIOSH docket as instructed in the *Federal Register* notice.

This public forum will also be

recorded and transcribed and transcriptions will be made available within 30 days in the NIOSH docket office. Consequently, all discussions, presentations, and comments as part of this meeting are considered to be in the public domain and will be documented in the NIOSH docket. Therefore, if you have a question, you are asked to step to a microphone and identify yourself and your affiliation.

This forum not only satisfies our Office of Management and Budget peer review requirements for a highly influential scientific assessment document, which this document is, but we also see this as an opportunity to allow the scientists, the subject matter experts who are also the authors of the document to present and also to hear from stakeholders with the goal of providing a document that is scientifically sound, has relevance and utility, and is developed according to a rigorous, consistent,

and transparent process.

Towards that end, I will be introducing members of the diacetyl team. According to the agenda, the first part of the morning will be dedicated to the scientific and technical presentations of specific sections of the document. The second half of the morning will focus a little more on some of the recommendations and authoritative guidance that is provided. There will be a break at 10:00 and then another break near noon for lunch.

When we return at 1:00, there will be opportunity for stakeholders and members of the public, first who have signed up, to give brief presentations and comments. Those again will become part of the public record and archived in the NIOSH docket. If time allows, there will be other opportunities following those presentations for other members of the public and those present to provide comment.

So without further ado, I would

like to begin with our first presenter.

Commander Lauralynn Taylor McKernan is an Environmental Health Officer in the U.S. Public Health Service, a certified industrial hygienist, and has been working as a research industrial hygienist for NIOSH for 14 years.

Commander McKernan received her Master of Science in Public Health from the University of North Carolina at Chapel Hill and a Doctor of Science degree in Environmental Health, specializing in industrial hygiene from Harvard University.

Commander McKernan has conducted industrial hygiene field studies in a variety of occupations and has 20 peer reviewed publications in topics ranging from bioaerosols on commercial passenger aircraft, blood lead monitoring techniques, diacetyl sampling, and lessons learned for first responders.

Dr. McKernan is the project officer for the criteria document, and she will be

presenting an executive summary on the criteria document and an exposure assessment summary as well.

COMMANDER MCKERNAN: Good morning.

Thank you, T.J. Good morning. On behalf of the entire diacetyl 2,3-pentanedione criteria document team, thank you for coming this morning. Thank you for risking the elements, those of you that have traveled. The public meeting is a critical element of the criteria document process. We really need your input, we value it, and we thank you for being here to provide it today.

The Criteria Document Team is comprised of 22 authors from six different divisions across NIOSH. And as T.J. mentioned, several of us will be providing the highlights of the draft criteria document for you this morning. Then, this afternoon we will be hearing your comments. Throughout the day I expect that we will have a positive exchange and interaction of ideas.

Many of our authors will be speaking today but we also have several authors that are in the audience that will not be speaking. I want to acknowledge all of the authors and contributors to this document. In addition to the 22 authors, there are also approximately 10 contributors. This effort has been comprehensive and I thank the team for their contributions.

So, here is a brief overview of my presentation this morning. First, I am going to give you an update about the organization of the criteria document, then go through our process on the scope of the document. Then I am going to shift gears a little bit and provide an executive summary of the document, including our rationale of the recommended exposure limits within it. And then I am going to provide a synthesis of the exposure assessment chapter in the document.

The criteria document contains a review of relevant information related to

diacetyl and 2,3-pentanedione and also provides the rationale and criteria for establishing appropriate risk management recommendations.

Hopefully, you received a copy of the criteria document when you came in this morning. If you didn't, please ask for one on your way out.

Yesterday, someone called it an encyclopedia, a preliminary encyclopedia, and I think that is true. Within the document there are several chapters that fall within two main parts. The first section is the synthesis of the scientific literature to date, as well as the quantitative risk assessment both from epidemiologic data and animal data. And so this morning you will see that our presentations follow that format, and it includes an overview of the exposure assessment, the health effects of exposures to workers, the toxicology effects of exposure,

the quantitative risk assessment for workers, the quantitative risk assessment based on animals, and then the basis of the standard. The second part of the document is the guidance portion of the document.

Within the guidance portion of the document, we have several sections. Each one of these sections will also be reviewed for you this morning. The first one is a hazard prevention and control. Specifically, it makes recommendations for engineering controls that facilities can implement, as well as work practices to reduce exposures. And finally, if necessary, what criteria you should use to establish appropriate personal protective equipment procedures.

Another element of the guidance section is medical monitoring and surveillance, and finally components of an exposure monitoring program.

NIOSH follows a rigorous and cohesive process to develop a criteria

document. It begins with a topic concept memo that is reviewed by our lead team and if approved, then a criteria document team is established.

Once the team is established, they work diligently to produce a product, and that product then goes through a comprehensive review internally. Once that review is complete, then it goes before external peer review and public comment, which is where we are now. The public meeting is a critical element of this process. And as I already said, it is very important to receive your feedback and your comments, both from the peer reviewers but also from the public.

We strongly recommend that you provide comments to our docket. There are a number of ways that you can submit your comments, you can fax or email them to us, or you can submit them online directly through the docket. All of those comments will be accepted from the public until October 14,

2011. We really hope that you take the time to incorporate your comments into the docket.

After we receive comments from public comment and our external peer reviewers, we carefully consider them. Then, we will respond to them and amend the document accordingly. After the document has been amended and has gone through another rigorous review internally, it will be finalized and published.

So let's talk a little bit about why we are here. Let's go back to chemistry.

So these are chemical diagrams for both diacetyl and 2,3-pentanedione. Both diacetyl and 2,3-pentanedione are both alpha-diketones.

The diacetyl and 2,3-pentanedione molecules contain two carbonyl groups; oxygen molecules attached to carbon by a double bond. So there is the double bond and here is the carbonyl groups on both sides.

You can see that the figures are very similar to one another. Diacetyl is a 4-

carbon alpha-diketone and 2,3-pentanedione is structurally very similar to diacetyl, as it is a 5-carbon alpha-diketone.

The odor threshold for both diacetyl and 2,3-pentanedione is also very similar, ranging from 0.01 parts per billion to 0.02 parts per billion. The odor threshold for both these compounds is very low in air.

Diacetyl is used extensively in the flavoring and food production industry and occupational exposure to the substance has been associated with severe obstructive lung disease, bronchiolitis obliterans and a decrease in lung function. Bronchiolitis obliterans is a life-threatening disease and decreased pulmonary function has been associated with reduced quality of life and increased mortality.

2,3-pentanedione has been used as a substitute for diacetyl. And this is a concern not only because of its structural similarities to diacetyl, but also because

preliminary animal studies show similar pathology as seen with diacetyl in exposed animals.

Here is a brief history of some of the sentinel events. In 1985 two workers with fixed obstructive lung disease suggestive of bronchiolitis obliterans were observed in a facility where flavorings with diacetyl were made for the baking industry. The link between exposure to diacetyl and the risk of bronchiolitis obliterans was identified in the early 2000s, when a series of health hazard evaluations in the microwave popcorn industry confirmed a relationship exists between diacetyl exposures and lower pulmonary function. From 2000 to 2006, two cases of bronchiolitis obliterans were identified in two California flavoring plants and this resulted in industry-wide surveillance.

NIOSH evaluated the cross-sectional pulmonary function data from the diacetyl exposures at

microwave popcorn plants, and NIOSH conducted analysis to determine the exposure-response and identified the risk of pulmonary function decrease at various levels of diacetyl exposure. NIOSH found that a relationship exists between diacetyl exposures and lower pulmonary function.

Utilizing this quantitative risk assessment, NIOSH recommends that exposures to diacetyl be kept below a concentration of five parts per billion as a time-weighted average during a 40-hour work week. That is an eight-hour time-weighted average during a 40-hour work week.

NIOSH has determined that workers exposed to diacetyl at this concentration should have no more than a one in one thousand chance of suffering reduced lung function associated with diacetyl exposure and less chance for developing bronchiolitis obliterans.

To further protect against the

effects of short-term exposures, NIOSH recommends a short-term exposure limit or a STEL for diacetyl of 25 parts per billion over a 15-minute duration. Additionally, NIOSH recommends an action level of approximately one-half the recommended exposure limit or REL of 2.6 parts per billion.

In many operations, 2,3-pentanedione and other substitutes are being used to substitute for diacetyl. As I mentioned, they are very similar structurally.

There is little health effect on these substitutes, but it is appropriate to consider some of them as potentially hazardous as diacetyl. Specifically, 2,3-pentanedione is not only structurally similar to diacetyl but also published reports on the toxicity of 2,3-pentanedione suggests that in rats it causes airway epithelial damage similar to that produced by diacetyl.

Because of this, NIOSH recommends keeping occupational exposure to 2,3-

pentanedione, below a level comparable to that for diacetyl. However, analytical limitations of the recommended method for 2,3-pentanedione, that is OSHA Method 1016, indicate that 2,3-pentanedione can only be reliably quantified to 9.3 parts per billion.

This is slightly higher than is what is recommended for diacetyl and is the reason that the proposed recommended limit is 9.3 parts per billion. It should not be misconstrued to infer that 2,3-pentanedione is of lower toxicity than diacetyl.

NIOSH recommends that exposure to 2,3-pentanedione be kept below a concentration of 9.3 parts per million in an eight-hour time-weighted average during a 40-hour work week.

NIOSH also recommends a STEL for 2,3-pentanedione of 31 parts per billion during a 15-minute period. And because the REL is established at the quantitation limit, there is no action limit -- we are not

proposing an action limit for 2,3-pentanedione.

This is an important point, so I want to make sure that I made it clearly. Because of the reliable quantitation limit of the OSHA method 1016, the proposed REL for 2,3-pentanedione is 9.3 parts per billion, versus diacetyl, which is five parts per billion.

We feel that engineering and work practices are available to control diacetyl and 2,3-pentanedione below the recommended exposure limits. Validated analytical methods are available that allow measurements at the RELs. This is significant because although NIOSH considers the health effects and risk assessment when creating the REL, we also look at achievability and analytical feasibility.

NIOSH recommends that employers develop and implement a comprehensive occupational safety and health program to protect workers with potential exposure to

diacetyl, 2,3-pentanedione, and other potentially hazardous flavoring chemicals. This program should include exposure and medical monitoring, implementation of exposure controls, and it also should facilitate the selection of appropriate personal protective equipment, if appropriate. All of these components, again, are covered in great detail in the guidance portion of our document.

While the focus of this document is on diacetyl and on 2,3-pentanedione, NIOSH has concern about other flavoring substitutes with structural similarities to diacetyl, which are potentially capable of producing similar toxic effects as diacetyl. Therefore, NIOSH recommends that such exposures be considered and controlled as low as reasonably achievable.

I'm going to shift gears entirely now and provide a summary of the exposure assessment information. In your document, this would be contained in Chapter 1 and

Chapter 2.

It is difficult to quantify the number of employees directly involved with flavor manufacturing and more specifically having diacetyl substitute exposure in the United States. According to the EPA, Non-Confidential Inventory Updating Report, diacetyl had an aggregate production volume between 10,000 and 500,000 pounds. According to the North American Industry Classification System category 311, which is the most relevant category, there are 1.5 million workers in food manufacturing. However, not all of these workers would necessarily have diacetyl exposure. According to FEMA, 6,520 employees work directly in flavor manufacturing or laboratory activities.

Employers in the food manufacturing sector are generally small business owners with 89 percent in establishments employing fewer than 100 workers and nearly 53 percent of these establishments employing fewer than

ten workers.

Measurement of diacetyl and 2,3-pentanedione exposures is helpful in preventing flavoring-related lung disease, even though flavoring exposures are often more complex. Diacetyl and 2,3-pentanedione can be monitored using personal and area air samples, since the predominant route of exposure is inhalational. Results from air sampling can be compared with established criteria, such as the proposed NIOSH recommended exposure limits.

Measuring diacetyl and other alpha-diketone exposures may help to identify hazards, guide corrective actions such as engineering controls, identify improved work practices, and select appropriate personal protection to reduce or eliminate exposures.

Several investigations have been completed by NIOSH and others within the flavoring and food production industries. Exposure conditions vary widely, depending

upon site-specific parameters and the processes employed. Many diacetyl samples have been collected to evaluate occupational exposures in the workplace. The specific sampling methods utilized will be covered in great detail in just a few moments by my colleague, Dr. Robert Streicher.

Within Chapter 2, there are detailed descriptions of every study that we evaluated that cover exposure assessment investigations. There are a series of tables, this is a snapshot of one of those tables.

NIOSH conducted health hazard evaluations at six microwave popcorn plants from 2000 to 2003. In general, diacetyl concentrations were higher in the mixing rooms.

I am only going to highlight a few things on these slides, but there is a full description and evaluation of each of these studies in your criteria document.

So as you can see here, there are

several studies identified. The top line is the index plant, the second one is synthesis of all six of the microwave popcorn health hazard evaluations that NIOSH completed. And as you can see, exposures are typically higher in the mixing rooms, but they are also present in packaging areas and in some instances, the QC lab.

White, et al. conducted a repeat monitoring campaign at four microwave popcorn facilities and approximately half of the 639 samples collected were below the limit of detection after correction for humidity.

NIOSH also conducted evaluations at three California flavor manufacturing facilities where we measured exposures to diacetyl and other related compounds. The objectives of these surveys included identifying common work practices, plant processes and procedures, as well as characterizing potential exposure within the flavoring industry. Most of these studies

were completed and the samples were collected not only in the liquid production side of facilities, but also the powder production side, and some of them included spray drawing operations as well.

At one plant, the mean time-weighted average diacetyl exposure after the method correction was from a full-shift air sampling in the powder production facility, was 2.7 parts per million.

Martyny, et al. also conducted a study at a 16 flavor manufacturing facilities.

During this study, he actually conducted what we call worst-case sampling where we had them use their formulations with the highest potential exposure to diacetyl based on the content of diacetyl in the formulation. These exposures ranged from zero to 60 parts per million. However, they were not corrected with the new NIOSH correction factor. So the values published likely underestimate exposures.

NIOSH has also conducted health hazard evaluations at food production facilities, including a bakery mix production plant, a popcorn plant, and three office building cafeterias.

At the bakery mix production facility, workers combined liquid and powder flavorings. At this facility NIOSH observed 2,3-pentanedione for the first time. This sampling occurred because one of the formulations had eliminated diacetyl but had added 2,3-pentanedione in its place.

No diacetyl was detected at the popcorn production -- I'm sorry -- the popcorn popping plant. And then at the office building cafeterias, diacetyl was not detected on the area samples.

This concludes a quick synthesis of the exposure assessments that have been conducted to date. Obviously, there is more information in your criteria document, which we encourage you to review and provide comment

on.

At this point, I believe I have some time to answer some initial questions. The way we are going to do it this morning is, each presenter is going to talk and then we will have some time for a few questions after each presentation while it is fresh in your mind. Later today we will also have open questions as well.

So if anyone wants to start the process, I am happy to answer any initial questions that you may have. Again, as a reminder, please come to one of the microphones, identify yourself by your name and your affiliation before you ask your question.

MS. MASHAYEKHI: Good morning. Thank you. I am Azita Mashayekhi with the Teamsters Union. I actually have a couple of questions but if you guys will be covering it later, that is fine. We can wait.

I just wanted to follow up on what

you said, Lauralynn, about industries that you guys went into for health hazard evaluations.

And as far as I know, you have done some work in dairy or at least, you know, groups that NIOSH are looking at; candy, snacks, dairy, even there was a study I believe where exposure to oil in the kitchens was an issue.

So I am not sure if that is something that is -- I am not sure if it is in the document or if people will comment on later. So that is one question.

Another question is about maintenance workers. I did see the sections of the facilities that you mentioned. But maintenance workers were covered, right, in these studies? People who were cleaners and maintenance workers.

COMMANDER MCKERNAN: Okay, so there were two questions there. The first one, you mentioned several different food production facilities and the fact that NIOSH has conducted studies in a variety of those.

The first couple, you mentioned the baking powder production, that is included in the criteria document in detail in Chapter 2 and the also the medical aspects of those investigations is also thoroughly reviewed. Dr. Kay Kreiss will be providing a synthesis of that work shortly.

The second half of your question, was candy production and snack production. There is an ongoing effort that NIOSH is involved in-actually Dr. Brian Curwin is leading that effort. He is here with us today. Those study results are not final and, therefore, are not in the draft criteria document at this time. However, the work is ongoing. Brian, I don't know if you want to say anything else on that?

DR. CURWIN: Yes, just you know --

COMMANDER MCKERNAN: You have to use the microphone.

DR. CURWIN: Oh, okay. So yes, I mean the studies, we have the data now. We

are just analyzing it and synthesizing it. We just haven't got it to a point where we can publish it in this document yet. But it should be getting there soon.

We went to some chocolate manufacturers, bakeries, dairy, snack food.

COMMANDER MCKERNAN: Go ahead.

DR. EGILMAN: Thanks. I am David Egilman and I am just going to try to put this in the form of a question.

Since you talked about controls, this cover picture, is this what you mean? Not closed systems? Stick a worker on a respirator and have it all open and pouring like this? A picture is worth a thousand words. In this case, many more than all of you gave today, at least.

So I wonder if -- So the question is, is this picture how you suggest that controls be done?

COMMANDER MCKERNAN: You know, no matter what picture you use, there are always

issues. But actually, if you look at that picture, there is an engineering control hood behind the gentleman that we actually evaluated.

But in the criteria document, we have a series of at least 13 different figures for engineering control hoods that we recommend. That is what we would recommend that people do. Those figures are very detailed. They have not only design configurations but also airflow. And I know Jennifer Topmiller will be reviewing what we recommend.

But we appreciate the comment and certainly we will take that under advisement.

DR. EGILMAN: Well I would suggest you take one of those controlled systems where the worker is not on a respirator and put that on the cover.

COMMANDER MCKERNAN: Okay. We appreciate the comment and we will definitely take that under consideration.

MR. UNGERS: Hi, Lauralynn.

COMMANDER MCKERNAN: Good morning.

MR. UNGERS: Les Ungers, Ungers and Associates. Just a quick question on the time-weighted average.

Is there any reason specific to diacetyl that you chose an eight-hour time-weighted average versus the more traditional ten-hour that NIOSH has done?

COMMANDER MCKERNAN: No.

MR. UNGERS: Okay. Any general reason for that?

COMMANDER MCKERNAN: No, there is not a general reason. I mean, you could certainly make comments if you would prefer that we do a ten-hour. I believe the decision to do an eight-hour time-weighted average reflected that what we observed in the field most of the time were eight-hour work days.

MR. UNGERS: Okay, thank you.

DR. LENTZ: Thank you, Lauralynn. And thank you, too, to the stakeholders and

the public for those excellent questions and I hope there will be more time to engage in further discussion like this.

Our next speaker is Dr. Bob Streicher. Dr. Streicher earned his Ph.D. in organic chemistry from the University of Cincinnati in 1987. Immediately upon graduation, he joined NIOSH as a research chemist in the Methods Research Branch of the Division of Physical Sciences and Engineering.

Dr. Streicher's research activities focused on the sampling and analysis of mono- and poly-isocyanates in air.

In 1998, Dr. Streicher became a Section Chief in the Methods Research Branch and in 2007 was promoted to his current position as Chief of the Chemical Exposure and Monitoring Branch of the Division of Applied Research and Technology.

Dr. Streicher has coauthored 29 publications and holds two patents. Since 2008, Dr. Streicher has served as project

officer on a project investigating various sampling and analytical methodologies from measurement of diacetyl and other flavoring compounds.

Dr. Streicher will be talking about sampling and analytical methods for diacetyl and 2,3-pentanedione.

DR. STREICHER: Thank you. As Dr. Lentz indicated, I will be talking today about the sampling and analytical methods used for diacetyl and 2,3-pentanedione exposure assessment.

Here is a general outline of what I will be talking about. My talk today will focus on the methods that are the most pertinent toward this criteria document. I will start off with speaking about the origin of OSHA Method 1013 for diacetyl, and I will continue with a very similar method, OSHA Method 1016 for 2,3-pentanedione.

OSHA Method 1012 for diacetyl is more sensitive, developed to reach lower

detection limits, and I will talk about that next. I will talk briefly about NIOSH Method 2557 because most of the historical measurements for diacetyl were obtained using Method 2557, and it was discovered a few years ago that there were issues related to humidity that were causing underestimations when using 2557. So I will finish my talk, talking about the work that has been done to correct those historical measurements.

So I will start off with OSHA Method 1013 for diacetyl. In 2003 OSHA released Method PV2118 for diacetyl and acetoin. Method 1013 is really primarily modification of 2118 in two major areas. The first point was to try to increase the sampling capacity of 2118. The capacity when you sample for diacetyl on these methods and silica gel sorbent is really not, the capacity is not dependent on the amount of diacetyl you are collecting. It is really dependent on the amount of water you are collecting in the air.

So in order to improve the method, two things were done. A larger sampling bed was used, a 600 milligram silica gel tube, actually two silica gel tubes of 600 milligrams. And also the silica gel was specially dried to remove the water before you start it.

The second problem the 2118 had was that having two beds within the same sorbent tube, upon storage the diacetyl would migrate from the front bed to the back bed. And when you would analyze, you wouldn't be able to know whether you actually had breakthrough during sampling.

And so method 1013 instead uses two single-bed tubes so that after sampling the tubes are separated and there is no possibility of confusing whether breakthrough has occurred or not.

So sampling in Method 1013. As I said, you use two tubes containing 600 milligrams of specially dried silica gel. The

recommended flow rate is 0.05 liters per minute for three hours. And that corresponds to a nine-liter sample. I believe in humid air the breakthrough was actually determined to be about 12 liters. So there is a little safety factor in limiting it to nine liters.

For a short-term sample, 0.2 liters per minute is recommended for 15 minutes. The one specification is to make sure that the sampling tube is protected from light during and after sampling.

The analysis in 1013 involves extraction of the tubes with 95 percent ethanol, five percent water, containing 3-pentanone. 3-pentanone is an internal standard, and using it improves the precision and accuracy of the method.

The analysis is done by gas chromatography and flame ionization detection.

And the reliable quantitation limit is 0.37 micrograms per a nine-liter sample. And that corresponds to an air concentration of 41

micrograms per cubic meter or 12 parts per billion.

Now, a very similar method for 2,3-pentanedione is Method 1016. The sampling procedure is identical to Method 1013 for diacetyl, except that the maximum volume that can be obtained is slightly larger because pentanedione breaks through a little bit later than diacetyl does. So you can do a ten-liter sample. But the same flow rates, 0.05 liters per minute for long-term sampling and 0.2 liters per minute for short-term are recommended.

As with diacetyl, it is recommended to protect the sample from light. But in addition to that, it is indicated that you need to ship the samples cold and store refrigerated prior to analysis because the pentanedione has shown to be more sensitive to instability with temperature.

The analytical portion of the method for 2,3-pentanedione, Method 1016, is

also very, very similar to 1013 for diacetyl.

Extracting again with 95 percent ethanol, five percent water, and the same internal standard, gas chromatography flame ionization detection. However, the chromatographic conditions have been changed to accommodate the slightly later eluting 2,3-pentanedione.

The reliable quantitation limit is 0.3 micrograms per a ten-liter sample, corresponding to 38 micrograms per cubic meter air concentration, which is 9.3 parts per billion.

Now, you can sample using this method and analyze for both 2,3-pentanedione and diacetyl simultaneously, but you will then be limited to the nine liter air sampling volume maximum that is recommended for diacetyl.

A more sensitive method that was developed for diacetyl is Method 1012. The sampling side of this is identical to Method 1013 that I have described already. You then

extract the sampling tubes with 95 percent ethanol, five percent water, but in this case containing pentafluorobenzyl hydroxylamine hydrochloride. The PFBHA reacts with the diacetyl to create a derivative that can be detected at much lower levels than the underivatized diacetyl.

There is also a different internal standard that is used here, 4-Bromobenzylbromide.

The analysis is gas chromatography with electron capture detection, which takes advantage of the derivatizing reagent's properties.

And the reliable quantitation limit in this case is 0.041 micrograms per a nine-liter sample, which corresponds to 4.6 micrograms per cubic meter air concentration or 1.3 parts per billion.

Now, a couple of points to make about Method 1012. You can analyze samples that have already been analyzed by Method 1013

because the sampling portion is identical. Only in this case, you need to add the derivatizing reagent after the fact, rather than extracting with a solvent that contains the derivatizing reagent. And that results in a dilution of your sample, raising the reliable quantitation limit by a factor of two to 2.6 parts per billion.

Now, this derivatization procedure is not validated for 2,3-pentanedione. So there is no corresponding derivatization method for 2,3-pentanedione.

I will talk briefly about NIOSH Method 2557 because there is so much historical measurement that was obtained using this method. You sample, in this case, with carbon molecular sieve sorbent tubes and extract with acetone/methanol mixture. And like the other OSHA methods, use gas chromatography with flame ionization detection.

However, several years ago, it was

found that this method gives poor recoveries of diacetyl when sampling in moderate to high humidity environments. So as a result of this, with a lot of data, trying to make that data useful for risk assessment purposes, a group of NIOSH researchers in collaboration with OSHA did a study to try to work out a procedure which correct those values that were compromised by the problems with the humid environment. And therefore, that leads to the study that I will be talking about next.

The details of this work are in this publication by Cox-Ganser et al in the *Journal of Occupational and Environmental Hygiene*. This paper has been incorporated in its entirety into the criteria document as an appendix.

Basically, what these researchers did was they generated known atmospheres of diacetyl at different concentrations and different humidities and collected samples by method 2557. They also collected some samples

by the OSHA Methods which did not have the same problems with humidity and also did this in a way that they knew what the concentration was supposed to be as well during the generation.

What they found was that the bias in the measured value using 2557 was affected by absolute humidity, the length of the storage of the tubes before the analysis, and by the actual concentration of the diacetyl. And they then proceeded with that information to develop a mathematical model that gives the corrected diacetyl concentration, based on the measured concentration from 2557; the absolute humidity, and that information was available by taking the relative humidity on the day of the measurement, day of the sampling I should say; and the temperature and calculated the absolute humidity; and then also by the storage time prior to analysis, prior to extraction of the tube before analysis.

So that is all I have. Thank you

for your attention and I will answer any questions, if you have them. Can you please go to the mic?

MR. HARNETT: In the I think it was 1013 Method or it might have been 1012 --

DR. STREICHER: Please identify yourself.

MR. HARNETT: Oh, I'm sorry. Peter Harnett. You indicated a detection limit of 0.041 micrograms. And there are now some, rather than the GC-ECD method, there is a modified method some folks are using that is GC-MS. And they are reporting out at 0.03 micrograms. So it would give you a slightly better detection limit.

DR. STREICHER: Who did you say again was doing this?

MR. HARNETT: Well I can tell you one lab that does it and that would be Travelers Industrial Hygiene Lab.

DR. STREICHER: Okay, thank you. Do you have a question?

DR. EGILMAN: Yes. David Egilman, Brown University.

Am I correct that you could only correct one or two of the previous studies because the relative humidity or absolute humidity had not been noted at the time the sampling went on? I am talking about all the NIOSH studies. You went back and tried to correct them for this boo-boo.

DR. STREICHER: Yes. I may not be the best person to answer which studies were able to be corrected or not.

DR. KREISS: This is Kay Kreiss. All of the NIOSH health hazard evaluations had relative humidity, temperature, and time to extraction in the analytical lab with which we could correct the historical measurements. So all of the NIOSH studies could be corrected.

In addition, the studies that were conducted by Ken White and Jim Lockey also were able to be corrected. The studies by John Martyny at National Jewish did not

collect that information. So that publication is not able to be corrected.

And there was one effort in a California flavoring plant in which NIOSH did not collect relative humidity and temperature.

So the vast bulk of information on which the risk assessment was made, in fact all of the human information in which the risk assessment was made were made with corrected values.

DR. EGILMAN: Okay. I didn't see in the charts, I know it said that for two of them there were corrected values. In others it didn't say that. That's why I asked the question the way I did.

So is that data available some place?

DR. KREISS: All of the measurements that are listed in the criteria document have been corrected with the one exception that the quartile analysis for exposure-response in the cross-sectional study from the index plant has not yet been

corrected but is in the process of being corrected.

So all of the measurements given in the criteria document have been corrected.

DR. EGILMAN: Okay, thank you.

DR. LENTZ: Okay, thank you Dr. Streicher. And you just heard from Kay Kreiss, who also happens to be our next presenter this morning.

Dr. Kreiss received her medical degree from Harvard, completed her internal medicine residency at the Beth Israel Hospital in Boston, and became an Epidemic Intelligence Service officer and completed her preventive medicine residency at the Centers for Disease Control and Prevention in Atlanta in the area of Environmental Health.

At the University of Colorado and National Jewish Health, she built an occupational medicine research clinic and accredited residency program.

Fifteen years ago, she came to

NIOSH in the Division of Respiratory Disease Studies in Morgantown, West Virginia, where she has led the Field Studies Branch. Under her direction, her branch has worked on several emerging occupational respiratory diseases, such as flock worker's lung, dampness-associated asthma, alveolar proteinosis in indium workers, beryllium disease, and flavoring-related bronchiolitis obliterans.

Please welcome Dr. Kathleen Kreiss, who will talk now about health effects of exposure in workers.

DR. KREISS: Thank you, T.J.

I have listed here the health effects that have been described in workers exposed to diacetyl and other flavoring chemicals. Obstructive lung disease such as bronchiolitis obliterans; restrictive pulmonary functions; rapid lung function decline, which can occur either with obstructive lung disease or restrictive

pulmonary functions; asthma; mucus membrane irritation; and dermatitis. And in my talk, I am going to highlight some of the evidence that is presented in the criteria document for each of these health outcomes in flavoring exposed workers.

The rare disease bronchiolitis obliterans is the most unusual disease found in microwave popcorn workers. This photomicrograph from a microwave popcorn worker's biopsy shows scarring constricting a bronchiole, which is the smallest airway. The arrow points to what is left of the airway opening, which is narrowed, almost obliterated, trapping air in the air sacs of the lungs so that the affected worker has trouble blowing out air fast.

On the breathing test, air flow out is obstructed so that the amount of air that can be forced out in the first second, the FEV₁, is abnormally low and the proportion of air that can be forced out in that second is

abnormally low.

The scarring cannot be treated and affected workers have no benefit from asthma medications such as bronchodilators or anti-inflammatory medicines. And that is why some affected workers have been placed on lung transplant lists.

Because bronchiolitis obliterans is a rare condition, many workers are misdiagnosed as having asthma or chronic obstructive lung disease, both of which are common. However, medical tests can distinguish among these diseases in severe cases.

In 2000, the Missouri Department of Health and Senior Services requested NIOSH assistance in investigating eight former workers with bronchiolitis obliterans from a microwave popcorn production plant that employed about 135 workers. Four of these workers were on lung transplant lists, despite being young with ages of 21 to 51 years.

Although only one worker per shift was a mixer of heated flavorings in oil, four of the cases in these former workers were mixers.

NIOSH conducted a survey of current workers. This demonstrated that a quarter of current workers had abnormal breathing tests.

The prevalence of obstructive abnormalities on the breathing tests was 3.3 times the prevalence in the U.S. general population. These findings confirmed that there was a lung disease risk in the plant but no known hazard was present.

NIOSH measured chemical levels in plant air in various jobs and areas. We constructed a job exposure matrix with which we estimated cumulative diacetyl exposure for each current worker who participated. We found that increasing quartiles of cumulative diacetyl exposure were associated with both increasing prevalence of breathing test abnormalities and with decreased breathing test measurements. This was consistent with a

dose-response relationship.

NIOSH then worked with plant management and workers to lower exposure to flavoring chemicals over nearly three years, with seven repeat medical surveys every four to six months. Among workers present at the time of the initial survey in November 2000, chest symptoms, breathing tests, and breathing test abnormalities did not improve. This was consistent with an irreversible disease. However, eye, nose, and throat irritation decreased.

For new hires while exposure controls were being implemented, symptom rates were much lower, breathing test measurements were higher, abnormalities in breathing tests were fewer, and no average changes occurred over time, suggesting that controls were effective in removing the risk for most employees.

For workers who were tested in all eight surveys, they had high average decline

in the amount of air they could blow out in one second in the first year of follow-up. This high average decline fell in the second year and became normal in the third year. This showed that ongoing risk in this group of workers fell to normal as exposures decreased with the engineering controls and personal protective equipment.

NIOSH went on to survey workers at five additional plants in the microwave popcorn industry. Including the index plant, cases of bronchiolitis obliterans syndrome occurred in five of the six plants, consistent with an industry-wide risk.

Mixers in the six plants had more respiratory symptoms and lower breathing test measurements compared to persons who had never spent even one day mixing. Mixers who had worked more than 12 months had more symptoms and worse lung function than mixers who had worked 12 months or less, suggestive of an exposure-response relationship.

Packagers in plants where mixing tasks were open to the packaging areas or conducted in the packaging area had more respiratory symptoms, more airway obstruction, and lower average breathing measurements than packagers in plants where mixing was isolated.

An academic researcher found that mixers had more obstruction both before and after respirators became mandatory in four microwave popcorn plants owned by one company compared to non-mixers, as did workers with higher cumulative diacetyl exposure.

In 1985, NIOSH found two definite cases of bronchiolitis obliterans and two suspect cases in an Indiana flavoring manufacturing plant that served the baking industry. The cause was not determined but diacetyl was used in that plant frequently.

In the mid-1990s, an academic physician diagnosed an index case of bronchiolitis obliterans in a flavoring manufacturing plant. A plant survey uncovered

four more cases, all of whom had normal lung functions at hire.

In California, pulmonary physicians recognized bronchiolitis obliterans in flavoring exposed workers in two California flavoring plants. The California Department of Public Health and Cal/OSHA responded by asking flavoring manufacturers to report questionnaire and spirometry data at six month intervals in a prevention initiative supported by Cal/OSHA consultation; 20 of about 27 companies responded and 16 had usable spirometry data.

Only 18 of the 467 workers in these companies had spirometric obstruction but the distribution of severity of obstruction was very abnormal. The prevalence of severe and very severe obstruction was 2.7 times higher than expected and 15 times higher than expected in workers less than 40 years old, in comparison to the general population.

Four flavoring manufacturing

companies each had four cases of obstruction and these companies each used at least 800 pounds of diacetyl per year. Workers in companies using this much diacetyl had an odds ratio of 4.5 compared to the risk of workers in companies using less diacetyl. Since cases of obstruction clustered in companies, having a coworker with obstruction was a risk factor.

Of the 17 workers for which we had occupational history, 16 had worked in production and one had worked in production support. Those with moderate or worse obstruction had worked nine years, on average, compared to 1.5 years for persons with mild obstruction.

Only half of the workers with obstruction had chest symptoms; one of six with mild obstruction, three of seven with moderate obstruction, and all five with severe or worse obstruction. This means that symptoms cannot be relied on for screening. Many of these workers did not have medical

testing results submitted to the California Department of Public Health.

Of the 13 with post-bronchodilator spirometry, 12 had fixed obstruction that is consistent with clinical bronchiolitis obliterans. Of the 289 workers with good quality serial spirometry data, 21 had abnormal decline in forced expiratory volume in one second or FEV₁ and the abnormal decline rate was greater in companies using at least 800 pounds of diacetyl per year; 7.3 versus 3.0 per thousand person months of follow-up, the three being the rate in workers in companies using less diacetyl. The workers in the four companies with 4-person clusters of obstruction had higher abnormal FEV₁ declines as well.

Of the 21 with abnormal FEV₁ declines over time, only one had an obstructive abnormality, meaning that these workers were in addition to those with probable occupational lung disease denoted by

abnormal obstruction on spirometry.

Some cases of restrictive spirometry existed in almost every microwave popcorn plant and many of those with fixed obstruction had restriction as well. With our concentration on the rare disease of bronchiolitis obliterans, we have only recently turned our attention to restrictive spirometry associated with flavoring exposure.

In a recent health hazard evaluation in a flavoring production plant, we found that 30 of 106 workers had abnormal restrictive spirometry, three had obstruction and one had a very severe combination of obstruction and restriction.

The 28 percent prevalence of restriction was 3.8 times that expected for the general population, adjusted for body mass index, race, ethnicity, gender, age, and smoking status.

Of 70 workers with two or more measurements, 13 or 19 percent had excessive

decline in forced expiratory volume of one second or FEV₁ and five of these 13 still had FEV₁ within the normal range. Workers in areas with higher potential for flavorings exposures had seven-fold the odds of excessive decline in FEV₁ compared to workers with lower potential for exposure, suggesting that the pulmonary function declines are work-related.

I have mentioned two examples of excessive decline in FEV₁ in investigations of obstructive disease in California flavoring workers and restrictive lung functions in a flavor manufacturing plant. In both investigations, many workers had FEV₁ within the normal range, suggesting that they will develop spirometry abnormalities if the excessive declines continue.

In workers with serial spirometry, cases exist of loss of a liter or more lung function within four to five months, both in the index microwave popcorn plant and in California flavoring plants. In the index

microwave popcorn plant, the median duration of employment for the eight former workers was two years and half were on lung transplant lists, indicating very severe impairment.

In the Indiana flavorings plant studied in the mid-1980s, the two employees had severe lung disease within five to seven months of employment.

The figure shows that in the index plant interventions to control exposure lowered average decline in forced expiratory volume in one second or FEV₁ in the workers who were tested in all eight cross-sectional surveys. From 144 milliliters (mL) decline in the first year to 40 mL average decline in the second year to 22 mL in the third year. Thus, control of exposure normalized average annual FEV₁ decline.

Asthma is an obstructive lung disease that differs from bronchiolitis obliterans and emphysema in having reversible air flow limitation in response to

bronchodilators and normal lung function between asthma attacks.

Unlike bronchiolitis obliterans, work-related asthma symptoms and lung function worsen in relation to exposures at work and improve when away from work. In the index plant and another microwave popcorn plant, workers reported twice the prevalence of physician-diagnosed asthma. But most of these may have been misdiagnoses since nearly all workers with obstruction had no improvement after bronchodilator in spirometry tests.

Diacetyl is an irritant which can trigger worsening of pre-existing asthma. Diacetyl is a skin sensitizer which would theoretically cause asthma in sensitized workers.

In one small business that added flavorings to popped popcorn, all three workers developed work-related asthma, one of whom died of his severe asthma. Diacetyl had been historically present but aldehydes were

the predominant compounds in the air of the plant when NIOSH conducted measurements.

Eye and nose irritation is frequent in both microwave popcorn and flavoring plants, with some flavoring plants having higher prevalences of post-hire mucous membrane irritation than many microwave popcorn plants.

In the index microwave popcorn plant, mucous membrane irritation decreased from 65 percent among production workers at the initial survey to 33 percent after implementation of controls. In three plants, workers had severe eye irritation historically in relation to particular butter flavorings, starter distillate, or diacetyl, which precipitated ophthalmology attention in two and use of full-face respiratory protection for mixers in the third plant, all years before the respiratory hazard of butter flavorings was known.

In the index microwave popcorn

plant, one worker had disabling skin rash that was demonstrated to be related to butter flavorings in the plant with patch tests to all eight butter flavorings in the plant. His skin disease improved when he stopped work in the plant.

Post-hire skin problems were reported by 12 to 36 percent of production workers in popcorn and flavoring manufacture with liquid flavoring producers having a particularly high rate of 60 percent of skin problems post-hire in one flavoring plant.

Cross-sectional plant studies taken singly are often limited because they report associations that may or may not be causal. In the body of work by NIOSH and other scientists presented in the criteria document, all of the criteria for interpreting associations as causal for severe occupational lung disease have been met.

The first criterion is that the exposure has to precede disease development to

be causal. In plants where longitudinal spirometry was performed, this criterion was met by showing that spirometry fell rapidly in some individuals into the abnormal range within months. In addition, control of exposure led to the cessation of the progressive damage in both sentinel former worker cases in the index plant and current workers.

The strength of association is apparent in the 10.8-fold increase in prevalence ratio of airways obstruction in nonsmoking workers in the index plant, compared to the expected rates for the nonsmokers in the general population.

Many different clinicians and scientists found cases of clinical bronchiolitis obliterans in five of six microwave popcorn plants, in many flavoring plants, and in workers manufacturing diacetyl in the Netherlands. This demonstrates consistency of findings.

Workers with higher diacetyl exposure had higher prevalence of disease in the index microwave popcorn plant, in the six aggregated microwave popcorn plants, in California flavoring manufacturing workers and in flavoring workers with excessive FEV₁ decline.

In the next talk, you will hear the evidence that inhaled diacetyl and 2,3-pentanedione cause respiratory epithelial damage in rodent airways that is analogous to the injury in the airways and terminal bronchioles of workers.

And finally, inferring cause from epidemiologic and clinical studies requires consideration of alternate explanations. The age distribution, clinical course, and medical tests are inconsistent with smoking as a cause of fixed airway obstruction.

And that concludes my remarks. And do we have time for any questions? Okay, one or two questions.

MR. HARNETT: Hi, I'm Peter Harnett. Dr. Kreiss, how did you deal with folks who were out of work with confirmed lung disease or lung illness in terms of establishing incidence and prevalence rates?

So in other words, because of their sickness or disease, they have recently left employment at the plant.

DR. KREISS: Thank you for that question. In the cross-sectional studies in the index plant, which was the plant in which we had the most attention to former workers, we did not include those former workers in the prevalence rates of abnormality. So in that sense, the rates that we found in the index plant on the cross-sectional basis were underestimates of the burden of disease in people who had worked in the plant.

For the risk assessment, Dr. Park will be talking about that later. He did present an analysis that is in the criteria document of incidence based on symptom

occurrence that included former workers. But those are the only analyses in which former workers were included. I think there were a couple of other plants in which there was one or two former workers that participated in NIOSH health hazard evaluations but those plants were not used, their data were not used in the risk assessment.

MS. NOWELL: Good morning, Dr. Kreiss. My name is Jackie Nowell and I am with the Food and Commercial Workers Union.

Please correct me if I am wrong or explain this. Am I hearing you correctly that there was spirometry data before exposure and that you were able then to measure change from exposure to the butter flavoring or am I hearing you wrong?

DR. KREISS: None of the microwave popcorn plants had pre-placement or pre-employment spirometry data. There was a flavoring manufacturing plant about which an abstract has been published that did have pre-

placement spirometry data and that information is included in the criteria document.

We established temporality as a criterion for a causal relationship in those sets of data for which we had serial spirometry. So that included the index microwave popcorn plant in which we saw spirometry declines during employment. It included a flavoring manufacturing plant that supplied spirometry data, again not with pre-employment data but showing excessive declines during employment and in California, flavoring plants where again we had spirometry during employment that would allow us to look at excessive declines and the evolution of abnormality within some of those working populations.

MS. NOWELL: Thank you.

DR. TOWNSEND: Hi, Kay. Mary Townsend, Pittsburgh.

I didn't get to read all of this. It is a very interesting talk that you did.

But I hadn't seen the HHE from Indiana before, where you were talking about like the 30 percent prevalence of restricted impairment. Is that population primarily Caucasian, those workers? Because this race adjustment factor on NHANES if you have Asians is the 0.94 that ATS uses gives a lot of "restrictive impairment," which is why the ATS committee that I am currently on is probably going to come out recommending based on the MESA study with John Hankinson that we use a 0.88 factor, which then means people aren't called restrictive.

But if it is Indiana, my guess is it is not Asians, it is Caucasians. Is that - - Because when you first said it, I thought maybe it was California.

DR. KREISS: No, the recent health hazard evaluation that was published this summer in 2011, was in Indiana. And I don't recall the racial distribution but it certainly would not have included many Asians

and might not have included very many African Americans.

DR. TOWNSEND: Okay.

DR. KREISS: But that is something that we will look at and include that information.

DR. TOWNSEND: Because that hugely impacts how your decisions are.

The other comment or question -- What was the other question? I've kind of forgotten it. Oh, well. Oh, right.

You said of the "usable spirometry." And what fraction was usable from that plant because very often what we find is even if you achieve repeatability, it isn't really maximal inspirations and so it looks useable but it isn't really. And where that happens a lot is when maybe you only have like say a third of the spirograms end up being usable. I wondered about that, too. Do you have any idea?

DR. KREISS: The 289 I mentioned

were from the California data. So they represent data from 19 or 20 different providers. And there were real problems in the quality from many of those providers.

Because looking at serial data requires higher spirometry, we restricted our analysis to the 289 people who met criteria that we wouldn't use at NIOSH for our own because obviously many of these providers didn't provide enough information with which to review curves but we did require them to have evidence of repeatability and statements in the report about acceptable curves. We did not have raw data submitted, although it was requested by the California Department of Public Health.

DR. TOWNSEND: Okay. And in the Indiana plant where you were finding all that restrictive impairment, the 30 percent, was it also a low? Because that was not your testing. That was using existing data.

DR. KREISS: It was contractually

acquired data by the company.

DR. TOWNSEND: Right.

DR. KREISS: Again, --

DR. TOWNSEND: Which sometimes is garbage, as we know. Yes.

DR. KREISS: Right. We actually looked at within-person variation for that data set and it was five percent.

So it wasn't as good as we would have hoped but then we used that five percent within-person variation to adjust the criterion for excessive decline. And the decline we used was 12.4 percent as the criterion for abnormality in that group.

DR. TOWNSEND: Okay. And can I ask you one overall question?

As you were talking about I think it is reviewing the paper that probably is in press about the California data, it sounded as though what we are looking at is some people who get clobbered by this exposure. Does that sound correct?

In other words, you had some people who had terrible airways obstruction but not millions of them. Do you know what I am saying?

DR. KREISS: Well the data that I presented this morning that had to do with the obstructed people within the California flavoring manufacturers, there were only 18 people with obstruction in that data set of 400 and some people.

And so the prevalence of obstruction was not abnormal but the distribution of severity was very abnormal. So people with severe or very severe obstruction were prevalent in much greater proportions than we would expect in the general population.

So in that sense, one could say that if you were, of the 18, six had mild obstruction and seven had moderate obstruction and the remainder would have been people with severe and very severe obstruction.

DR. TOWNSEND: All right, good.
Thank you very much.

DR. EGILMAN: Can I have one with
Kay?

DR. LENTZ: If you have a quick
question, Mr. Egilman, we will take it really
quickly.

DR. EGILMAN: Okay, thank you.
This is Dr. Egilman from Brown University.

The temporary worker problem is an
issue in some of the plants, particularly a
ConAgra plant, and it is a problem in two or
three ways. First, the people who get
"clobbered" tend to do it relatively soon and
they leave. And they are not in any studies.

The second problem is that what is
written as the baseline in these studies are
actually levels of PFTs that are taken after
they have worked there between six months and
a year. And then so you are missing people
who are sick and you are also getting mistaken
baselines when that occurs.

Now I don't think that occurred in the plants that I am familiar with in NIOSH but it is certainly true in the ConAgra plant.

And the last thing is in terms of the Asians, I think that is a first generation phenomenon, Asians who emigrated here. I think it is going to be less true of people who were born here and grew up with a normal, you know, McDonald's diet.

DR. KREISS: Thank you for your comments.

DR. LENTZ: Okay, thank you for the questions again and thank you Dr. Kreiss. As she indicated, we will move from the human health studies and HHEs into the discussion of the toxicology.

Dr. Ann Hubbs is a veterinary pathologist. She received her D.V.M. from Texas A&M, an M.S. from Purdue, and Ph.D. from Colorado State University. In addition, Dr. Hubbs has practiced veterinary medicine from 1981 to '83, and received a certificate

of residency in veterinary pathology from Colorado State University. She is board-eligible in laboratory animal medicine, and a diplomate of the American College of Veterinary Pathologists.

Dr. Hubbs has been with NIOSH within CDC since 1992 and is also an adjunct associate professor at West Virginia University. She is the author or coauthor of more than a hundred peer reviewed papers and abstracts, principally dealing with the toxicological pathology of workplace agents and has received many awards for many of her publications and her research.

Dr. Hubbs has, in addition to these awards for her scientific publications, received awards from the Department of Health and Human Services, CDC and NIOSH for her scientific skills in responding to several important events, including responses to the anthrax events of 2001, Hurricane Katrina, and monkey pox.

DR. HUBBS: Good morning. We are going to talk about the toxicology data on 2,3-pentanedione and diacetyl. When we look at the structure of the alpha-diketone that we know as diacetyl, we commonly look at this with the ketone groups shown this way. I prefer to look at it this way because this shows the dancing electrons that help make diacetyl a compound which is reactive and can cause protein cross-links. Notably, that can result in the inactivation of proteins and also if we look at these structures, when we look at 2,3-pentanedione, which is this compound over here. This is diacetyl. If we add the dancing electrons, we can see why we would predict that this compound also will be reactive, can cause protein cross-links, and can inactivate proteins.

Both diacetyl and pentanedione tend to particularly react with the arginine groups and pentanedione is reported to be somewhat more reactive with arginine groups than

diacetyl itself.

Both compounds are metabolized. The principal metabolic pathway that has been described is the metabolism in the presence of NADPH, in the presence of an enzyme, which I am going to abbreviate here as DCXR because it is easier for us to say, but it is known as dicarbonyl/L-xylulose reductase as a full name, and it results in the production of the corresponding hydroxy ketone, irrespective of whether you are looking at pentanedione or diacetyl. You are just going to have an extra methyl group on the pentanedione product. And the resulting cofactor is then NADP.

So I first want to talk about the experimental inhalation toxicology studies. And what these show is that, of course, the normal rodent airway, much like a human airway, has a nice protective carpet that is lined with mucous that is produced by these cells. And it is cleared up by beating cilia, which maintain a nice clean airway for all of

us.

After exposure to diacetyl, the picture has been remarkably changed. Instead of those nice cilia, we see a loss of cilia. We see shortened, flattened cells. We have lost the nice mucous-secreting cells, and the epithelial cells are dissociated and often absent. Profound damage to the airway epithelium. Now this particular image is from a pretty high dose exposure.

When we looked at the effects of 2,3-pentanedione and here we are looking at two levels of the airway, this is the first nasal airway, which is section T-1 in NTP studies. Or if we look further back and again we are looking here at nasal airways. And we look at the curve for pentanedione, which is the pathology score going up. It is more affected higher up but it still goes up. As we go further back, and that is in red and in black, is the pentanedione effect. And we have added in a control group here that is

diacetyl shown here in white and green for these respective portions of the airway. The effects on the airway epithelium tend to be comparable.

So summarizing the morphology data, butter flavoring vapors, the mixtures that contain diacetyl, cause airway epithelial damage. If we look at single agent exposures to diacetyl, we find they cause airway epithelial damage in rats and in mice.

Importantly, in rats and in mice, the nose is the most affected site. But we also know that bronchi and bronchioles are affected at the higher exposure doses. Recently a new study has demonstrated that bronchiolitis obliterans is produced by experimental aspiration of diacetyl and I will discuss that a little more in a few seconds. And acute exposures to 2,3-pentanedione are comparable to diacetyl in their ability to cause airway epithelial damage.

So what other toxicology data was

needed? A pharmacokinetic model predicts that more diacetyl is removed by the nose of rats than by the nose of humans. So if you look at a given exposure concentration as shown here in the Morris and Hubbs paper as a 100 part per million exposure, rats are able to absorb a high percentage of the inhaled diacetyl. If a person is at rest and they are nose breathing, there is going to be less absorbed by the nose but people will go to oropharyngeal breathing, particularly under conditions of exercise. And there is a significant percentage of workers that always will breathe through their mouth because they have nasal obstruction.

If you look at what happens in a mouth breathing worker and you compare that with what happens in the obligate nose breathing rodent, the rat, you are going to see that there is almost a ten-fold greater absorption by the nose of the rat than by a mouth breathing person.

Importantly, a recent publication from the Morris Laboratory shows that the dose to the bronchiolar epithelium of humans when they are lightly exercising, as we would anticipate in the worker conducting manual work, there can be more than a 40-fold greater dose to the bronchiolar epithelium than experimentally exposed rats in pharmacokinetic models.

I mentioned earlier that diacetyl instillation causes bronchiolitis obliterans in rats. So a large single dose of diacetyl by intratracheal instillations bypasses the rodent nose. But possibly more important than the demonstration that bronchiolitis obliterans itself can be produced by diacetyl in this model is the demonstration of the long accepted basic principle that abnormal repair of the injured bronchiolar epithelium is a precursor lesion to bronchiolitis obliterans.

So, when we look at human relevance of the toxicology data, damage to the

respiratory epithelium and the small bronchioles has long been established as the basic cause for bronchiolitis obliterans and that is supported by the recent work from the Palmer group.

The respiratory epithelium is damaged by butter flavoring vapors as a mixture, by diacetyl, or by 2,3-pentanedione.

Inhalation of diacetyl produces higher doses to the bronchioles of humans than it does to the bronchioles of rodents.

Diacetyl instillation causes bronchiolitis obliterans in rodents and clinical bronchiolitis obliterans is seen in workers inhaling diacetyl.

The toxicology also gives us an indication of functional changes. Oh, I'm sorry. This is a picture of the human disease.

So if we look at the functional changes that occur after inhalation, we know that acute diacetyl inhalation decreases tidal

volume in mid-expiratory flow rates in exposed mice, that a prior high dose exposure decreases the sensory irritation effects of a subsequent exposure, so that they may not be recognized, at least in rodent models.

Acute high dose exposures in a recent published abstract from our group were demonstrated to cause an increase in the number of substance P positive neurons in ganglia of exposed rats. Mice exposed to 50 or 100 parts per million diacetyl have decreased respiratory rates after a six week exposure and mice exposed to 100 parts per million have decreased minute volume after a six-week exposure.

Effects of diacetyl and 2,3-pentanedione on the trachea in vitro also support there being functional changes. So we see a variety of effects at ten to the minus seventh to one millimolar in guinea pig trachea. We see that methacholine, which constricts airways, that that methacholine

response is increased in vitro after inhalation in vivo of diacetyl.

We see similar effects to exposures to 2,3-pentanedione, although they occur at lower exposures and importantly these in vitro affects do not involve the epithelium, suggesting that the epithelium is not the only thing that is affected by these agents. And importantly, it is a complex situation where in vivo methacholine challenge is actually decreased after exposures to 2,3-pentanedione.

And ion transport in the epithelium is affected at diacetyl concentrations.

There are some additional toxicology considerations. Diacetyl is mutagenic in vitro and prior skin exposure to diacetyl can sensitize to subsequent exposures.

So in conclusion, diacetyl is a reactive alpha-diketone. Diacetyl and mixtures of butter flavoring vapors do damage to airway epithelium. Airway epithelial

damage is believed to be the underlying lesion for bronchiolitis obliterans in humans. Pharmacokinetic modeling indicates that at a set concentration in air, more diacetyl reaches the deep lung of humans than reaches the deep lung of the rat. And the structurally related alpha-diketone 2,3-pentanedione is also able to damage the airway epithelium.

Are there any questions?

MS. MASHAYEKHI: Thank you. Azita Mashayekhi with the Teamsters Union.

I have a question and I think you probably would be the best person to bring it up with because I don't think there is any more sessions later that would discuss these substances.

I was wondering if you could elaborate on or anyone on the panel on other substances that NIOSH mentions would be covered by this criteria document, you know, those that would be structurally similar to

diacetyl and expected to have similar or worse toxic effects.

I know that NIOSH had requested in February or earlier on in the *Federal Register* to get information about those substances and I know that FEMA submitted, and actually I am looking at the document that FEMA submitted about other substances, such as let's say 2,3-hexanedione and 3,4-hexanedione, and then also those that are not alpha-diketone substances such as acetoin and diacetyl primer.

So I just wanted -- I don't see discussion of this in-depth in the document. I am just wondering what universe of data is available to you on some data and also toxicology and if you expect to do more.

DR. HUBBS: The diacetyl and pentanedione criteria document, as with all NIOSH criteria documents, is based upon peer reviewed scientific data. So, we do not have sufficient peer reviewed scientific data on the toxicology and human health effects of the

substitutes other than 2,3-pentanedione to include them within the criteria document.

We do know from the recent publication that was from Day et al. that some of these other substitutes are present in the workplace, including 2,3-hexanedione and 2,3-heptanedione. And I do not recall whether or not he saw 3,4-hexanedione -- he did not see 3,4-hexanedione.

We are attempting to conduct additional toxicology studies on other agents that may be present in the flavoring workplace. However, we need peer-reviewed scientific data to write a criteria document.

Thank you.

COMMANDER McKERNAN: I'd like to add one comment on that. As was mentioned in the executive summary and also the rationale of the basis of the standard, NIOSH is concerned about compounds that are structurally related to diacetyl. We recommend that folks use the precautionary

principle and control exposures to structurally similar compounds to as low as reasonably achievable.

DR. BORAK: May I ask one more question? Jonathan Borak, Yale. It is probably my own slow thinking but you have said something Dr. Hubbs and in the document it states -- Let me jump in one paragraph from the first to the last sentence.

"Diacetyl inhalation elicits substantial histopathologic changes to airway epithelium." And the last sentence of that paragraph says, "The effects of diacetyl in isolated airways from naive animals does not involve the airway epithelium."

And you had just also said that in one of your last slides. And I don't follow that. It is probably my own problem and I thought maybe you could just clarify that.

DR. HUBBS: Dr. Fedan's laboratory did that work. He is here today. That is based on functional changes as opposed to

pathology changes but I will let him take that question.

DR. FEDAN: Thank you. We found effects of diacetyl both on the airway smooth muscle and on the epithelium. In those studies, we were looking at function of the airways and we wanted to examine whether or not diacetyl would have any effect on the absence of epithelium, which we removed from those experiments and we did find effects on the muscle directly.

DR. BORAK: And is the effect comparable to the magnitude without the epithelium?

DR. FEDAN: Yes. The effect in the smooth muscle is comparable in magnitude without the epithelium present and that was the thinking that we employed when we hypothesized a possible effect on the muscle.

DR. BORAK: Just as a throwaway, I may not be the only person who does not see the connection in there. And it might be in

rewriting that one paragraph would help to clarify it. Thank you.

DR. LENTZ: Thank you for that suggestion.

In the interest of time, I would like to continue with our next presenter, Mr. Robert Park. He is an epidemiologist, who has been with NIOSH in the Risk Evaluation Branch for 12 years located in Cincinnati.

Prior to joining NIOSH, Mr. Park spent 16 years investigating illness and injury in the auto and related industries. Worker populations included those exposed to metal working fluids and to emissions from welding, painting, forging electronics assembly and other manufacturing operations, as well as ergonomic stresses.

At NIOSH, Mr. Park participated in a risk assessment for silica and lung diseases and also for lung cancer related to hexavalent chromium and cadmium. Other work has focused on neurobehavioral effects of manganese, and

back injury in nursing home employees.

Mr. Park has an M.S. in occupational health and biostatistics from the Harvard School of Public Health. He will be talking about the quantitative risk assessment based on worker data.

MR. PARK: Good morning. I think we have heard a pretty compelling case now for causation of respiratory diseases with diacetyl and other related compounds.

Risk assessment is the stuff that follows, where we try to establish a quantitative relationship between prior exposure and these outcomes, with the ultimate goal of defining levels of risk corresponding to lifetime work at different exposure levels.

You have already heard about the six health hazard evaluations done in popcorn plants. Four of them looked like we could possibly use them for risk assessment purposes based on exposure and outcome data. Three of them we decided to analyze. And one of them,

we chose as the primary basis for the risk assessment.

The one we chose is the index plant that Dr. Kreiss referred to. It is a plant where there were eight surveys done over a period of 32 months. In this plant there were, at one time or another, 360 active employees who participated in one or more surveys.

Our analyses are based on employees who were active on their first survey. They may have subsequently become inactive but returned for an assessment.

We did two primary approaches in the risk assessment. We looked cross-sectionally at the loss of breathing capacity in the surveyed population. In this case, we primarily looked at their last survey, if they had more than one. We also defined cases and onset and modeled the rate of new case onset in the population.

You have already seen exposures

summarized from some of these plants. This just shows that the mixing areas had the highest exposures. Generally most workers were exposed on the production line where flavorings are added. Quality control levels are lower, although they have peak exposures because they are actually popping popcorn and opening bags. And then maintenance is generally lower.

So we are going to be looking at these pulmonary function outcomes, FEV_1 for example. And this is just an attempt to show you how much variability there is in the NHANES population. That is a large national sample. NIOSH has studied it in some detail and established prediction equations. That is, we can somewhat predict somebody's FEV_1 based on their age, height, gender, race.

And so the x-axis here is the predicted value and the y-axis is the observed value in the NHANES population. And you can see at a given predicted value, there is still

a fair amount of variability. So no matter how good our statistical models are, we are still dealing with some inherent variability due to, well smoking is probably going to contribute to some of those points that are falling below, allergies, all kinds of other factors we don't have data on.

So the trick in risk assessment is to come up with an appropriate exposure metric and then do statistical models that relate that metric to the outcomes. And so at this index plant, this is looking at percent of predicted FEV₁. For each individual we can calculate from those previous equations their predicted value and then ask what percent of their predicted value did they actually have.

In general in a healthy population, half the people would be above 100 percent of predicted and half would be below. And so we are doing a multiple regression model of percent of predicted using different metrics.

And so you see here that if you just look at

their average exposure, discounting any duration, that is the least predictive model.

And the R-squared there is the percent of variability that is explained by the model. So you can see that they are all pretty low but they go from 12 percent up to almost 18 percent with the better predicting metrics.

If we look at duration without regard to what the exposure levels were, now we get a somewhat better prediction. And then with cumulative exposure, that is cum DA, DA for diacetyl, somewhat better. We get a better prediction with the second lowest record there, which is the square root of cumulative exposure. And that is kind of an interesting finding which we will be discussing further.

These are some of the actual models for three of the outcomes. This is cumulative exposure. This is the square root of that. And so I just want to show we have smoking data and this number here suggests that

somebody smoking one pack a day for a year would lose about 0.5 percent of their FEV₁. So for two years smoking, they would be down one percent. A roughly comparable effect was observed for exposure at one part per million of diacetyl. So in 20 years, somebody would lose ten percent of their FEV₁ capacity.

And these other metrics are somewhat better fitting, are a little less interpretable because it is not a linear relationship.

This is looking at three of the study sites. This is the index one that we are actually using. And two of these other ones that had at least some adequate exposure data and outcome data were found to have much higher exposure response estimates. And this is pretty surprising. This is based on much less exposure data. We chose to go with the index plant because it had much more extensive exposure data but also over time we could see a very substantial decline in exposures over

time at this site. And we have pretty good reason to think that the initial, at the first survey, the initial exposures are probably a pretty good estimate of what the exposures were prior to that first survey, which is a crucial issue.

And these two plants, our speculation is that they had had previously much higher levels and at the time of the NIOSH survey, they had been lowered but we don't have strong evidence on that.

This is looking at another measure of impairment. And this is a measure that is a little more appropriate for obstruction. This is the FEV_1 divided by the forced vital capacity. That is the total volume of air that somebody can hold in their lungs. So we are looking at the proportion of that capacity that can be expelled in one second.

And we see the same pattern here. Much higher slopes for these two other plants.

And they are all statistically significant,

of course.

So in addition to looking at FEV_1 cross-sectionally, in a survey we also define what we call a case two different ways and then modeled the rate of new cases occurring over time. So the first definition is the FEV_1 is below the lower limit of normal. The lower limit of normal is a construct just like the prediction equations, where the clinicians have defined a relationship that they think is clinically useful. So based on age, height, gender, and race again, there is an equation that gives somebody's lower limit of normal. And that is specific for FEV_1 and also for the ratio FEV_1 over FVC.

In order to do this analysis, we have to know when somebody became a case. Ideally in an epidemiological study, one would like to start with a population at their first exposure, follow them over time with frequent repeated assessments and decide when they became a case. We don't have that here.

So what we did was, based on the questionnaire data, we asked when does somebody first start reporting continuing symptoms? At what point in time did they develop a cough and it didn't go away? And there were five different symptoms that we used and we took an average date and we used that as the date of onset.

Now you can see that if somebody didn't have symptoms, they would not be a case. So this whole analysis is restricted to developing pulmonary impairment in people who were symptomatic. As Dr. Kreiss pointed out, there is a whole other 50 percent of individuals who are experiencing declining FEV₁s who are not symptomatic at the level of falling below their lower limit of normal.

So this rate analysis is going to be a major underestimate of what is really going on.

So these are some models of rate, using Poisson regression. If you look at

duration alone, this is somewhat surprising. It is a negative effect; that is the rate declines with increasing duration. It is not significant. If you look at cumulative exposure, alone, it is positive but very insignificant.

So this is strange. Normally you would expect to see in a typical occupational disease that the outcome, adverse outcome, would increase with duration and even more so with cumulative exposure.

If we put both terms in the model, things become a little more interesting. The duration effect is now significant and more negative and the cumulative effect is positive and much more positive and approaching statistical significance.

If we go down to this metric, things are quite statistically significant. So this is a very bizarre observation. You don't usually see this, a strong negative duration effect and a strong positive exposure

effect. So this is saying that following people over time in this population, their baseline rate is declining. But taking into account their exposure, the rate of new cases is increasing highly significantly.

This just summarizes those observations. These are the predicted rates, using a uniform baseline rate, classifying observation time on duration and on cumulative exposure. So normally we would expect to see no duration effect but just an increasing rate with cumulative exposure. But what we see here is a pretty dramatic decline in the rate with increasing duration at the lowest exposure level. And then we see the usual increase that we would think would happen.

So this is why we are seeing these strange models and we are interpreting this as evidence that there is variable susceptibility in the population, that in the first months or year of exposure people are at much higher risk. So one explanation would be that early

hires who are responding are leaving employment, that some fairly extreme selection is going on like that.

So this is a complication in a typical risk assessment. One doesn't usually see something like this. So we took some steps to try to deal with this. This is a statistical model. This is now a linear relative rate model in which we have a multiplicative term for just demographics, age, gender, smoking, and so forth. Then we have a linear additive rate term which includes pack years, cumulative duration -- I'm sorry, cumulative diacetyl. And also this term which is somewhat novel. This is a term that includes duration as an exponentially declining function. So this is like saying there is increased susceptibility at early exposure and it decreases exponentially in time. That is just an attempt to describe this changing susceptibility situation.

And it turns out using a half-life

of two years seems to fit better and using average diacetyl exposure squared fits somewhat better.

At this level of analysis there is not a whole lot of statistical power to distinguish other models but this one seems to be pretty useful. These are those two terms.

And this term is actually dominating. This is a term that says that risk is very high at zero duration and declining over time.

This is a very low intercept here, very small, which means basically smoking and diacetyl are accounting for most of the new cases that appear in this population. And with roughly comparable contributions after long duration but with this much higher contribution at short duration.

So this is the model that we used to subsequently develop risk assessment based on rate. There are two risk assessment paradigms that we use. One is benchmark dose and basically this is saying we have some

outcome that we know the distribution of and exposure is causing this outcome to shift.

So at increasingly higher exposures, everybody in the population has shifted over a bit. This assumes that everybody has the same response, uniform susceptibility. And what benchmark dose does is it tries to figure out how many people have fallen below some definition of impairment like the lower limit of normal. So with increasing exposure, how many additional people have fallen below that level and are now impaired that wouldn't have been otherwise?

So this is a benchmark dose calculation. These are levels of exposure. This is the corresponding 45-year cumulative exposure. This is a shift in that distribution so it starts out at 100 with no exposure and then it shifts over.

So for example, at 0.2 or cumulative exposure of 9.0, nine times 0.5,

which was the coefficient from the original regression, we would expect a 4.5 percent drop in FEV₁ and with that this is presenting two definitions of impairment. Sixty percent of predicted is a fairly severe pulmonary impairment. And these are the numbers of people out of a thousand that in a 45-year exposure would now be impaired that wouldn't have been otherwise. So at one ppm, 12 percent, at .05, about 3 percent and so forth.

This is a much less severe level of impairment, the fifth percentile corresponds to roughly 80 percent of predicted. Historically, this was used often clinically in defining abnormal and again, it is these numbers of excess cases.

Using the lower limit of normal to define impairment, it makes the benchmark dose calculation a little more complicated because there is no longer a single distribution that is getting shifted. Every person has a different distribution, depending on their age

and height and so forth. So, we came up with a different method but pretty similar results.

Again for different levels, different numbers of excess prevalence.

Now going on to the second approach, which is modeling rate of new cases.

This involves using a life table approach where in the normal population we know how many people have survived at different ages across time and we can apply the rate of new cases in each age interval, calculate how many new cases there would be and then subtract those folks from the surviving population over time and basically come up with a lifetime excess risk of being a new case.

And so again, we get these kinds of numbers. So at 0.01 ppm, there would be three out of a thousand new cases, using the second case-definition, over a lifetime.

This is an additional life table-based calculation. In the published literature, it is pretty clear that FEV₁ is

itself a risk factor for mortality. Studies have been done that carefully control for age, gender, race, BMI, and so forth and there seems to be an independent contribution of FEV₁ to somebody's mortality rate. And that is not entirely surprising. People that are at the point of dying have a very stressed medical situation and breathing capacity might figure into what happens.

Based on the literature about one percent loss in FEV₁ is associated with a 1.5 percent increase in mortality. So now we can turn the crank and do what we did previously.

We can predict FEV₁ loss from exposure and we can predict mortality from FEV₁ loss. And so doing that we get these numbers of excess deaths for a 45 year exposure at these levels of diacetyl.

This is a summary of what you have seen. And so it is kind of interesting there is a fair amount of concordance across these different methods. Even this one, which is

surprising. This is mortality that is not related to bronchiolitis obliterans. It is just a generic effect of losing FEV₁. These individuals would also be developing, in some cases, bronchiolitis obliterans and have other increased mortality resulting from that. So this is an underestimate of mortality.

The NIOSH proposed REL is 0.005 parts per million. So that corresponds to about one in a thousand. If we use this outcome measure and the others are pretty close, this is just that same table turned inside out. So here is a level one in a thousand and these are the corresponding parts per billion diacetyl over 45 years that result in that excess risk.

So in summary, we have an exposure assessment that we think is pretty extensive by most occupational disease standards. There are hundreds of air-samples over time. We have used several definitions of impairment and got quite a high concordance across them.

Cross-sectional studies have major limitations, most or all of which seem to result in our expecting underestimation. We have missed asymptomatic cases. There has been a lot of probably selection out of the population before NIOSH got there, such that at the first survey it is already a survivor-biased population.

And then there is this mystery of this variable susceptibility. There might be other explanations for this but in any case it has this impact on the nature of the outcome over time and so we proposed one way to deal with that.

Forty-five year exposure is sort of a standard in risk assessment for OSHA. In this case, if there is a susceptibility issue, it raises other issues because one population followed for 45 years is going to be quite different from five populations followed for nine years. There is going to be an additional loss with each new hire group.

And then most of this work implies or requires some sort of low dose extrapolation which is linear. So this just indicates that actually 13 percent of workers in the index study had career exposures below 0.01. So there is a fair amount of low exposure data in this analysis and 0.01 is only a factor of two above the proposed REL.

So there would have to be enormous deviations from linearity to really change our results.

And that is it. Thank you.
Questions?

DR. CHECKOWAY: Harvey Checkoway, University of Washington. I have a couple of questions, Bob.

First off, the selection or susceptibility, would you call that a healthy worker's survivor effect? And is there any way practically that NIOSH could contact workers that left and put some reality on this and ask why people left work? I don't mean

the cases but just why other workers left work. So that is one question.

The other question is is it possible to use the Netherlands study as a sort of replication sample for the risk assessments? Is that data in the right form for you to use? Could you get access to that and is that something you would consider?

And just to make a comment, it is going to be discussed a lot but I mean nobody works 45 years at anything, especially with an acute exposure causing an acute outcome like this. So that is really seemingly very unrealistic to make a risk assessment on 45 years but I understand that that is the standard.

MR. PARK: Okay. You're going to have to help me with number one, two, and three.

DR. CHECKOWAY: Yes, well the first one was just the practical aspects of can NIOSH contact workers that left.

MR. PARK: Okay. In this plant, actually some former workers did come in for subsequent surveys. I presume there was some outreach to achieve that but Dr. Kreiss could say more about what the potential is for contacting former employees.

I mean, ideally, you would like to know who was hired over time and follow all of them. But I don't know if that is feasible.

DR. KREISS: In the index plant, workers were almost always hired as temporary workers by contract and there were many temporary agencies that supplied workers to this company.

When we initially were working with the Missouri Department of Health and Senior Services, there was certainly an attempt to find out what workers from contract agencies had been employed but we weren't able to get that information systematically.

So we were really at a loss of really knowing the denominator for those

former workers. We made estimates. We actually had a comparable number of former workers come to be screened as current workers in the initial survey but we really never had a very good handle on the denominator. And I think with these lower age workers, it is very hard to locate them.

So I don't think that that is feasible.

With respect to the Netherlands data, the amount of exposure data available for that cohort is minuscule. The researchers published what they had, made many, many assumptions but we never had very good description of what the methods were either for exposure characterization or for analytic analysis of those samples.

So I don't think that that would be a feasible population to look at.

You know obviously, there may be risk assessment work based on human population that would be available using the ConAgra

serial data. And that serial data, it is not published yet, but my understanding is that there are four or five years of follow-up. So that would be another population that could form the basis of risk assessment.

MR. PARK: On the 45 year question, for a disease that does not have this kind of susceptibility issue, instead of doing 45 years, one could use average duration of employment. That of course would underestimate the public health impact because if people are working nine years on average instead of 45, then there have been five times as many people doing that amount of popcorn tonnage. And so if it is a linear effect, it is going to be about the same. But if you just look at one population for nine years, it will be one-fifth of the impact.

Now in this case where there is this apparent high risk at short durations, that is a whole different issue which I think the policy makers have to address because

there is a big impact of short duration.

DR. CHECKOWAY: Thanks.

MR. SARGENT: Ed Sargent, Redstone Group.

Does your risk assessment support the recommended STEL for diacetyl?

MR. PARK: It doesn't address it. It doesn't address it at all. So it isn't used in the support for that recommendation. Correct.

MR. SARGENT: And I guess maybe the question I also have is maybe for Kathleen. Is there any data where you looked at effects over the first day of a workweek and perhaps the first day after the weekend, and then the workweek? So I am looking at the changes over the first initial day of the workweek and then changes over the entire week.

DR. KREISS: With respect to that question of a temporal association of pulmonary function or symptoms with regard to work, bronchiolitis obliterans does not have a

temporal association with work. And so from a clinical point of view, once people became impaired, they noted no improvement away from work on a weekend, or even a long vacation, or even in the course of years. The only improvement of the former worker cases who, of course, all had moderate to severe disease was that over the course of years after exposure ceased, they tended to have less cough. But in terms of their pulmonary functions, their exercise ability, there was no improvement at all. This is a disease that is very different from occupational asthma where we expect to see changes that are temporally associated with work.

MR. SARGENT: But I am thinking of the earlier, looking at the spectrum of the changes, maybe looking at earlier pulmonary effects.

DR. KREISS: Is your question whether in the development of fixed airways obstruction there might be a time in which

people had asthma for example?

MR. SARGENT: Or some restrictive airway changes that could be seen earlier.

DR. KREISS: I really --

MR. SARGENT: I'm looking for a justification for a short-term exposure limit is what I am looking for.

DR. KREISS: I think your question about the natural history is fascinating and one that we don't have good information on. There are cases that have been seen for example in California of people who were thought to have asthma as they developed bronchiolitis obliterans but those case reports aren't published and it is hard to know. It would really require somebody who was clinically managing somebody as they got sick. And with medical surveillance, as we have recommended, that information may become available.

Now, with respect to short-term exposure limits, I think that is an entirely

different question but I would like to think about it some more. The question for us, for short-term exposure limits, was is there evidence that high-level exposures for short durations of time can have effects. Because that is the justification for controlling high peak exposures.

And we certainly felt that peak exposures might be very important. One reason we felt that was that in the sentinel, in the index popcorn plant, there were a group of six workers who worked in quality control, each popping about a hundred bags of microwave popcorn every eight hours. And their average exposure levels were about a quarter of what the packaging line workers were. And yet, in the cross-sectional evaluation in November of 2000, five of those six workers had obstruction. So they had a really disproportionate signal of abnormality and yet their exposures were much lower on average.

And in reflecting about that, there

were a couple of possibilities. One is that when you pop a bag of popcorn and you open it, you will have very high peaks when you are opening the bag that will be very evanescent.

And secondly, the proportion of the volatiles in the quality assurance area that diacetyl accounted for was much lower than in the plant area in general. Because at the high temperatures of a microwave oven, virtually everything that is in the flavoring is going to volatilize and so that includes less volatile contents. So they had a qualitatively different exposure than people in the packaging line, for example. So we thought well maybe that is factoring in, too.

You know, the fact that in some plants the mixers actually had relatively low exposures compared to the index plant but still had high rates of obstruction and clinical bronchiolitis obliterans, again pointed to the fact that the peak exposures when somebody lifts the lid to dump in

flavorings, for example, might have a disproportionate effect.

Dr. Hubbs tried to get some sense of that in an animal model. I'll let her speak to that.

DR. HUBBS: Yes, in the animal models to address the short-term exposure potential, we actually in one study, now this is only dealing with the acute effects but we had animals with the same time-weighted average exposure that were divided into two groups. One of those groups got that exposure continuously over a six-hour period. The other got that exposure as four approximately 15-minute bursts. That told us that those four 15-minute bursts could do it as well. Importantly, that was just a short-term exposure effect. It is just dealing with the acute airway effects but we do know those four short-term exposure limits can produce that precursor lesion, which is airway epithelial necrosis.

So at this time there is some limitation to the data but certainly there is solid peer reviewed data that does indicate short-term exposures can be a problem.

Now in terms of the criteria document to clarify things, are you suggesting that in the risk assessment section that we clarify that the risk assessment is for the exposure limit and that the short-term exposure limit, I think we described that in the basis for the recommended exposure limit.

I think we describe it as principally being based upon the toxicology data. So that is another section that will be described later here.

But you would like some additional clarity within the document as to what the supporting literature is for each of the recommendations?

MR. SARGENT: Yes.

DR. HUBBS: Okay, thank you.

DR. KREISS: I think the other

thing Lauralynn could comment on. In deriving the short-term exposure limit, we had no quantitative data. We just used sort of rule of thumb of what NIOSH has done in the past. Is that correct?

COMMANDER MCKERNAN: That's correct. And so you will notice that the short-term exposure limit is five times the recommended exposure limit. For diacetyl, our recommended REL is five parts per billion, so the STEL is 25 parts per billion.

MR. HARNETT: Yes, Peter Harnett.

Mr. Park, I had gone back and looked at the NIOSH 2006 study. It came out in 2006 and had noted that the work had begun in 2000, if that is correct.

MR. PARK: On the index plant?

MR. HARNETT: Yes.

MR. PARK: I believe that is correct.

DR. KREISS: The data for the index plant were collected from the fall of 2000

through late summer of 2003.

MR. HARNETT: Okay. And then how many different times was air sampling conducted?

DR. KREISS: Nine times during that period.

MR. HARNETT: Okay. And in looking at data, I am just curious about this. Was there communication with the plant about what the initial air sampling results were?

DR. KREISS: Absolutely. With each survey an interim report was prepared that gave the plant the air sampling measurements which were much easier to convey than the health measurements.

So the summary of the measurement and health data together was disseminated to the plant in August 2001 for the first two surveys because the third survey actually was that month.

MR. HARNETT: Okay. And then along with that, were there suggestions on

changes to work practices and perhaps engineering controls?

DR. KREISS: Oh, absolutely. I mean, as soon as we became engaged with the current workforce, which we added walkthroughs of the plant in September of 2000 and again I think in October. And at the end of October, beginning of November was when we did the first health survey. As soon as we realized that a quarter of the plant had abnormal pulmonary functions, we worked very closely with the plant and actually brought powered air-purifying respirators to the plant to put the mixers in that started right after the survey.

The first attempt to look at engineering controls was in January. We provided written recommendations on the basis of that survey.

So we had worked with the plant to essentially try to isolate the mixing room, which was clearly the source of the flavorings

right away. And so really with every survey the justification for the surveys was to see how were exposures coming down with the implemented controls and changes in work practices like lowering the temperature of the holding tanks, exhausting them.

MR. HARNETT: Right. I got it.

So what I am curious about is in a quantitative risk assessment, I am assuming you used all of the data that NIOSH had collected, what one would expect to happen and NIOSH did the appropriate thing obviously making recommendations on work practices, et cetera, but are you looking at data that becomes skewed because as those work practices are discussed and implemented by the plant, the exposure levels are likely to come down dramatically. And the initial cases that you found there were likely a function of exposure prior to 2000, whereas air sampling data collected around say 2005 is going to demonstrate, I would imagine, significantly

lower air sampling results from whatever, 2002 through 2005 due to work practices and engineering controls.

MR. PARK: There were dramatic changes, drops by more than a factor of ten or even a hundred over that two and one-half year period. There was an exposure matrix developed that took that into account, not only the measured levels but also known changes in the plant configuration.

And so this speaks to the question of what exposure metric to use. If we are using the right metric and we have a good estimate of the actual exposure, then it shouldn't matter that things were dropping.

DR. KREISS: The assumption was made that the measurements that were taken in the fall of 2000 represented historical measurements in the plant. There are limitations to that assumption. For example, when the plant started making microwave popcorn in 1986, they had many fewer lines for

production than they had when we got there in 2000. But from the beginning, they were using diacetyl containing flavorings.

So exposures may have been lower in the remote past but this was a plant that -- I mean in fact we had some difficulty convincing the plant that there was a hazard, even when we showed them their data because you know, they had consultants that told them that everybody in that area of Missouri had bad lung function anyway.

So you know, I think that there was certainly no attempt on the part of the company to lower exposures before we got there. Because even after we got there, they had a hard time believing that.

MR. HARNETT: I understand that with the initial sampling. And I just wanted to get off this issue for a sec but I think I made my point and you answered it.

The other thing I wanted to point out or would be interested in knowing is if

this is the case I am aware of, there was a QA individual who reported with an eight hour time-weighted average of 0.2 parts per million, if I remember correctly. And at that time, was he or she taking samples from the mix tank? Because that ends up being around 2000 and earlier the practice was to take your jar and literally put your head inside of the mix tank to get your sample.

Things have changed appreciably now. Namely, the production floor worker will capture the sample sometimes with a stick that is immersed into the tank, cap it off and move it over to the QA room.

DR. KREISS: In microwave popcorn QA only popped popcorn. They didn't take any samples to assess the constituents of flavoring. I can't speak for flavoring houses where there may be a different kind of quality assurance practice.

DR. LENTZ: I'd just like to break in at this point. I think the discussion is

helpful and we will keep going for about five more minutes with these questions because this is an important section of the document. But I would like to give our presenters an opportunity to take a bio break.

(Laughter.)

DR. EGILMAN: Let me just follow up on that. I think I was next.

There has never been any quality assurance worker in a popcorn plant who took samples out of a mixing vat. That is a fake rumor that has been put out by industry to try to explain away some of the data. It never happened anywhere. I interviewed most of those workers and examined most of the workers at the index plant. It never happened there.

It never happened anywhere. They didn't have any way to test it in the QA room.

The turnover case issue, there are about 700 workers from the ConAgra plant who were hired by three separate companies. I have their names. I don't think it is worth

going after them but you can do it if you are interested. The data is available.

The short-term exposure data can come from the Lockey QA worker study. Lockey has, and I have given these to NIOSH, the actual data is different. It shows three or four obstructive cases in QA workers. He reported no one had obstruction who was a QA worker in the published paper. That is just not true. In addition NIOSH reports one or two others.

Lockey has very good short-term data on those 27 QA workers from the four ConAgra plants and that data should be looked at because I think it will be human data that will support a STEL.

There has never been a study that showed any difference quantitatively or qualitatively of any substance that is different from popcorn popped from a bag and that measured over a slurry. It just isn't out there. The only one who looked at that at

all, and NIOSH never did although repeatedly in their papers they put in oh, the popcorn effluent is qualitatively different from a slurry, with no data, no NIOSH studies looked at that, ConAgra looked at it. And there is no significant difference between the measurements of fumes and releases from popcorn bag and a slurry.

In fact, there is much more variability between slurries. There are hundreds, perhaps thousands of different formulas for slurries with as few as five and as many as probably 50 compounds in there. So the inter-slurry differences are much greater than the popcorn slurry differences in the only data that I know that exists.

So I think that has been used as a way of falsely reassuring people about popcorn. It is just not true. Because although the inference of the statement is well it is qualitatively different, it is worse; the inference is it is qualitatively

different, it is safer. That is how the public is taking it.

And that's all. Thanks.

Oh, the amount of diacetyl changed dramatically in 1993. The reason for that was fat-free popcorn. The way they made popcorn fat-free was they substituted pure diacetyl for the oil. Okay? Because that made a caloric difference.

And so the percentages of diacetyl in fat-free popcorn which began to be pushed around 1992-1993 is when the magnitude of exposures went way up.

DR. LENTZ: Thank you, Dr. Egilman and we have time for one more.

DR. TOWNSEND: Can I? One more. I will be quick. I know it is break time. I am desperate myself. Mary Townsend, Pittsburgh.

This is a question about the modeling. It is very complex what you have done and I didn't get a chance, as I was saying, last night to read all of this. But

when you are trying to say what parts of the time related things are, you do not want time in your dependent variable. And percent of predicted is confounded by age still because you get increasing proportions of people falling below a certain whatever percent of predicted as they get older.

So I wondered, and that would be a problem if you have a wide age range that you are looking at. And I think your workforce probably goes from about maybe 20 to maybe, what, 50 or 60? So it is fairly wide.

I wondered if you tried instead of modeling percent of predicted FEV_1 if you tried using deviation from the predicted. And I presumed that you are holding your predicted values at the NHANES, so that you are using a constant reference source.

But I wondered if you tried that because what that would do is totally anything, any age, any duration, it is always a problem the collinearity of what is due to

aging, what is due to smoking, what is due to occupational length of exposure, as you know.

But you don't want to have your dependent variable also still not being, you know, just having age totally removed from it. Do you --

MR. PARK: Maybe. For the first analyses for the multiple regression, just doing a cross-sectional analysis.

DR. TOWNSEND: Yes, the first, where you were looking at your index plant I think it was.

MR. PARK: Yes, and looking at percent of predicted.

DR. TOWNSEND: Yes.

MR. PARK: So that is already age adjusted.

DR. TOWNSEND: Well but it isn't totally age adjusted. Percent of predicted is not totally age adjusted because the variability of the people remains fairly constant as you age and percent of predicted, in order to be the same, you have to be

assuming that the people are pulling together as they age and they are not.

And that is why the ATS, since 1991 has said don't define abnormality as 80 percent of predicted. It is because of that fact that it isn't constant. It doesn't totally account for aging effects. And that is why the lower limit of normal was recommended in 1991 and now NHANES models it statistically not clinically so that it cuts off five percent of healthy, nonsmoking people.

So in other words, what that is saying is that the variability of the population is normal, it's not, and it doesn't get tighter as you age and percent of predicted assumes that it does, in order to be saying that 80 percent at age 35 is the same as being 80 percent at age whatever it is. But 80 percent at 35 is probably going to turn into a 75 percent at age 55 or whatever.

MR. PARK: And the basis that we

actually use for the REL was on the lower limit of normal definition, --

DR. TOWNSEND: Yes.

MR. PARK: -- not on 80 percent.

DR. TOWNSEND: So then I was wondering what the modeling was about because there you were identifying whether it was cumulative or duration. You were looking at all these variables to say what would be in the model or something. But that is when I kind of like I didn't have a chance to read it ahead. So it is complex.

MR. PARK: I agree.

DR. TOWNSEND: And I am sure you are far more experienced with all that part than me. But I know lung function and it disturbed me to see percent of predicted as your outcome variable anywhere.

COMMANDER MCKERNAN: Thank you for your comment and I would encourage you to put that comment in writing in our docket. Please recall that you have until October 14th to put

those comments in our docket.

There have been really good comments in the questions and answers periods.

I want to encourage all the folks that have made comments and questions to please go ahead and put those in the docket so that we can carefully consider them and amend the document accordingly.

Thank you.

DR. LENTZ: Okay, we will break at this point and we will have an abbreviated break just to try to get us a little bit back on schedule. But we will return here and resume at 10:45.

(Whereupon, the foregoing public meeting went off the record at 10:34 a.m. and resumed at 10:52 a.m.)

DR. LENTZ: Okay, I'd like to welcome people back and again, please ask you to take your seats.

We will be continuing on a risk assessment theme with a quantitative risk

assessment based on animal data. Dr. Dave Dankovic has a Ph.D. in toxicology from the University of Michigan. He did a postdoc as a scientist at the University of Texas Health Science Center in Houston and a second postdoc at the Battelle Pacific Northwest Laboratory.

Dr. Dankovic came to NIOSH in 1988 in the Experimental Toxicology Branch and subsequently joined the Risk Evaluation Branch in 1991. He currently serves as the Senior Team Lead for the Risk Evaluation Branch. And again, Dr. Dankovic will be talking about the toxicologically based risk assessment for diacetyl and 2,3-pentanedione.

DR. DANKOVIC: Hello. Can you hear me okay on this? Okay, good.

So I will be talking about the toxicologically based risk assessment. To make it clear, there are two separate assessments that I will be talking about. One was a toxicologically based risk assessment for diacetyl and the second one is a

comparative potency analysis comparing 2,3-pentanedione to diacetyl.

The first one, the animal based risk assessment for diacetyl was actually done under contract for OSHA by Dr. Bruce Allen. This report was provided to NIOSH and essentially we have adopted that risk assessment without modification.

I would like to make it clear that this toxicologically based risk assessment for diacetyl is not the primary basis for the NIOSH REL. The NIOSH recommendation is based on the human data. We do feel that the animal based risk assessment provides supporting evidence for that recommendation.

The complete Allen report is in the criteria document, the draft criteria document that is available. So I am going to only summarize it very briefly. I guess it would really help if I remembered to advance my slides when I am talking. Every half of what I just said is on these two slides.

So the toxicologically based risk assessment for diacetyl data were from Morgan et al in 2008. This was actually a pilot study so it was very small numbers of animals.

Only five animals per dose group, male, C57 Black 6 mice. It is an inhalation study; 25, 50, 100 parts per million, six hours a day, five days a week, that's pretty standard, for either 6 or 12 weeks of duration.

This is what Bruce Allen does with his benchmark dose analysis. You will have to read his report. It is somewhat complex. But there were multiple measures of dose that were considered either the inhalation, the concentration itself, or concentration addressed by a scrubbing factor for different parts of the respiratory tree, or the computational fluid dynamic model that Dr. Hubbs referred to.

There were a couple methods of extrapolating to humans. I seem to be having a problem remembering to advance my slides.

In any event, let's see -- Dr. Allen also investigated whether the six- and twelve-week exposures could be combined statistically, which he did, and provides a justification for that.

This is all in the report. It is summarized in the body of the criteria document and the entire report is in an appendix. So you can, you know, you are welcome to look at that.

So I am just going to sort of jump to the chase here and say that the risk assessment based on benchmark dosing suggested human dose estimates in the range of ten to a hundred parts per billion. Allen did note that the experimental protocol that this was based on involved less than lifetime exposures, less than say equivalent to an occupational lifetime and indicated that those benchmark doses might be adjusted downward, somewhat, or should be adjusted downward, in order to issue a toxicologically based REL for

diacetyl. But since the actual REL is based on human data, that is something of a moot point.

But we do feel that the range that he came up with of ten to a hundred parts per billion and considering that it should probably be adjusted downward provides good support for the actual NIOSH REL that is based on the human data.

In addition, we have tried to look at the very limited amount of data that is available on 2,3-pentanedione and compare the potency of this chemical, this substitute flavoring with that of diacetyl.

So to try to be clear, when not extrapolating directly from this mouse data to a human REL, what we are doing instead is comparing the potency of 2,3-pentanedione to the potency of diacetyl in animals.

The data were published in an abstract form by Morgan, et al. in 2010. However, the individual data were provided to

NIOSH. So we have more detailed information than the abstract itself. This was an inhalation study in rats and mice. You can see the concentrations of 50, 100, 200 parts per million of pentanedione. This was six hours a day, five days a week for a total of two weeks plus two days, so a total of 12 exposures and six animals per dose group.

Again, this was a pilot study. So it is rather small numbers of animals.

I should note that there is an erratum which is in everyone's book. It is in the front cover and in writing this section, I inadvertently referred to some male animals as female and I had to clarify a little bit precisely what groups of animals were compared to what for clarity. So there is an erratum statement pasted in the front of everyone's draft criteria document.

So in doing the comparative potency analysis, again what we are doing is trying to compare 2,3-pentanedione toxicity to diacetyl

toxicity. And we have done both a qualitative and quantitative comparison.

Qualitatively, I think actually was explained very well by Dr. Hubbs on the basis of both acute studies and these somewhat longer duration studies that both diacetyl and 2,3-pentanedione target the same anatomical sites in the respiratory tree. Essentially, there is toxicity seen in the entire respiratory tree from the nose to the lungs with the most sensitive site being in the nose in the animals.

And the pathology produced by both chemicals is very, very similar, if not identical. So that qualitatively the toxicity of these two closely related chemicals appears to be very similar.

For a quantitative comparison, what we have done is tried to do a benchmark dose analysis focused on estimating the 50 percent response rate, the BMD50 for pentanedione and diacetyl. This is the dose at which 50

percent of the animals are affected. It could also be referred to as the medium effective concentration or EC50, if you are more familiar with that terminology.

And again, I would like to note that we are comparing the mouse BMD50 values to each other. We are not extrapolating that value directly to a human risk estimate.

So what we have done is compare the mouse BMD50 for diacetyl to the mouse BMD50 for 2,3-pentanedione. In order to do this type of benchmark dose analysis as compared to potency analysis based on benchmark dose, what we have to do is identify endpoints where both the 2,3-pentanedione data and the diacetyl data are suitable for estimating benchmark doses. Given that these are pilot study data with very small numbers of animals, that is a major limitation that we need to find endpoints where there is at least one partial response dose group and it is hard to get a partial response when you only have five or

six animals in a dose group. So that did limit our choice of endpoints considerably. But there were at least a couple where we could do such a comparison. One of those is the nasal suppurative exudate in the male mice and the other was bronchial inflammation. And in this case, we were comparing the male mice for diacetyl to female mice for 2,3-pentanedione. So what we have done is compared the BMD50s for 2,3-pentanedione and diacetyl for those two endpoints.

And there are tabular values within the draft criteria document. I will show it graphically here. You can see that the two endpoints are shown. The nasal endpoint in the blue diamonds and the bronchial endpoint in the red squares. Obviously the points labeled PD are the 2,3-pentanedione and the ones labeled DI are for diacetyl for comparison. And what the points represent for pentanedione this is exposure of two weeks and two days and for diacetyl the next point is

for six-week exposure. And the rightmost point in each grouping is diacetyl that is the combined six and 12-week exposures, as was done in Dr. Allen's diacetyl risk assessment.

Either way, what you see is it appears that the BMD50 for pentanedione is a bit higher than the BMD50 for diacetyl, which would indicate a slightly lower degree of toxicity for pentanedione. The point estimates comparing pentanedione to diacetyl would indicate the pentanedione toxicity is 67 to 74 percent of diacetyl toxicity based on the nasal endpoint, or 53 to 58 percent based on the bronchial endpoint.

However, I think the graph makes it abundantly clear that given the small numbers of animals, the confidence limits around these estimates are very broad and strongly overlapping between pentanedione and diacetyl.

So at this point, based on this limited pilot study data, we cannot rule out the possibility, I don't think, that they are

actually equal potency.

At this point, I mean, this represents what we do know. You know, it is possible that the pentanedione is somewhat less potent than diacetyl but it is also possible that they are of equal potency.

And with that, I guess I will take questions.

DR. EGILMAN: With respect to the relative potency, I think Morgan's animal studies seemed to indicate that pentanedione is a worse per unit volume than diacetyl, in terms of its health effects.

DR. DANKOVIC: I am not aware of what specific data from Morgan you are referring to. Could you --

DR. EGILMAN: Well there is an abstract out, I think, that showed fibrosis within one or two months -- I'm sorry, I think within 13 weeks of exposure. I think Kay may know more about that.

DR. HUBBS: This is Ann Hubbs. At

the poster session of the SOT, Dan Morgan did present images of fibrosis within bronchi. The published data is in the abstracts.

I am unaware of and I may not be recalling it from the abstract. Is your comment that there is actually peer reviewed published data that says there is fibrosis in the bronchi with 2,3-pentanedione? Because we are limited to the peer reviewed data and the data that was submitted for the risk assessment.

DR. EGILMAN: I don't recall this in the abstract. I know it is in the poster.

Okay? I know I spoke to him about it. And so I think as I recall, and I may have recalled this wrongly, it is the only substance that he has seen that produced fibrosis in such a short period of time and that it was a much worse pathologic effect than diacetyl.

DR. HUBBS: We would very much like to include the information on fibrosis. And

if you can find a peer reviewed published data set with that, I would love to receive that as a comment for the docket and we would love to incorporate that into the document.

DR. EGILMAN: You know, it is Morgan's data. We both agree, it is in his abstract.

DR. HUBBS: We agree that --

DR. EGILMAN: It is in his poster that the abstract relates to. And the abstract is peer reviewed because there is a process of peer review for presenting at the meeting.

And so it seems to me that that should qualify.

COMMANDER MCKERNAN: Thank you for the comment.

DR. DANKOVIC: We are, of course, in contact with Dan Morgan and the NIEHS folks. And you know, this is an evolving field. There is more data coming out. So you know, we will have to, at some point, make a

determination when to cut it off and also determine as new data become available what we can legitimately incorporate in this document.

So again, I second Ann's call. Please, we would very much welcome this as a written comment and we will try to address it.

And I expect, you know, that more data will become available as we are going along in the document development process.

DR. EGILMAN: Okay. The only comment I think I could make would be whether it is peer reviewed if it is an abstract that relates to a poster. It is not my data. It is Morgan's data.

DR. DANKOVIC: I understand that.

DR. LENTZ: All right. Thank you, Dave. And thank you for the question, too. We are at that point of the agenda where we are moving from the science and technical issues to the guidance sections, description of those sections specifically.

The first guidance section we will

discuss is hazard prevention and engineering controls. Jennifer Topmiller is a team leader in the Engineering and Physical Hazards Branch of the Division of Applied Research and Technology, or DART, within NIOSH. She has both a BS, an MS in Mechanical Engineering from the University of Kentucky and over 20 years of experience working as a research engineer and a research supervisor at NIOSH.

Ms. Topmiller has been a project officer or a co-project officer for several large engineering control projects. These include a study of the potential for disease transmission in commercial aircraft cabins, a study of emissions from mail handling equipment and a project to control dust emissions from woodworking machinery.

Ms. Topmiller is a member of the American Conference of Industrial Hygienists, Industrial Ventilation Committee and this committee publishes and regularly updates the *ACGIH Industrial Ventilation Manual on*

Industry Standards in Industrial Ventilation.

She is also leading a team writing a document to summarize the use of engineering controls in the nanotechnology industry.

MS. TOPMILLER: Thank you, Dr. Lentz. As Dr. Lentz said, I am going to start talking about engineering controls. We are kind of switching gears now to look at the hazard prevention aspect of the document.

In this talk, I will be introducing first the concept of engineering controls and some of the general considerations that apply to flavorings and their use. I will then go through a number of specific engineering control examples that are recommendations for use with flavorings or in the flavored food industries. Some of these include benchtop weighing and handling, bag dumping, bag filling, charging tanks and mixers, drum filling. And then I will briefly touch on work practice controls.

Traditionally, in industrial

hygiene there is a hierarchy of controls that is used to determine how to implement hazard controls for a particular process. Generally, the closer to the top of the hierarchy, the better and more complete the control is. So the first type of control that we try is elimination or substitution of the hazard, followed by engineering controls, then work practice controls and finally personal protective equipment.

For flavorings, eliminating or substituting would involve using a different chemical to produce the same effect. And because the toxicity is not often known, this is generally not recommended. So I am going to be focusing then on the engineering controls.

There are some general precautions that will help reduce the risk for employee exposures in flavoring related industries. First, it is very helpful to isolate the rooms where the flavorings or the flavoring

chemicals are handled. This can be done by having them in a completely separate room with a door or an area that can be enclosed by flexible curtains.

Also these rooms or areas should be maintained under negative pressure. And what that means is that there is more air exhausted from that particular room than there is from the area surrounding it. And that way the contaminants in the room will stay in the room and they will not leave the room and go into the surrounding areas. The air from outside will be drawn into the room.

Also, when local exhaust ventilation is used, particularly with an exhaust hood, a local exhaust hood, installing a pressure gauge on the hood so that the worker can immediately see if the hood is operating at the proper parameters is important.

Another method for this is to put an on/off light near the hood so that the

worker can see immediately if the hood is working or not. There have been cases where just in general industry where workers don't realize that the hood is off. And this way, they can automatically see if it is off or not.

Also, and this is a general ventilation practice, keeping hoods away from doors, windows, air supply registers, and aisles reduces the impact of cross drafts, people walking past, and it makes the hoods operate more effectively.

Also, it is important to provide supplier to replace some of the air that is exhausted. This is just a general industry practice also.

And when the air that is exhausted from contaminated areas that is used for local exhaust ventilation, it is very important that the discharge stacks are placed away from air intakes, doors, windows, any way that they could be re-entrained so that that air is not

reintroduced into the work environment.

There are a number of production processes that are used in flavorings industries that are used generally throughout industry and there are accepted engineering controls that work for these processes that help to reduce the potential for worker exposure. And a couple of these that I am going to be talking about include benchtop weighing and handling, bag dumping, bag filling, charging tanks, and drum filling and emptying.

Often in flavoring manufacture, small scale weighing is done in a small area on a benchtop. These are very common tasks that are used throughout flavoring production and also in flavored food industries like bakeries, dairy production, and snack food manufacturing.

It has been found that a ventilated back draft work station works very well for this type of small batch mixing. It is

designed to maintain a velocity of 100 to 150 feet per minute at the face of the enclosure.

These studies show that this can effectively reduce emissions 90 to 97 percent.

And this is an example of such a control. This is a large control that goes all the way down to the bottom. The enclosure is on the side. The worker obviously can walk up to it. The front is enclosed with flexible curtains. And this in the back is the exhaust hood. There are slots across the back of the exhaust hood that draw the air in. And the slots help to maintain an even distribution of the airflow across the exhaust hood.

This is just another example of a control like this. It is just for a slightly smaller scale operation. The weighing process is enclosed right here on the benchtop and there are sides on here. And the air is exhausted again through the slots and out the back and up through the exhaust pipe.

The manual handling of powders is

often done in many industries, including food and flavoring processes. Large bags, often 50-pound bags are opened and dumped into hoppers or larger mixers to be combined with other ingredients. And generally what happens, an employee will open a bag and then it will be dumped in through a screened grate into the hopper.

And this is a ventilated bag dump station that is generally used for this type of a process. There is an enclosure here. These are again flexible curtains. The rest of the process is enclosed. Exhaust comes out through the back and out through the exhaust pipe. And another piece of this operation, typically is that the worker will then take the bag, compress it and throw it away. And this control actually has a place for the bag to be placed that is inside the hood, so that the dust that is emitted from that part of the process is actually contained as well.

Bag filling is something else that

is typically done. The outlet from a large mixer will often be -- the ingredients that are mixed in there will often be placed into smaller batch-type containers or into small containers possibly to be shipped to another plant.

And so this is the mixing container and then this is the bag. And the next slide.

One way that this can help contain the dust from these types of processes is an inflatable seal. This is a bladder that can be placed inside the opening of the bag. And when the bag is pulled up over, the bladder inflates and it creates an airtight seal so that when the ingredients are dumped into the container they can't escaped and then the bag is then sealed and removed.

Charging tanks and mixers is also a source of exposure in flavorings and many other industries. Often ingredients are added to a tank that already has components in it and this can cause additional exposure because

of the displacement of air that is caused when the additional ingredients are added.

One control that we evaluated was a ventilated tank hood. And what this hood does, it can be opened to allow ingredients to be added but also it is exhausted. This helps to keep the exposure, if it is a volatile ingredient, it helps to remove that while it is closed but it also continues to draw air while it is open while ingredients are being added. It was found that this type of control reduces exposure approximately 76 percent compared to a non-ventilated hood.

A ventilated mixing booth is another effective control that can be used for larger mixing operations. Portable tanks can be actually rolled up to the booth and then the vapors that are emitted from the tank are captured by the exhaust at the back of the booth. It provides flexibility because any type of operation that is portable can actually be used in this booth. And this is

an example of such a control.

Again these are exhaust slots across the back. The exhaust goes up the top and you can see that the worker is here. He is in the tank and there is a side view of that. And again, 100 to 150 feet per minute face velocity is what is recommended.

And these are some other examples of controls that can be used for tanks or mixers that have an opening. This is a small local exhaust hood that is placed just near the opening of the tank. This one shows another circular exhaust that is placed around the opening where the mixer is inserted into the tank. And this again is just another small local exhaust hood placed around the bung hole.

Often powered pumps manually or powered pumps are used to transfer liquids from barrels to mixing and feed tanks. And the use of ventilation at the barrel opening has been recommended to help with the capture

of vapors during this chemical transfer. And the recommended airflow is again 100 feet per minute across the cap opening.

This one is a little harder to see but this shows a barrel which contains whatever ingredient we are trying to control.

And this is a semicircular exhaust hood that is placed around this. And this is a larger hopper container which has an exhaust hood at the back. And this again is a barrel which shows a port that allows ingredients to be added as well as an exhaust port to help remove the vapors.

And just briefly, work practice controls, which are sometimes called administrative controls, are procedures that can be followed by both the employers and the employees to help control hazards in the workplace. And some of these include these are just general considerations are good housekeeping practices, clothes transfers, containers, and processes, general hygiene

procedures, such as hand washing and not eating at work stations. For flavorings, one that is particularly applicable because of the volatility of the substances is reducing process temperatures for the priority flavor in chemicals. Also cleaning practices for the equipment, one that has been suggested is cold washes before the hot wash to again, reduce the volatility, the emissions.

Limiting access to priority flavoring chemicals by again keeping these in a separate room so that not all workers have access to them, only the ones that need to have access to them. And again, it is important to have a hazard training and communication program.

In conclusion, traditional industrial hygiene practice suggests following a hierarchy of controls. This is in any industry.

Engineering controls that have been used and tested in other industries are

typically applicable to flavorings processes. Local exhaust ventilation, process enclosures, and work practice controls have been recommended to reduce employee exposures.

Thank you. I will take any questions.

MR. BURKE: I'm Patrick Burke from the Food Safety Inspection Service and they are starting to use diacetyl in poultry for flavoring of poultry carcasses. One of the questions that I have had was say in the mixer and they are cleaning the mixer and disposing of the mixer stuff. Do we have any engineering controls on that instead of sometimes they might just be dumping it down the drain. Have you looked into that?

MS. TOPMILLER: You are concerned about the disposal?

MR. BURKE: Yes, disposal where basically there was some offgassing and possibly vapors going into near the inspection force.

MS. TOPMILLER: That is something we will need to consider.

MR. BURKE: Okay.

MS. TOPMILLER: I'm not aware of anything at this point but definitely we will consider.

MR. BURKE: Okay, thank you.

MS. TOPMILLER: Thank you.

MR. SARGENT: Ed Sargent, Redstone Group. Does your lab or your group have any data to support that any of your engineering control recommendations will meet five ppb REL or a 25 ppb STEL?

MS. TOPMILLER: Do you want to take that one? Why don't you take that one.

COMMANDER MCKERNAN: As Jenny Topmiller just mentioned, the engineering studies that have been done by NIOSH will show that concentrations that the engineering controls are approximately 90 to 97 percent effective at reducing exposures. So we feel that there is support there that shows that

exposures can be reduced below the proposed RELs.

Additionally, there are OSHA site visits where sampling has occurred before and after engineering controls were implemented. This data also supports that in specific operations, concentrations can be monitored below five parts per billion.

DR. LENTZ: Thank you, Jenny.

Next we will turn, again in hazard prevention, to the use of personal protective equipment. Jay Parker is a physical scientist at the National Personal Protective Technology Laboratory Division of NIOSH for the test and evaluation branch. He is involved in respirator testing and certification. Jay holds a BS degree in biology and chemistry from the State University of New York at Binghamton and an M.S. degree in toxicology from St. John's University in New York.

He has worked continuously in the field of respiratory protection and PPE for 36

years and is certified in the comprehensive practice of industrial hygiene by the American Board of Industrial Hygiene. Jay is also the past chair of the AIHA Respiratory Protection Committee.

MR. PARKER: Thanks, T.J.

This section of the criteria document deals with personal protective equipment, specifically respiratory protection and we will be talking about assigned protection factors for the respirators that can be used for protection against diacetyl and 2,3-pentanedione and the maximum use concentrations. And I also will be talking about dermal, eye, and face protection.

As we have already seen, there is a hierarchy of controls where engineering and administrative or work practice controls are always used first before respirators.

We did have a question this morning about the cover of our criteria document draft and I would just like to mention that in my

experience, I have seen many cases where companies have engineering controls but they still have the workers wear respirators. I guess it is an additional line of defense that they are using. So that might be an explanation of the picture that we have on the cover where you do see a worker wearing a respirator but there are engineering controls in place at the same time.

You do have to do an exposure assessment for proper respirator selection and I will get into that a little more later. Respirators can be used during implementation of engineering controls during short duration maintenance procedures, during emergencies, and when engineering controls cannot reduce exposures below the REL.

And respiratory protection should be provided when exposures may exceed the NIOSH REL of five parts per billion time-weighted average, or 25 parts per billion STEL for diacetyl, or 9.3 parts per billion TWA or

31 ppb STEL for 2,3-pentanedione. Also when there are exposures to other chemicals and the limits may be exceeded or when there are exposures of concern to diacetyl substitutes that do not have occupational exposure limits.

If respirators are to be used, the employer shall develop and implement a written respiratory protection program with required work site-specific procedures and elements for required respirator use, as required by the Occupational Safety and Health Administration.

The program shall be administered by a suitably trained administrator but there is no formal certification requirement for a respiratory protection program manager, at this time. There never has been.

Let's take a quick look at the standard elements of a respiratory protection program. These are all required by OSHA. You have to have procedures for selecting respirators for use. You have to have the medical evaluations of employees, fit testing

procedures for tight fitting respirators, procedures for the proper use of respirators in routine situations and emergency situations, procedures and schedules for cleaning, disinfecting, storing, and inspecting, repairing, discarding, and otherwise maintaining respirators.

If you are using air supplied respirators, you need procedures to ensure adequate air quality, quantity and flow of the breathing air. You have to train your employees in the respiratory hazards to which they are potentially exposed. And the training of the employees has to include how to use the respirators, including how to put them on, take them off. You have to explain limitations on their use, depending on the type of respirator and how to maintain them. And there needs to be a procedure for regularly evaluating the effectiveness of the program, auditing the program.

If the employer is using air

purifying respirators for gases and vapors, which have the cartridges and canisters, you have to have a cartridge canister change schedule, which has to be based on objective information. The point here is to ensure that we are going to change out the cartridges or canisters before the end of their service life if they don't have ESLI, which is an end of service life indicator. And there are very few end of service life indicators on the market today.

That analysis has to include the data or the change schedule has to include the data and information used to establish the schedule that has to be in your program. And warning properties, such as odor and irritation cannot be used as the sole basis for determining change schedules. We used to use warning properties prior to 1998. OSHA changed the regulations in 1998 requiring this cartridge change schedule.

If you do experience abnormal odor,

irritation, a respirator user should always leave the area and then should check the respirator to see if the cartridges need replacement or there might be a problem with the fit that needs adjustment.

Okay, now this is the assigned protection factor table for respirators that are going to be used against diacetyl and 2,3-pentanedione. The air purifying type of respirators that you can use would be a full face piece, air purifying with organic vapor P100 cartridges. These compounds are both liquids at room temperature. Therefore, they could generate a mist. So we want to have a particulate filter. We want the most efficient particulate filter available, the P100 filter. There is also a potential for vapor. That is why you need an organic vapor cartridge. It is all one piece, usually the OV-P100 type cartridge or canister. It has an OSHA assigned protection factor of 50. Therefore, the maximum use concentration is 50

times the REL or 0.25 parts per million or 250 parts per billion. For pentanedione it works out to 460 parts per billion.

Now the full face piece air purifying respirators and negative pressure respirator, you can have a positive pressure powered air purifying full face piece respirator with organic vapor high efficiency cartridges. There is no P100 cartridge for PAPRs but there is the essentially equivalent high efficiency cartridge. So it is the same basic type of cartridge or canister. The OSHA assigned protection factor is now up to 1000 because it is a positive pressure device. Maximum use concentration becomes five parts per million for diacetyl or 9.3 parts per million for 2,3-pentanedione.

You can have a PAPR with a hood or helmet instead of a full face piece. An advantage there is that fit testing is not required. You can also wear spectacles. You can wear your own spectacles and you can have

a beard in most cases. The OSHA assigned protection factor is 25/1000. The reason why it has a sliding scale there is it depends on whether the manufacturer has performed testing and can provide data to the employer to demonstrate that this particular respirator is capable of providing an assigned protection factor of 1,000. That is done by conducting a workplace protection factor test.

For example, if you don't have that data, the assigned protection factor is 25. So therefore, the maximum use concentration would be either 120 or 5000 parts per billion for diacetyl and 230 or 9300 parts per billion for 2,3-pentanedione.

Now there is another type of PAPR which has what we call a loose-fitting face piece. A loose-fitting face piece is not the same as a regular hood. It is a type of hood that has a partial seal to the face. And that has an assigned protection factor of 25. And therefore, the maximum use concentrations for

diacetyl are 120 ppb and 230 ppb for 2,3-pentanedione.

Now you can also use a supplied air respirator, SAR, in the positive pressure mode that could be continuous flow or a pressure demand type with a full face piece. OSHA assigned protection factor is 1000. That will take you to 5000 parts per billion of diacetyl or a maximum use concentration of 9300 parts per billion.

You can also have a supplied air respirator with a hood or helmet. Again, you wouldn't need to do fit testing and you can have the glasses and the facial hair. Again, you have the sliding APF of 25/1000, giving you a maximum use concentration of either 0.12 or 120 parts per billion or 5000 parts per billion for diacetyl and 230/9300 parts per billion for 2,3-pentanedione. The SAR also comes with a loose-fitting face piece. The OSHA assigned APF is 25. Maximum use concentration is 120 parts per billion for

diacetyl and 230 parts per billion for pentanedione.

The maximum use concentrations will be lower than shown when those concentrations are equal to or exceed immediately dangerous to life or health levels, what we call IDLH. But there is no IDLH for diacetyl or 2,3-pentanedione that we have developed here. And the reason for that is we wanted to come up with an IDLH but we didn't have LD50 data and that is required for developing an IDLH.

For escape purposes, you would want to use a gasmask, which is a full face piece and OV-P100 canisters or the self-contained breathing apparatus.

Now OSHA does require that all respirators selected for use in the workplace shall be approved by NIOSH under the provisions of our regulations, Title 42, C.F.R. Part 84. And there is a listing of all the NIOSH certified respirators. It can be found on our website on the NIOSH certified

equipment list.

Now when you select a respirator, you have to take a look at the particular situation that you have in your workplace. You need to consider worker activity, worker location, time period of use, and whether it is routine, non-routine, emergency or rescue use. These are the kinds of considerations you look at when you are determining whether you are going to be using an airline respirator where you are connected to the air hose. That could be a problem in mobility. Regarding the length of use, if you are going to use a respirator all day long, a powered air purifying respirator might be a better choice than a negative pressure air purifying respirator. So those are the kind of things you need to look at.

With respect to dermal protection, you will need to use chemically resistant gloves or sleeves or other appropriate types of protective clothing to protect skin when

you are handling liquid, paste, or powdered flavoring ingredients containing diacetyl or 2,3-pentanedione.

Diacetyl and 2,3-pentanedione are diketones. The gloves supplier should be contacted to ensure that appropriate glove materials are selected. We have seen that gloves and protective clothing made from butyl rubber, Teflon and Tychem are effective in reducing skin contact with ketones and diketones to prevent skin irritation.

Eye and face protection shall be provided when there is a hazard from flying particles, molten metal, liquid chemicals, acids or caustic liquids, chemical gases or vapors, or potentially injurious light radiation. OSHA regulations at 29 C.F.R. 1910.133 contain the specific requirements.

Diacetyl and 2,3-pentanedione are irritating to the eyes and skin. You do need to use goggles for chemical splash for eye protection. If you are wearing a respirator

with the full face piece, hood or helmet, your eyes are already going to be protected so you don't need to wear goggles. If you are not wearing a respirator and you are using goggles, it is a good idea to use face shields in conjunction with the goggles. Face shields are always used in conjunction with goggles or spectacles as required by the ANSI eye and face protection standard Z87.1-2003. A face shield with a polyethylene terephthalate visor should provide good chemical resistance against diacetyl and 2,3-pentanedione.

You also need to perform an analysis, including exposure assessment of each operation involving diacetyl and 2,3-pentanedione or any other food flavoring compounds for establishing when to use skin, eye, and face protection.

So in summary, respirators should not be used as the primary method for controlling inhalation exposures but respiratory protection should be provided when

exposures may exceed the NIOSH REL. Maximum use concentrations are given for each type of respirator. Diacetyl and 2,3-pentanedione can cause skin and eye irritation. Chemical resistant gloves should be used when handling liquid, paste, or powdered materials containing diacetyl and 2,3-pentanedione. And eye and face protection, such as goggles and face shields should be provided for liquid splash protection.

Thank you. Are there any questions?

DR. EGILMAN: There is LD50 data on diacetyl from BASF. And that is from a 1993 study, which is referenced in my peer review paper. I just realized sitting here that your first argument was going to be that it wasn't published and peer reviewed. So I point out that there is lots of other information in this document that you rely on that is not peer reviewed, that you misinterpreted too. You will hear that later.

For example, all the thresholds, the density, and I haven't gone through it but there are a lot of other things in there that are not peer reviewed. And you rely on MSDS et cetera for things that you use in the report. So I don't understand why you can't also rely on BASF's own LD50 data and other LD50 data.

And my mama told me when I was deep in a hole to stop digging. Apparently, this is advice, and I just repeat this advice. If initial comments about the picture were well maybe it was a closed system and people double up, they use a belt and suspenders, they use birth control pills and condoms. Well with respect to birth control pills and condoms, maybe that is a good idea but it is not a good idea for workers to be wearing respirators when they don't need to wear them. It is a bad idea. It is a bad policy. You can overwarn and you can overprotect. And by doing so, you undermine all warnings and all

protections.

COMMANDER MCKERNAN: Thank you very much for your comments.

MR. PARKER: Thanks for the comments.

PARTICIPANT: There is data at the March SOT meeting here in Washington this year from NIOSH that diacetyl is a skin sensitizer and a mouse local lymph node assay. Based on that data, I think there might have been data for pentanedione, too, but I don't remember. It is going to be classified as a skin sensitizer under either if OSHA gets the GHS incorporated, but under the European globally harmonized system for classification labeling.

So that means that you will be obligated to put a classification of a skin sensitizer and then you will have to recommend safety precautions based on that, on your MSDS. So I think in your section of the document, you mentioned that it is a skin and eye irritant. I think you need to also

include the fact that it is a skin sensitizer and make sure that you comment that your protection is going to protect against a dermal skin sensitizer.

MR. PARKER: Thank you. That is a good comment.

DR. MYERS: Warren Myers, West Virginia University.

Jay, on your respirator table, I noticed there was no recommendation concerning a half face piece. Could you elaborate on that please?

MR. PARKER: Yes. We didn't recommend half masks because we know that diacetyl and 2,3-pentanedione are both potent eye irritants. So it is normal policy in respirator selection that if you are dealing with a compound that is capable of eye irritation, you should use a full face piece, not a half mask, to avoid any problems there.

I guess there are cases where, depending on the level of eye irritation,

goggles and a half mask might work but --

DR. MYERS: Yes, that was my point.

You obviously have recommendation to use goggles stand alone. I guess my question is if there is potential for requiring the use of goggles, does that not also indicate there is a requirement to use a respirator.

MR. PARKER: Not all goggles are gas tight.

DR. MYERS: But there is the gas tight for eye irritation. Correct?

DR. PARK: There are gas tight type goggles. Right. Okay, yes. That is a good comment. We will take that under advisement and consider that.

DR. MYERS: Okay.

MR. PARKER: Thank you.

DR. LENTZ: Okay, thank you, Jay.

We will move along with the guidance sections and welcome back Dr. Lauralynn Taylor McKernan to talk about the section on exposure monitoring.

COMMANDER McKERNAN:

I want to take just a quick moment to thank all of you for being here and staying here throughout the morning. I think this has been a really enlightening exchange. I know I have learned a lot this morning and I appreciate all the comments. And we are going to be very busy after this public meeting, after the public and peer review comment period, carefully considering all these comments.

So thank you. And I hope that you fully stay engaged throughout the rest of this morning and this afternoon.

Because of time, I am going to concisely review our guidance for exposure assessment.

It is Chapter 10 of our criteria document and I will be here at the conclusion of the meeting to have further discussion with folks, if helpful. But I am going to be more brief than I had planned, just so that we stay somewhat on schedule.

Employers should develop and implement a comprehensive occupational safety and health program to prevent occupational illness, injuries, and deaths. Exposure monitoring is a critical component of this program. Exposure monitoring can be used to determine worker exposure to diacetyl, to 2,3-pentanedione and to other flavoring chemicals that are used in the workplace. It can help you evaluate the effectiveness of work practices, as well as engineering controls and, if necessary, can also facilitate the selection of appropriate personal protective equipment.

Before you begin any exposure monitoring campaign, you should have a clear, concise set of goals that you want to achieve.

Some objectives of sampling campaigns can include characterizing the flavoring chemicals present in the workplace; to insure compliance with existing occupational exposure limits; to assess the effectiveness of engineering

controls or practices; personal protective equipment; and assess training or other methods used for exposure control.

Exposure monitoring can be helpful to identify areas or specific tasks or jobs that have higher exposure or ones that require additional exposure control.

Additional objectives of samplings include to evaluate exposures related to production process changes. Facilities will commonly change how they do things. Exposure monitoring is always helpful to make sure that exposures are still where you think they are as well as to evaluate specific high-risk job categories and to ensure that exposures do not exceed exposure guidelines or standards. Finally, exposure monitoring can be helpful to measure exposures of workers who report symptoms or illnesses.

Exposure monitoring should be conducted by qualified industrial hygiene personnel. Appropriate sampling, handling,

storage, and shipping methods should be used.

With alpha-diketones, you have to protect against light and in some cases also utilize refrigeration to protect samples.

We recommend that you work closely with your accredited analytical laboratory so that the appropriate sampling is advised.

Regarding what to sample, it really requires preliminary knowledge of the specific flavoring chemicals that are being produced or used. This information can be obtained from the facility where you will be sampling, perhaps also a walkthrough survey where you actually observe workers in their processes.

The chemical, physical, and toxicological properties will also help you decide what you should be sampling, and also specific chemical quantities or percent of formulations involved.

When deciding whom and where to sample, your sampling protocol will be based on the objectives that you have established

and we have already reviewed what some of those objectives may be. But also additional considerations can include the distance from diacetyl, 2,3-pentanedione, or other flavoring chemical exposure source; how mobile the worker is and where he is working in relation to his work environment; air movement patterns; specific tasks or work patterns; individual work habits; and exposure controls.

Regarding how to sample, Dr. Streicher reviewed the various analytical sampling methods. They are in use right now but I would caution that this is another area where the field is continuing to evolve and is continuing to move. And so as practicing industrial hygienists, it is really important that we stay on top of the current methods and the recommendations. And so there are various locations where sampling methods are posted.

I highly recommend that you keep your eye on the NIOSH flavoring website that we have. Also OSHA has a fantastic website with

analytical methods.

And so I am not going to go into specific details on that, although there are many things that you can sample in addition to gas and vapor methods and here is just a few of them. Additionally, in the criteria document I believe it is the last appendix in the entire document, we have a kind of how-to step-by-step sample on how you would be collecting samples. There are a lot of seasoned industrial hygienists in the room right now. I encourage you to take a look at that appendix and see how we did and if we caught everything that we should have in there regarding good industrial hygiene practice.

Regarding outcomes of exposure monitoring, as far as interpretation of results, of course you can compare results before and after engineering controls or after work practice changes to see if they were effective or not. And then you can also compare results to recommended occupational

exposure limits such as our proposed recommended exposure limit for both diacetyl and 2,3-pentanedione, as well as others that are available.

Notification is another important element of exposure monitoring programs and employers should establish procedures for the timely notification of workers and workers should know the identified exposure hazards and any subsequent actions taken to reduce exposures.

Employers should ensure that workers understand their role in helping to maintain a healthful workplace.

So in summary, there is a lot of professional judgment that goes into exposure monitoring. There are analytical methods available. They are evolving. We suggest that you use the ones that we have recommended and new ones as they become fully validated.

And please take a look at the document and provide any additional comments

you have on our exposure monitoring recommendations. Thank you.

DR. LENTZ: Thank you, Lauralynn.

Our next presenter is again, Dr. Kay Kreiss. She will talk about the guidance and recommendations regarding medical monitoring and surveillance.

DR. KREISS: Thank you, T.J. Medical monitoring of flavoring exposed workers is necessary because many flavoring compounds have no inhalation toxicity information and no regulations. And although we know that diacetyl as an individual chemical is hazardous to the lungs and 2,3-pentanedione has comparable toxicity in animals, we have little information about other constituents of flavorings that may be hazardous.

In addition, proposed regulations are constrained by the limitations in measurement methods for 2,3-pentanedione and hence proposed regulations are not fully

protective.

The goals of medical monitoring of flavoring workers are two-fold. The first is to identify workers who may already be affected by flavoring exposures with screening tests. The purpose of screening is to prevent affected workers from developing worse lung disease, which is irreversible.

In addition, recognition of sentinel cases of affected workers alerts management and coworkers of possible risk. The second goal of medical monitoring is primary prevention so that unaffected workers remain healthy. This goal requires identification of risk factors by epidemiologic surveillance of the entire worker populations so that management can intervene and workers can protect themselves.

In addition, examination of serial screening data can document whether interventions are indeed effective enough in protecting the health of new workers or

reversing reversible effects.

So there are several characteristics of clinical bronchiolitis obliterans that dictate requirements of medical screening. In the index microwave popcorn plant a quarter of the workers with abnormal obstructive spirometry had no chest symptoms, despite having fixed obstruction. In California, half of the workers with obstruction had no chest symptoms.

So symptom questionnaires cannot be relied on for early detection of disease before substantial impairment.

Many workers develop lung function abnormalities within months of being hired and lung function can fall a liter or more in four to five months. This means that spirometry testing is required more frequently than annually as is practiced in most chronic occupational lung diseases. For this reason, we recommend spirometry at six month intervals and in settings where flavoring-related lung

disease has been recognized testing should be every three months.

Clinical bronchiolitis obliterans is irreversible and unresponsive to medications. For this reason, attempts are needed to identify early abnormalities before impairment occurs. This means identifying workers whose spirometry is still normal.

The best tool we have to identify at-risk workers while normal is to identify those with excessive decline in forced expiratory volume in one second or FEV₁.

In the sentinel plant, in California flavoring workers, and at a flavoring plant with restrictive abnormalities, excessive decline was found in workers with higher likelihood of exposure to diacetyl and flavorings.

The components of a monitoring program are a questionnaire; spirometry at six month intervals and more frequently if there is work-related respiratory illness in

subgroups of a plant; assessment of excessive falls in FEV₁ over time; follow-up of abnormals and the plant conditions that resulted in abnormality, as well as referral of those with abnormalities. And to meet surveillance needs analyses are needed of screening data.

Primary prevention requires finding risk factors. Some questions for these analyses of screening data are whether there is excess abnormality overall, whether subgroups in the workforce defined by area or job tasks, for example, have worse measurements, or prevalence of abnormalities in other subgroups. In California, most flavoring companies changed providers, some several times. If records cannot be transferred from one provider to a subsequent provider, assessment of pulmonary function declines and other indices of health is not possible. With medical confidentiality rules, employers need to have providers get releases

from employees so that medical record transfer can occur when the company changes providers.

Surveillance of the worker population can identify risk factors so that interventions can be made. Then the effectiveness of interventions can be evaluated in terms of the intended health consequences. This requires communication with the company and with industrial hygienists serving the company.

What we are recommending differs from common occupational health screening practice. An irreversible disease requires identification before impairment, that is, while workers still have normal spirometry and no symptoms. The purpose of the questionnaire is to provide information that will be useful in looking at the whole population for risk factors, such as job, area, task, and use of personal protective equipment. It could even be used to assess training needs in the workforce by exploring whether a worker

understands what is necessary to protect him or herself. Thus, the questionnaire is a primary prevention tool so that preventive interventions can be made. It is not to rule out symptoms in a workforce.

Occupational clinics are not accustomed to evaluating excessive declines in spirometry within the normal range and may have difficulty meeting this objective without contractual specifications that I will address later.

To be successful in primary prevention, screening and surveillance requires multidisciplinary follow-back to the workplace to intervene if abnormalities are clustering in processes which need to have exposure reduction, workers need enhanced respiratory protection, or management and workers require further training to enhance prevention.

In my earlier talk on health effects of flavorings, I mentioned two

examples of excessive decline in FEV₁ in investigations of obstructive disease in California and restrictive lung functions in a flavoring manufacturing plant. The average normal decline in FEV₁ in healthy population is about 30 milliliters per year, but this number cannot be the criterion of excessive decline because of the variability of FEV₁ measurements in individuals. The criteria for excessive decline depend on spirometry quality, which is reflected in intra-individual variation.

A good spirometry technician coaches the worker to take in the deepest breath possible and blow it out as quickly and as long as possible. Here, she checks that repeat measurements are within 150 milliliters and that the blowing out maneuver continues until a plateau is reached, indicating that the person can't get much more air out. Quality can be monitored by evaluating printouts of the three best curves in a

worker's test session for repeatability and plateau and other things, such as a rapid start and no cough during the maneuvers.

For World Trade Center responders under medical surveillance, spirometry technicians need to have excellent spirometry quality in 80 percent of test sessions. In California flavoring workers surveillance, only one of 13 commercial providers of spirometry met this quality requirement, and only two of four academic providers met this quality requirement.

The American Thoracic Society has guidance on reliable and accurate equipment for spirometers, as well as how results should be reported that allow quality assurance checks. Technicians need to attend a NIOSH-approved spirometry course and refresher training at intervals. However, training does not guarantee adequate performance.

Some professional associations have instituted certification of spirometry

technicians by reviewing their performance on a set of submitted test sessions. Ongoing review of spirometry quality may assist in improving technician performance.

Companies purchasing spirometry services can motivate good quality spirometry by having independent audits performed and requiring pre-specified quality requirements in their contracts for payment.

Recognizing the common poor quality of spirometry in worker monitoring programs, the American Thoracic Society and the American College of Occupational and Environmental Medicine recommended that FEV₁ measurements that fall by 15 percent or more in a year or 15 percent and 30 mLs per year thereafter, should trigger evaluation. This criterion of 15 percent for abnormality is insensitive for good quality spirometry.

NIOSH has published two studies following healthy workers with serial spirometry which suggest that a ten percent or

more decline in one year is a reasonable criterion for abnormality. And the American College of Occupational and Environmental Medicine has endorsed this criterion for good quality spirometry programs for workers in which lung function may rapidly deteriorate, as in flavoring workers.

NIOSH has free software called SPIROLA that allows a medical provider to tailor the criterion for excessive decline to the within person variability of the provider's spirometry program.

Finally, if companies don't plan for the availability of spirometry measurements to subsequent medical providers, serial assessment of spirometry may be impossible over long periods of time. In California, 60 percent of companies changed medical providers at least once, and some workers were tested by up to four different providers.

As I mentioned in my earlier talk

today on health effects of flavoring exposure, excessive declines in FEV₁ are associated with the same risk factors as obstructive abnormalities in California flavoring workers and in the index microwave popcorn plant, and to areas with higher potential for flavoring exposure in a plant with excessive restrictive abnormalities.

Serial spirometry identifies additional workers who the provider must be concerned about but who still have spirometry that is normal. For example, with high quality spirometry in California flavoring workers, 20 of 21 with excessive declines were still in the normal range of spirometry. Of course the workers who had fixed obstruction on their first test usually didn't have further tests in the workplace.

In the flavoring plant with excessive restriction, five of 13 with excessive declines in FEV₁ still had normal FEV₁s. These workers need follow-up

spirometry tests within a month and if excessive decline is confirmed, medical referral for further testing and careful follow-up so that they don't progress to abnormality. A multi-disciplinary response is indicated with attention to control of exposures in the workplace.

As with attention to excessive FEV₁ declines, occupational medicine providers uncommonly conduct epidemiologic analyses of screening data for surveillance. However, such analyses are critical to primary prevention of lung disease in flavoring exposed workers.

For finding risk factors for excessive decline and spirometric abnormalities, all workers with current or past exposure should participate so that findings are representative of the worker population. If the number of workers is large, the overall population under surveillance can be compared to national data

from the third National Health and Nutrition Examination Survey. Public use data sets allow the monitoring physician to examine excesses in chest symptoms, spirometric abnormalities, while adjusting for age, gender, race, smoking rates, and body mass index categories.

Questions about possible risk factors should be customized to the particular facility so that subgroups can be examined who might be at higher risk. Subgroups can be compared to each other to identify a risk that requires intervention. And interventions can be evaluated for effectiveness in preventing adverse effects in new workers, in improving reversible effects, such as mucous membrane irritation, and in assessing compliance with protective measures.

Examples of all these uses of surveillance exist in the criteria document and also in NIOSH health hazard evaluation reports and publications.

So in summary, medical monitoring is necessary for the serious diseases associated with flavoring exposures, since regulations don't exist for many flavoring chemicals and diacetyl substitutes may have comparable toxicity.

Proposed regulations are constrained by analytic limitations for quantification for 2,3-pentanedione and will not protect all workers. Medical monitoring for flavoring exposed workers requires new skills and practices for many occupational medical providers in order to accomplish preventive goals.

The first is attention to excessive FEV₁ decline in serial lung function tests that will be performed more frequently than spirometry in other occupational settings. The second is that spirometry quality has to be excellent to fulfill this recommendation and this will be a challenge to common occupational medicine practice. And the third

is that primary prevention of occupational lung disease in this industry requires an epidemiologic approach to screening data, both cross-sectionally and over time. This approach constitutes surveillance.

Thank you. Do you want to take questions now or only in the afternoon?

DR. LENTZ: If there are questions right now, we have time for one or two.

DR. EGILMAN: Again I have made this report to some NIOSH people, these cases of unknown caused lung disease that are serious can be best picked up through a national surveillance program linking all of the lung transplant units and for the liver ones, all the liver transplant units.

And you need to train them in how to do an occupational environmental and now, I guess, food survey, but that is where these cases show up in the end. And it is really an efficient way of potentially catching cases before they become an epidemic. And I think

it is not that much work.

I tried to do it, but I am a nobody and a nothing. And so the lung transplant units wouldn't even respond to my letters. But NIOSH is a somebody and a something, and they could do that. You could do that.

DR. KREISS: Thank you.

DR. LENTZ: May I ask if Jackie Nowell is still in the room? No, she's already left. Ms. Nowell had requested if there were time to give her prepared remarks.

She is on the agenda for this afternoon, but she had to leave.

So given that we have run a little bit long, this concludes the first section and the formal presentations by the NIOSH subject matter experts and scientists and researchers and authors of the criteria document.

We will adjourn at this time and return at 1:30 for the afternoon session-- first to hear the prepared comments by those who have requested time to be on the agenda.

We do ask that those persons who have prepared PowerPoint presentations return about ten minutes early at 1:20 so that they can load them onto the laptop.

So we will adjourn now and we hope that you will stay engaged and return for the afternoon comments and more opportunities for questions. Thank you.

(Whereupon, at 12:16 p.m., a lunch recess was taken.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:32 p.m.)

DR. LENTZ: Okay. Welcome to the

afternoon of the criteria document review session for 2,3-pentanedione and diacetyl. This morning we heard from all of the NIOSH subject matter experts and researchers who wrote various sections of the draft criteria document. This afternoon, we have reserved time for first the individuals who have expressed interest in presenting some prepared remarks, and we will allow that. And as time allows, we will also try to accommodate questions and then other comments from the public.

I would like to welcome first Dr. David Egilman.

DR. EGILMAN: Okay, let me start with the disclosures on the bottom here, but I have served as a consultant at the request of workers involved in litigation related to injuries from diacetyl in popcorn.

Some of the things I have already talked about, on this PowerPoint I have mentioned the questions. I will just try to

skip them.

This is the last thing I mentioned at the end of the last session but I talked about the first two. But for these particular workers and I know this may be not exactly on point for this, I would suggest that NIOSH set up a registry for cases. It is particularly important because we don't have a treatment for these patients. We don't have optimal treatment. So if we had a registry and you worked with NIH, it would be possible perhaps to develop some research protocols to see if there are optimal treatments. Some of these people have been treated with dioxin, others with steroids, which I don't think from my anecdotal experience works much. Cytosan, I think, has been effective in some of the people.

But at any rate if you do this, it will be helpful. It would be unprecedented to put this into a TLV document like this, but, nonetheless, I think it is a good idea.

I'm just going to go over the data.

The criteria document talks about basically it takes data from the Jasper plant, Plant G, I think, and comes up with two TLVs in the human section. One is the one that is a three to five ppm -- ppb TLV and the other is a 0.9 ppb for nonsmokers. Smoking counterintuitively protects probably because the mucous that smokers get prevents the deep inhalation of the diacetyl. So I would suggest that it is unprecedented for NIOSH to take a higher TLV than is protective for nonsmoking workers and that based on the numbers, if you are going to rely on the human data, as you have said you are going to here, the ppb should be at 0.9 or 1.0, which is the number that protects nonsmokers. The three to five ppb or the ending 5.0 ppb protects smokers, not nonsmokers.

And I think it would be a terrible precedent to set a TLV that way. It would be the first time I know that data had been

analyzed for any TLV and similar data would of course, could be used in smoking and asbestos, et cetera, and it was never accepted that you'd set two different levels, one for smokers, one for nonsmokers. So the TLV should protect all workers, not just smokers.

I am just going to talk about some other data that supports the TLV as it exists.

ConAgra hired an ex-EPA person to do a structure activity analysis. By the way, all of the data that I am talking about is in a peer review paper by myself and Hank Schilling, which I will drop off here. It is titled A Proposal for Safe Exposure Levels of Diacetyl. It is peer reviewed, and it came out about four months ago, but it is not mentioned in the document.

And it is not a personal thing but I have data in there that is relevant to the discussion, the data that I have been referring to over and over again. This data, for example, only appears in that published

paper.

And what they have found was that structure activity relationship of this material was similar to TDI, which is not the most toxic of the isocyanates; HDI probably is. And that based on that analogy, the TLV would be about one part per billion because that is what the TLV is for, isocyanates.

So that is another piece of independent analysis performed at the funding of ConAgra that comes out with a 1.0 ppb number.

Okay, so and then in the document there is some allusion to other chemicals being potential causes of the disease or enhances the disease. The three that are mentioned are acetaldehyde, butyric acid, and acetoin.

There are lots of studies of acetaldehyde. There has never been a case of BO reported even anecdotally. There is no animal studies that indicate that it causes

BO.

Butyric acid, there is a study by Hubbs and Morris, butyric acid may or may not increase the amount of diacetyl that penetrates into the deep lung because of its inhibition of an enzyme that may reduce the -- may metabolize diacetyl. But I think I have got a quote here from Dr. Morris who is here, in his expert report in the litigation. "It is not known if an inhibition of this enzyme would diminish or enhance the effects of diacetyl." So if that is the opinion of the person who did the work and I think it is a correct opinion, there is no reason to put in these other chemicals like butyric acid or acetaldehyde. Acetoin, a little less is known but certainly there is no evidence it causes bronchiolitis obliterans. And I think it just confuses the issue to include that in the document without any data. If we are into this peer review construct, there is no peer reviewed data that indicates that either of

those three have anything to do with this disease or what we are talking about here.

So and this is -- NIOSH, for some reason, NIOSH gratuitously has made two statements on its website about consumer risk, indicating that there isn't any consumer risk, the last being in 2008. I don't know why NIOSH makes any comments about consumer risk, but they did so. This is -- the justification for me talking about this is people at risk was mentioned in the documentation. And people at risk include workers who pop popcorn in other places. So that would be like consumers.

So those people are also at potential risk. And by the way, what is their risk? Well there are three measurements of peak exposure levels in the QC lab. The baseline was between 0.6 and 0.8 and the peaks were four, seven, and 13. This is the FTIR method, which as far as I know hasn't been questioned.

If you look at the area under the curve, which we haven't done, I calculated the numbers based on Dr. Morris's suggestion that these peaks would last for about 15 seconds. They actually last for longer. That was a suggestion made in an expert report in the litigation.

But you look at the area under the curve there and the peaks -- there is going to be good amounts of -- the red is the diacetyl. Acetoin, I think, is the pink.

So if you look at a 15-second exposure at peak, which is a conservative estimate, you get these numbers for consumers, which is why the concern, I think, has been evident from some folks from industry here.

At four ppm, you get 67 ppb over 15 minutes. At seven ppm, you get 117 and at 13 ppm, you get 217 ppb over 15 minutes. So you are well over that STEL if you are popping bags of popcorn and opening the bags.

So those should be added to, if you

are going to go with the STEL, people at risk in the exposure group. And you are only NIOSH so you can't talk about consumer risk, although you do, but you can certainly talk about other workers who happen to be popping bags of popcorn. Okay?

And then I have cases of consumers who have developed these are all biopsies proven bronchiolitis obliterans which I believe to have been caused by consumers who consumed a lot of popcorn in many cases, sometimes not so much. But the disease association looks pretty good and hopefully these will be published and peer reviewed but probably not in time for you. And these are the exposures.

Lockey's PAPR mixers is another source of data which I don't think you have dealt with. These are also two, five, five, sevens but Kay said you could correct the numbers. But if you look at the numbers, there is a nine-fold increase -- there is a

5.7-fold increased risk for obstruction with a three-year exposure, and this would show a one to 2.9 ppb exposures were unsafe. Now that has got the two, five, five, seven problem and I don't know what the numbers are. That's why I asked.

The odor threshold that you have in the document is wrong. This is a math calculation. You put in it is 0.09 ppb based on Illovo Sugar un-peer reviewed MSDS. And in fact, when you do the -- the person reading this apparently misread it and thought it was ppb. It is actually milligrams per meter. It is 25 ppb. The same thing for the Blank paper that you do cite. The odor threshold is 2.8 to 5.6.

And if you look at a paper that NIOSH quotes deals with coffee aroma. But there is a paper specifically on point looking at diacetyl odor thresholds and they were 1.4 -- I'm sorry. It comes up to about 5.0 ppb.

This is important because at the

level that you have the odor threshold, it would serve as a warning for excess exposure but at the real odor threshold, it doesn't warn about excess exposure. So it is not just a trivial piece in this context.

And the last is relative density is also wrong in the way you put the density. The actual molecular weight density is three to one but the material in air, the relative density is 0.99 because it never reaches saturation. And if you want to understand this, I have got another PowerPoint that is going to be here, I think, Hank will talk about later. But it is in the Handbook of Chemical Hazard Analysis Procedures, which explains how to calculate the real density. And this is important and it also goes with Rosati, which you find that when you look at the particles when they are dispersed, they are 100 microns; 100 micron particles do not drop to the floor. They stay in the air. So that is an increased exposure because of the

properties of these. It is particulate in the air after exposure, which means the exposures are higher and longer than you would otherwise think. This is relevant to people popping popcorn and also relevant to workers exposed.

So it is important to get the density right. It is also important from a hygiene perspective. Because if someone looks at density and says it is three, okay well it goes to the floor. It is three times heavier than air. Well it doesn't go to the floor. It stays in the air. So for hygiene purposes and other purposes, people need to be aware that the density is about that of the air, a little bit lower, which means it stays in the air and only will leave the room as the air flow moves it out of the room.

And I have left all these relevant copies of the supporting documentation.

DR. LENTZ: Thank you, Dr. Egilman.

These will be kept and put in the NIOSH docket and will be available for viewing.

I would like to give my NIOSH colleagues first an opportunity if you have any questions for clarification for Dr. Egilman. If there are none, we will move on to the next presenter, Mr. Peter Harnett.

MR. HARNETT: Okay, before we get started I just wanted to thank Dr. Egilman first of all for correcting the quoted threshold on diacetyl. I had wondered myself when I read it because typically when one talks about odors, you begin to look at mercaptans with about a 20 part per billion odor threshold. So to see it listed at such a low level, I was surprised.

Excuse the fact that I am coming off a cold. I have got respiratory illness here. And then additionally, I didn't start on the 500 page document until Tuesday of this week.

So I have done some litigation work on the defense side. So I will mention that up front, and we will get started.

So what I did at the onset here is to outline some of the concerns that I saw in my review of the document. And you can see there is a smattering of IH issues and maybe a little bit of medical. So the clinicians and so forth, please speak up. I wouldn't be surprised if I did make some errors. All right, so we will get underway here.

There is no current proposed NIOSH ceiling value for diacetyl or 2,3-pentanedione. This kind of puzzled me because a lot of the activities are simply a minute or two in duration. And there has been some information in the past indicating that these very short-term high episodic exposures may be important in disease development.

So again, since there really isn't accurate real time monitoring instruments, perhaps the thought that NIOSH might consider a one or two-minute ceiling value and I think the analytical capability is probably there now.

Okay. Again, I had made this point a little bit earlier. I felt that in looking at it, for the key case that was used in the development of the quantitative risk assessment, that the averaging of air sampling from about 2000 through, what have you, 2005, 2006 could result in overestimation of the risk.

We will just skip these.

Okay, there is a lack of baseline physicals and spirometry results at the start of employment. If I understand what a case is, it is the REL is based on potential for one case in a thousand for a working lifetime for 60 percent of predicted FEV₁ or the fifth percentile of normal. And that is on page 129 of the document.

Okay, so this means that employees may start employment with exposure to prior chemicals known to result in decreased lung function. Some of these chemicals include chlorine, sulfur dioxide, nitrogen oxides.

Nitrogen oxides was one of the earlier mentions in the literature due to silo fillers disease of bronchiolitis obliterans. There is also high particulate exposure, cement, or exposure to alkaline dusts and cigarette smoke. Exposure to alkaline dust, they are seeing some bronchiolitis obliterans in the response workers at Ground Zero.

Also, you will notice there, too, the importance of some. The first group is irritant gases and the second are particulates.

And again, looking at the six companies that the study or the document does discuss, I believe there is few, if any, of the companies had baseline spirometry or baseline physicals conducted prior to employment.

I didn't want to get into this because I am not a physician, but select medical conditions may result in an employee starting employment with some fixed

obstructive airways impairment.

Okay, the broad net approach to butter flavorings, I think that makes it very difficult for industry to deal with it because NIOSH has -- this is a quote, by the way, on page 218. "While the focus of this document is on diacetyl and 2,3-pentanedione, NIOSH has concern about other flavoring substitutes with structural similarities to diacetyl or moieties that are biologically active and capable of producing similar toxic effects as diacetyl. Therefore, NIOSH recommends that such exposures will be considered and controlled as low as reasonably achievable."

So for me looking quickly at this, I would be pretty confident that would include a 2,3-hexanedione, which I believe is GRAS listed and acetoin. Does it include butyric acid, acetic acid, lactic acid, acetaldehyde? What about diketones in general? What about select ketones?

This is a photo of a portion of a

storage room at a flavor fragrance company. It is simply mind boggling to see the number of compounds that are used when batch operations occur at a flavor fragrance facility.

So, I want to talk a little bit about the actual mixed atmosphere in a microwave butter flavored popcorn plant. As I already mentioned, aside from diacetyl, you are likely to see acetoin, butyric acid, acetaldehyde, acetic acid, and lactic acid.

Current thinking and I know Dr. Egilman had said something a little bit different or quite different is that some of these compounds may exacerbate health effects of diacetyl and 2,3-pentanedione. There is some indication that acetaldehyde may exacerbate respiratory disease. Not to say it would single-handedly bring on obstructive lung disease but just that it may exacerbate the condition.

Additionally, NIOSH should consider

indicating that diacetyl and 2,3-pentanedione are surrogates for workplace exposures in microwave butter-flavored popcorn plants. Indeed, if there is some additive effect or synergistic effect from these other compounds, it is critical that it be indicated that it is a surrogate.

Okay, this had puzzled me when I came across it, again, because of the remark I had made about mercaptans. So thank you Dr. Egilman on this point. So he would correctly state that 25 ppb would not be an adequate warning property when wearing a respirator.

So since cooked butter or margarine is smelled very easily, it would strike me that we are likely to be above -- please disregard this language now -- but that we are likely to be above 25 ppb. Yes, 25 ppb.

So this can bring into the equation -- in the occupational community it would certainly bring into the equation cooks who are involved in handling a lot of margarine

and butter and doing such things as making omelets and so forth.

It would likely, since we all know that someone who gets busy cooking in a kitchen at home, when they are melting butter, they do indeed, or at least I do, smell butter in the air.

I think there are another couple slides. But let me just make a remark. And that would be related to a discussion of particulates. When you go into a microwave butter popcorn facility, there are a lot of fine particulates in the air. And right now, NIOSH is indicating they don't have the capability with the current method to see down around 5 ppb for diacetyl and 9.3 ppb for 2,3-pentanedione. So that brings up an issue with the encapsulated form and again, with the cases where diacetyl or another butter flavoring is absorbed through a substrate.

Additionally, what you find in a microwave butter flavoring popcorn plant is

you do find a lot of particulate matter. So, it begs the question how important are particulates with regard to the actual human dosing of diacetyl or 2,3-pentanedione.

So those are my comments. I may have skipped a slide or two there, but I think that pretty much covers what I want to say.

DR. LENTZ: Thank you, Mr. Harnett for the presentation and your comments. I would ask again whether my NIOSH colleagues want to address anything or make a comment.

DR. KREISS: I had a question on one of your comments.

You had made the comment that pentanedione and diacetyl exposures are generally going to occur in the workplace in a scenario where other compounds are present, which certainly is more often the case than not. Certainly the Netherlands work wasn't diacetyl in isolation but at least we had only a small number of compounds. But just to get to the point of your question, are you

suggesting that the NIOSH REL only be protective of workers that get exposed to diacetyl and pentanedione in isolation?

MR. HARNETT: Okay, so what I am trying to get at with that discussion --

DR. KREISS: Yes.

MR. HARNETT: -- is that if you solely look at diacetyl and then you build an exposure limit based on that, it may very well overestimate what should be an appropriate REL. Because there may, I think there likely is a contribution in the workplace by other compounds that are present, such as acetoin, such as acetaldehyde.

So I think NIOSH runs the risk of creating a REL that is more conservative or lower than it should be if they just default to using diacetyl or 2,3-pentanedione.

DR. KREISS: But the workers we are trying to protect will be in those kinds of environments, won't they? I mean, we are talking environments where we would expect

that there will be a variety of irritant gases present also.

MR. HARNETT: Yes. Yes, that is correct. And what the answer is to try to correct this and look for synergistic or additive relationships, it is remarkably hard.

There may be situations where you can truly come into a situation where diacetyl or 2,3-pentanedione might be used exclusively, but you know and I know that that is very, very rare.

DR. KREISS: Thank you.

DR. HUBBS: I have a question. I am curious about the intent of your statement about encapsulated flavorings. Are you concerned that NIOSH, that methods be developed for flavorings that are adhered or encapsulated that contain diacetyl? I mean, how do you see that as playing into again these recommended standards?

MR. HARNETT: Well, I guess it would be more of a tox question. One would be

do you know that an encapsulated form of diacetyl -- well, let's just talk about the sheer amount, maybe in a particle you have 100 nanograms. I don't know. Is that of more import in terms of health effect, than that same quantity being inhaled as a vapor?

DR. HUBBS: In terms of the tox question, I have a research proposal that is undergoing review by NIOSH right now to investigate that. We don't yet have data on that. Thank you for the comment, though. I appreciate the support, as do all researchers when they have grants that are coming back from review.

But in terms of the criteria document, which is what we are looking at today, what we know is possible. Because in fact, the particulate diacetyl has not gone through a risk assessment in the encapsulated form, which would be expected to produce few vapors.

But in terms of the criteria

document, which is dealing with the vapors, I believe that the risk assessment from which the REL was derived was working with a workplace where that would not have been a major confounder. Is that correct, Dr. Kreiss?

DR. KREISS: No, I mean, there were powdered flavorings used in virtually all plants.

DR. HUBBS: Okay, thank you.

DR. LENTZ: For the NIOSH panelists, are there any more questions for Mr. Harnett?

Then we will allow -- Dr. Egilman?

DR. EGILMAN: With respect to "encapsulation," it is designed to release on contact with water. That is particularly how it was intended to be used in popcorn. And so in most instances that I know of, the upper respiratory tract of human beings is wet, so that it will release if it is even in a particulate form. And I believe there is a

peer reviewed paper by Longo on that issue in IJOEH.

DR. HUBBS: So, Dr. Egilman, is your comment there that you would want NIOSH to potentially include some comments on the powdered form within the criteria document?

DR. EGILMAN: Not necessarily because I don't think -- I mean, I think you are going to cover it with respect to the exposure. The exposure is going to be there -- maybe. Thanks for reminding me. Yes. I mean, in other words, if you are doing monitoring, and you are only monitoring encapsulated material, that may under estimate the dose to the lung. Because it is designed to release on contact with water in the lung and elsewhere. So yes, you might throw that in. It is a monitoring question in terms of exposure.

DR. HUBBS: Okay, thank you.

MR. HARNETT: I will just add to that. And that is that diacetyl is likely,

like most organics, to adsorb to airborne particulate in the workplace.

DR. HUBBS: Yes. And actually that brings up another question I had about your comments. And one of the sections that you quoted here was discussing the structural relatives to diacetyl and the concerns we have that we don't have toxicology or epidemiology data on all the related compounds.

So in terms of what you would like us to do with that section, do you want us to be more specific in saying how those compounds would be related? Is that what your comment is?

MR. HARNETT: Well if I understand you, it would be helpful first of all, I think the net has been cast too wide to put it on someone to just say things that may be butter flavorings, please look at and keep the level as low as reasonably achievable.

I think for most people out there, they really don't know all the components of

butter flavoring, including the people who are purchasing the stuff at the flavor fragrance plants or a microwave butter popcorn facilities.

So I think you need to provide some definition there.

DR. KREISS: Then can I ask a question about that? Certainly in our experience in one health hazard evaluation, the food producer had stipulated to the manufacturer that the flavoring purchased had less than one percent diacetyl but the food producer had no information about what substitutes were used.

Would you suggest that we recommend in the criteria document that flavor producers be required to indicate the alpha-diketone substitutes that might be in the flavoring? Many food producers don't have the capacity or are in fact contractually prohibited from reverse engineering to find out what is in the flavoring. So how are they going to know how

to protect their workers if they don't know what is in the flavoring?

MR. HARNETT: Yes, let me just, I can't answer that question directly but I will just come at it anecdotally. And that is, I am aware of some companies that use a fermentation technique to produce butter flavoring. And they do take the time to identify the constituents of that fermented product. And off-hand the one that I am most familiar with does, indeed, contain diacetyl, acetoin, acetaldehyde, butyric acid, lactic acid. Those are a few quick ones.

Are they all butter flavorings? I don't know. Is acetaldehyde a butter flavoring?

DR. KREISS: Well certainly the Flavor and Extract Manufacturers Association told us very early that those chemicals were commonly found in butter flavoring. And as you say, if it comes from a starter distillate where those are all fermentation products, one

could assume that.

I guess my question was I don't think that 2,3-heptanedione and 2,3-hexanedione or 2,3-pentanedione are fermentation products, but they have been used in substitutes without any notification on material safety data sheets.

Do you think that NIOSH should recommend to OSHA that whatever diketone substitutes may be present should be identified without listing concentration, which would be trade secret, but at least indicate that those --

MR. HARNETT: I mean, my personal belief is that so far with Dan Morgan's work at NTP that clearly they should be identifying 2,3-pentanedione. It has been shown that -- it shows similar health effects, and I think it would be in a company's best interest to disclose that to a consumer or to a downstream worker.

DR. KREISS: But your point would

be to not identify substitutes for which there is no toxicology data yet.

MR. HARNETT: A case in point. What can you tell me about butyric acid? I mean, I am not a toxicologist. I don't know where to demarcate that line of what is a butter flavoring and what is not. That is my problem.

DR. HUBBS: Thank you for the comment, and we will discuss what compounds we should include in the cautions on ones for which we have limited toxicology data. Thank you.

DR. LENTZ: Dr. Egilman, do you have a question?

DR. EGILMAN: I have a comment on the last labeling issue. Dr. David Egilman. Two issues with respect to labeling. One is I didn't see it in the proposal. The second is an issue that you have to remember that there are falsely reassuring anti-warnings on all of these products because they all say FEMA GRAS

or FDA GRAS, generally regarded as safe.

So every mom and pop shop is getting a barrel of this with a label stuck on there saying the FDA says it is safe. So you have to deal with that because they are getting anti-warning information on those boxes and those bags and those buckets. It is critically important for you to deal with it.

The other issue is yes, you have got to, I think you have got to -- there is no trade secret. There is no legitimate trade secret. Everyone knows what chemicals are used. The amounts may be trade secret, but the listing of the names of the chemicals should be required and should be part of the standard.

DR. LENTZ: Thank you, Dr. Egilman.

And thank you Mr. Harnett.

We will go onto our next scheduled presenter and that is Dana Hollins.

MS. HOLLINS: My apologies. I don't have a nice presentation for everyone.

We have just prepared comments that I will read.

My colleagues and I believe that it is important for numerous stakeholders to be involved in the discussion regarding the possible health effects associated with diacetyl and 2,3-pentanedione and to assure, to the extent possible, that all pertinent and reliable scientific information is used in the decision-making process.

We have identified a few key issues within the criteria document that we believe deserve special attention. We have numerous comments which we believe NIOSH should give serious consideration and I will address a few of these today.

My first comment is in the Quantitative Human Health Risk Assessment section of the report. The risk assessment largely relied upon the findings from an updated analysis of the index facility that was recently published as Kanwal, et al. 2011.

There appear to be some limitations that should be further evaluated when reviewing data from a study of this group of workers.

Duration and cumulative diacetyl exposure were negatively associated with the finding of an FEV₁ below the lower limit of normal, i.e., pulmonary function decrements were observed in the lowest duration and lowest cumulative diacetyl exposure category.

That is, an inverse or J-shaped dose-response curve was observed.

Sixty-six percent of mixers, maintenance, and QC workers that were hired after the first NIOSH survey, i.e., after the facility began implementing exposure controls, already reported respiratory symptoms. Thus, newer cohort members almost certainly had preexisting respiratory conditions. If this finding is accurate, this subgroup may not reflect the typical person in the workforce.

The mean length of employment for workers hired after the first NIOSH survey was

six months. Prior to this, the mean length of employment was six years for similar workers.

Thus, it is quite likely that heightened concerns about the potential health hazards may have changed worker behavior, making them possibly dissimilar cohorts.

Workers hired after controls were implemented at the index facility were on average ten years younger than those who were hired before controls were implemented. This difference in chronological age as well as possible other factors make it difficult to reasonably compare these two groups.

My second comment. In the Quantitative Human Health Risk Assessment section of the report NIOSH stated that "high-risk cases were not largely associated with specific job groups such as mixers or quality control; many came from the general production line." This observation is contradictory to the expectation that higher exposure tasks, i.e., such as those performed in mixing areas,

would be associated with a higher risk of pulmonary function deficits.

As described in the criteria document, mean mixing room air concentrations were 2.36 ppm as opposed to lower concentrations of 0.49 ppm and 0.37 ppm in the production and quality control areas of the index facility; that is, the air concentrations were five times lower. This also does not seem to support earlier statements in the criteria document where "NIOSH found evidence of a dose-response relationship (i.e., worse lung disease or more workers affected) with higher diacetyl exposure."

The criteria document also stated that "the nominal standard for acceptable risk used was one per one thousand excess risk, a choice often used in OSHA regulation." It is our understanding that this is OSHA's risk criterion for regulating carcinogens; however, we know of no such policy for non-carcinogens.

To our knowledge, diacetyl is not considered a carcinogen and the endpoint modeled in the NIOSH human health benchmark dose analysis was changes in pulmonary function.

The EPA has conducted benchmark dose analyses for a variety of chemicals and this methodology has been cited by OSHA. Based on our review of the values posted on the US EPA Integrated Risk Information System website, the EPA has conducted benchmark dose analyses for approximately 33 chemicals, many of which are carcinogens. None of these analyses use an excess risk of less than five percent and those instances where an excess risk of five percent is used involve sensitive health endpoints such as neurological or reproductive effects. In addition, this data set may not be robust enough upon which to conduct a quantitative health risk assessment.

My fourth comment. The criteria document stated that there is a potential "high-risk" group in the updated analysis of

the index cohort, but such an occurrence would appear to be highly unusual, if not unprecedented. Further analysis and discussion as to why NIOSH believes this is a "high risk" subgroup, and the characteristics that make the members unique would seem appropriate. It is not clear that this cross-sectional data set is robust enough to fairly apply a low dose extrapolation model.

My fifth comment. We reviewed other chemicals for which NIOSH has recommended comparably low TWAs (i.e., one to 16 ppb). We found that these chemicals are sometimes more acutely toxic than diacetyl by factors of 100 to 2,000-fold and the chronic toxicity involves much more serious effects. Further, to our knowledge, all known inducers of bronchiolitis obliterans in humans including phosgene gas, chlorine gas, and nitrogen dioxide are highly reactive, caustic compounds and have been observed to cause deep lung destruction in animal studies at low

concentrations.

Diacetyl, on the other hand, does not cause even minimal deep lung effects in animals at concentrations high enough to cause severe necrosis of the upper respiratory pathway and death. In short, diacetyl does not fit the profile of a known BO inducer.

My sixth comment. We request that NIOSH make publically available all corrected air monitoring data collected by NIOSH researchers for which humidity, temperature, and/or storage time duration are available. We further request that these data be presented as individual samples, not as summary statistics, which is entirely appropriate and necessary for an occupational hazard of this magnitude.

And my final comment. In epidemiological investigations, multiple comparison populations are often necessary to evaluate health effects in potentially exposed worker populations. The NHANES surveys are

predominantly conducted in urban environments and may not be an appropriate comparison population for cohorts with more rural demographics. Thus, the NHANES cohort may not be the ideal comparison group. We recommend these data be compared to other generally accepted populations that are regularly used by pulmonologists (i.e., Knudson et al. or Crapo et al).

And I would like to say that I have received no outside funding of my travel expenses or time invested in preparing these comments. Our firm, who is engaged in consulting, believes we have a professional responsibility to share information with government bodies. We have in the past consulted and testified for flavoring manufacturers and as a result, have developed a body of knowledge about this issue. Scientists in our firm have studied this matter for four years and have published numerous papers.

I hope this panel will give these comments serious consideration and I have brought copies of my comments. Thank you.

DR. LENTZ: Thank you, Ms. Hollins.

DR. HUBBS: I have a question in regards to the reactivity of diacetyl. The same type of cells are in the deep lung as are in the affected noses. And the PBPK model shows that diacetyl will not reach the deep lung of rodents. So it is unlike chlorine.

Are you suggesting we ignore that data?

MS. HOLLINS: I am actually not a toxicologist. These are some comments from my colleagues.

DR. HUBBS: Okay.

MS. HOLLINS: I would be happy to provide some written comments further to explain these.

DR. HUBBS: I just wanted to clarify where those came from.

MS. HOLLINS: Sure.

DR. HUBBS: So with that, we will definitely consider that. Thank you.

DR. LENTZ: Are there other questions from the NIOSH panelists? And then --

Dr. Egilman.

DR. EGILMAN: Sure. Give Dennis my regards. Dr. Egilman from Brown University.

I think you made two criticisms or whoever wrote that included two criticisms. One was that it was "difficult," made it difficult I think is the words that you used, to do a comparison because there were different ages involved in the Jasper plant. I don't understand if there is some data that that is based on. I mean, everything is difficult. Some things make things more difficult. They can usually be adjusted for if there is some issue of what needs to be adjusted for. What specifically makes it more difficult? What has NIOSH not adjusted for, etcetera?

And the same, I think you made some other comments that were similarly vague and ambiguous about something else that was difficult to do.

Oh, I know. You compared the toxicity of diacetyl which can only result in a lung transplant and death with the adverse health effects of the other 16 things that have ppb levels. And you said that those were in general, I don't know what that means, less worse effects than the diacetyl effects.

Just, I don't understand that and I don't think it is correct. Because at least one of the major sets of chemicals that is in the ppb range are isocyanates. In at least 22 cases of bronchiolitis obliterans, there is not the kind of volume of that disease and death and severity as there is with diacetyl.

So it is kind of like, you know I guess from my perspective, in the eye of the beholder when you compare diseases that can kill you. They are still, both groups can

kill you. So I don't know if there is something I am missing in that argument.

MS. HOLLINS: Okay, that was a lot.

I guess with regards to the first comment regarding the ten years younger and ten years older, we just didn't feel like it was clear in the criteria document that there was control for the age groups, as well as possible other factors between those two cohorts.

And with regards to the second comment, we were just highlighting, we wanted to highlight the possible inconsistencies with the low recommended RELs and comparable LC50 with other chemicals.

DR. LENTZ: Thank you, Ms. Hollins.

We have a question from Dr. Kreiss.

DR. KREISS: I am not sure I understood. You questioned whether the one in a thousand excess risk was appropriate for a non-carcinogen. And what were you suggesting we use in place of that?

MS. HOLLINS: I wasn't suggesting anything else. I think it just should be clearer the justification for using the one in one thousand.

DR. KREISS: You mentioned something like a five percent risk. Was that your suggestion?

MS. HOLLINS: Yes. EPA uses five percent for carcinogens in benchmark dose analyses that they have conducted.

DR. KREISS: For non-carcinogens?

MS. HOLLINS: For carcinogens and non-carcinogens.

DR. DANKOVIC: Perhaps we should clarify that when EPA does that, it is a point of departure that they extrapolate down from.

MS. HOLLINS: Okay.

DR. LENTZ: Are these questions pertaining to Ms. Hollins' remarks?

DR. BORAK: Yes, if I may. Jonathan Borak, Yale. Just a point of clarification and it is one which several of

us spoke about over lunch. And the only reason I had privy to the conversation is I am one of the panel reviewers.

I think that there is something which can be misleading. That was the point I made at lunch. That in the human risk assessment chapter, there is reference to use of a benchmark dose approach and it is not really a benchmark dose approach. It is a modeling approach. There is a more formal and rigorous benchmark dose approach used in the animal risk assessment model, which is more traditional than the manner used by EPA.

And I raise this because I, as you did, thought that it was mislabeled. And in referring to it as a benchmark dose, it misimplies the method, not the method statistically but the utilization. Because in a benchmark dose, you take that benchmark dose and you take a lower bound on the benchmark dose and use that as a point of departure. That was not in fact done here.

So I would say that I agree with your point but the point should be viewed in the context that that is not actually what was done. What was done in that chapter was misdescribed as a benchmark dose.

MS. HOLLINS: Thank you.

DR. LENTZ: Thank you.

Dr. Egilman, again, a question?

DR. EGILMAN: No, she can go. Go ahead.

PARTICIPANT: The comment about the lung function, the very last comment. NHANES across the whole United States is a random sample. However, I really I never thought about what fraction of the people are in urban places versus rural before. But certainly it would be available.

Crapo was in Salt Lake City, so that is a city. Knudson is a very long time ago, before the standardization of spirometry really took off. So you don't want to go there. But that was Tucson and so those are

also cities.

So I don't think there is a better comparison, at least at this point. Both ATS, in writing, which is very unusual, as well as ACOM recommend that NHANES III is the current reference value to use.

And Crapo and NHANES are quite similar to each other actually. And in fact in our recent ACOM statement we recommended that if you had an older spirometer that preceded 1999 when NHANES came out, that you would use Crapo and not Knudson because the Knudson ones are old and flawed. Okay?

MS. HOLLINS: Thank you.

DR. LENTZ: Thank you.

DR. EGILMAN: Just picking up from the same point. Dr. Egilman --

DR. LENTZ: Okay, one more and then we have to move to our next presenter.

DR. EGILMAN: Okay. As I recall, and I think it includes people from Exponent but I am not sure. Every time I testify in

one of these cases from Jasper or wherever, the defense witnesses come in and say they got this from silo fillers. They got this from mowing the lawn. That there is no more dangerous place, according to the defense experts in these cases than these rural places. There are like, you know, rat holes for lung disease from the perspective of everybody who has testified in the litigation.

I mean, they come up with things that they were exposed to that I never heard of before. So I would hesitate to say slightly ingenuous or inconsistent what is said in courtrooms under oath and the kind of insinuation that these people live in some pristine mountain monastery where they don't smoke, drink, or anything else. These are not in Utah. You know, there are -- Mormons were in Missouri but not this part of Missouri. Okay?

So I don't think that that anecdotal comment really sways me that these

people come from a stock of ill-deformed lungs exposed to horrendous lung toxins.

DR. LENTZ: Thank you.

DR. EGILMAN: Because, you know, if they are in the factory, they are not in the silo.

DR. LENTZ: Thank you, Dr. Egilman.
Thank you, Ms. Hollins.

We will go to our next presenter. I would like to welcome Azita Mashayekhi to -- Mr. Harnett if you want to discuss with Ms. Hollins afterwards.

MR. HARNETT: I had been sitting here, though.

DR. LENTZ: Okay.

MR. HARNETT: So I was unclear on a couple of points you had made.

MS. HOLLINS: Okay.

MR. HARNETT: And it may just be me. Is it you or your company that is saying that diacetyl is not associated with respiratory disease?

MS. HOLLINS: No. No, not at all.

MR. HARNETT: Okay. And then what do you believe OSHA uses in terms of increased cases in the population in terms of creating a new standard for a non-carcinogen?

MS. HOLLINS: You know, we looked at some of the OSHA regulations and we have really only been able to look at formaldehyde, I think was the most recent one. And I don't recall off the top of my head what it was now.

MR. HARNETT: Okay. The reason is actually, again I am not well-versed in the area, is that my recollection of carcinogens is that OSHA typically uses one times ten to the minus fourth. That is one in ten thousand. It is very clearly stated by OSHA, I don't know if it goes on with NIOSH RELs but there is no attempt when you said in OSHA PEL to say it protects all people. But I would be surprised for a sensitizer like formaldehyde if they were not shooting for a number that would be something like one in a hundred or

one in a thousand. I would actually be quite surprised.

DR. LENTZ: Thank you for your comments. We will again move on to the next presenter. I would like to call Azita Mashayekhi to the podium.

MS. MASHAYEKHI: Good afternoon. My name is Azita Mashayekhi. I am an industrial hygienist with International Brotherhood of Teamsters Safety and Health Department here in Washington, D.C. Thank you, NIOSH for having us here. And I have given a copy of my comments to everyone with just minor changes made as I was sitting here.

I am just going to read it. These are not our final comments to the docket. Just some oral comments in support of the effort.

The International Brotherhood of Teamsters, IBT, welcomes the opportunity provided by the National Institute for Occupational Safety and Health NIOSH to attend

the public meeting on the draft document criteria for a recommended standard, occupational exposure to diacetyl and 2,3-pentanedione.

The IBT commends NIOSH for presenting a comprehensive review of scientific literature, a quantitative risk assessment and valuable guidance to reduce occupational exposures to diacetyl and 2,3-pentanedione. The information presented in this document will serve as a very useful tool to adequately and effectively reduce or eliminate significant risk of health impairment from exposure to these toxic chemicals and to prevent flavorings-related lung disease in the working men and women of this country.

While the focus of this document is on diacetyl and 2,3-pentanedione, the IBT fully supports NIOSH's concern about "other flavoring substitutes with structural similarities to diacetyl and capable of

producing similar toxic effects as diacetyl."

And NIOSH's recommendation that "such exposures also be considered and controlled to as low as reasonably achievable."

Our comments today are to serve as a statement of support for this effort and to urge NIOSH to move ahead with finalizing the criteria document. We will submit additional comments to the NIOSH docket at a later date.

The IBT represents more than 1.4 million workers nationwide, hundreds of whom are employed in industries and jobs where diacetyl and 2,3-pentanedione and other alpha-diketones are used. Our members perform a variety of jobs in the manufacturing of flavorings, foods, baked goods, and snacks, dairy, candy, confectionary, and baking products. They include production workers, warehouse workers, laboratory workers, quality assurance/control workers, shipping and receiving workers, maintenance workers, and janitorial workers.

Forty-one years ago when the Occupational Safety and Health Act of 1970 was enacted, it declared that the Secretary of Health and Human Services on the basis of such research demonstrations and experiments and any other information available to him shall develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels that are safe for various periods of employment, including but not limited to the exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience.

It was in 1985, over 16 years ago, that NIOSH conducted a health hazard evaluation at a plant in Indiana that produced flavorings for the baking industry and found severe fixed obstructive lung disease among workers in a mixing room.

And it was on January 15, 2004,

over seven years ago, that NIOSH recommended in an alert "that employers take measures to limit an employee's occupational respiratory measures to food flavorings and flavoring ingredients in workplaces where flavorings are made or used."

Since 2006, the IBT and its local union affiliates have been in the forefront of efforts to encourage and assist federal and state agencies in research and regulation of occupational exposures to diacetyl and related flavoring ingredients. In 2006, the IBT, along with the United Food and Commercial Workers International Union, UFCW, pointed to compelling epidemiologic and toxicological evidence linking exposure to diacetyl to severe respiratory impairment and disease and called upon OSHA to issue an emergency temporary standard and to initiate formal rule-making to protect workers exposed to diacetyl and other harmful flavoring-related chemicals.

In 2008, a Teamster local union submitted a request for a health hazard evaluation at a flavorings manufacturing facility in Indiana. Also in 2008, NIOSH received another Teamster Union request to perform an investigation of possible health hazards at a Teamster represented bakery mix facility in Los Angeles, California.

These investigations have resulted in important findings, which are described in the draft criteria document. At both plants, NIOSH found a pattern of spirometric restriction significantly higher than the prevalence for the U.S. adult population. At one of the plants, "employees with higher potential for exposure to flavorings had greater average annual decline in lung function and a seven-fold higher chance of abnormal lung function decline than employees in other areas with lower potential for exposure."

These findings and previous reports

suggest that the spectrum of health effects related to flavorings may be broader than fixed obstruction and include restrictive lung disease, according to NIOSH. And in both cases, NIOSH could not find "the results of any in-depth medical evaluations resulting from abnormal findings identified by the monitoring and surveillance program" to determine if those with restrictive spirometry have occupational lung disease. We urge NIOSH to continue exploring this possible association.

In light of the range of possible health effects, we fully embrace NIOSH's objective in recommending exposure limits "to reduce the risk of decreased lung function and the severe irreversible lung disease constrictive bronchiolitis obliterans associated with occupational exposure to these chemicals and to help prevent other adverse health effects, including but not limited to irritation of the skin, eyes, and respiratory

tract in exposed workers."

At one of the plants, although none of the applicable material safety data sheets for the evaluated bulk flavorings listed diacetyl or its alpha-diketone substitutes, NIOSH's analytical results of bulk samples of liquid and powdered flavorings indicated that aside from diacetyl, five of six contained alpha-diketone substitute compounds 2,3-pentanedione and three contained other alpha-diketones.

This finding confirmed the use of 2,3-pentanedione as a substitute for diacetyl and artificial butter flavorings. Research by both NIOSH and the National Institute of Environmental Health Sciences, NIEHS, "suggests that in rats 2,3-pentanedione causes airway epithelial damage similar to that produced by diacetyl," signifying that "all too often substitution is an unreachable panacea."

And here I just want to echo a

sentiment by Dr. Kreiss and others that you know, we think that flavor producers should be required to disclose the presence of alpha-diketones and other substitutes on the MSDSs.

That is really essential and we will put that in our comments.

Given NIOSH's comprehensive review and quantitative assessment of human exposures supported by animal risk assessments, IBT supports the recommended exposure limit, the action level and the short-term exposure limits for diacetyl proposed by NIOSH.

We also agree with NIOSH that the use of an action level in conjunction with periodic monitoring of worker exposures is helpful to protect workers.

In view of the capabilities and constraints of the analytical method, IBT also supports the REL and STEL recommended by NIOSH for 2,3-pentanedione.

As NIOSH notes, these limits are supported by validated analytical and sampling

methods that can be used to effectively measure worker exposures at the selected levels and by achievable engineering controls based on information from OSHA-sponsored site visits where diacetyl is used or handled.

In conclusion, we thank NIOSH once again for this opportunity to speak on behalf of our members and all affected workers and for producing criteria of a recommended standard for the recognition evaluation control of hazards from exposure to diacetyl or 2,3-pentanedione and other potentially hazardous flavoring chemicals.

This criteria document is at last a great step by NIOSH towards fulfilling its mandate to use scientific evidence to protect American workers from debilitating lung disease.

Thank you.

DR. LENTZ: Thank you, Ms. Mashayekhi. Are there any questions from my NIOSH colleagues or points of clarification?

Well thank you. We will put these comments in our docket and we look forward to the additional comments that you will be providing.

As mentioned earlier, Jacqueline Nowell of the UFCW International Union was not able to stay for the afternoon but she indicated that the UFCW will be submitting their comments to the docket.

For our final scheduled public presenter, we would like to invite Hank Schilling to the podium.

MR. SCHILLING: Actually, I have no further comments.

DR. LENTZ: Okay.

DR. EGILMAN: I stole his comments.

DR. LENTZ: Okay. Thank you, Hank.

Oh, I'm sorry. For the record, Hank Schilling stated that he has no further comments.

Okay. At this point, seeing as we have some additional time, we will allow any

other additional comments or points of clarification, questions from the audience.

DR. BORAK: Thank you. If I may, Jonathan Borak, Yale.

Mr. Harnett made a point and I thought it could be clarified because I think it is worth addressing. He raised the question of diacetyl as a surrogate in a mixture as opposed to the definitive agent. And I think that the issue, at least one that had occurred to me is as follows.

If the effect is a consequence of not only diacetyl but also other agents in some uncertain mixture, then the measure of diacetyl per se is probably smaller in terms of the magnitude of impact and leads to an impression that the diacetyl per se is more potent than it would be if it were alone. And if you follow that thinking, then the implication is that the limit being set on diacetyl is too low for diacetyl alone.

Now the problem is that, as you pointed

out, these are mixtures and the mixtures are somewhat uncharacterized and the mixtures are clearly harmful. And there is a need to do something.

And so the issue is either to model diacetyl alone or to be more encompassing in saying that what you are doing is diacetyl, the pentane-diketone and other flavorings, and make it a point that you are regulating the marker. Otherwise, there is a certain ambiguity as to what is being done. And if it is only the diacetyl which is labeled as the subject of your regulation or proposed guidelines, you will overregulate that one alone simply because it is not acting probably in most anthropocentric activities as a sole agent.

And I think that was his point and it concerned me looking at it from a risk assessment. I don't disagree with either the purpose or your incentive. And I raise this point only for the sake of clarity.

COMMANDER MCKERNAN: Thank you for your comment, Dr. Borak and we will carefully consider that as we move forward.

DR. EGILMAN: This is Dr. Egilman. Just a comment on that comment. You could say the same thing for asbestos because almost all of the studies studied asbestos in insulation products, which contained trymadite, cristobalite, this was heated and that is what gets produced, as well as silica and diatomaceous earth. They are mixtures. And in fact, there is better data for asbestos than there is here of a concomitant effect.

So I don't think there is a substantial enough body of evidence to show that any of the mixtures are worse than the diacetyl alone such that it should impact on the regulation and that is supported definitively, unless -- ChemRisk doesn't believe it causes bronchiolitis obliterans. Okay? But other than that and their willingness perhaps to participate in some

experiments, you are not going to get human data with diacetyl alone.

And so the only thing you can do is go to the animal data, which is where you get a pure exposure and you have got that. And this is, the enemy of the good is perfection.

And you are never going to get perfection. These are studies of human beings in real environments and nothing is ever going to perfect.

And if you demand more precision than is possible, which you haven't done yet, then you are never going to do anything. It is going to be worse than an 11-year delay. It will be an infinite delay.

So I don't think that that should stop you and I don't even think you really need to comment on that because there is no data. And if the industry wants to come forward with data on mixtures in animals, they can certainly do those studies. They have enough money to do those studies. They

haven't done it. They have more money than the government does to do those studies. It is their products and their responsibility to do them. And if they don't do them, I don't think they should come in here and say well our failure to do the right studies means that you can't regulate the product. That is nonsense.

One other comment, in terms of the warnings, which I missed completely, most of these, if not every other one I have looked at, these criteria documents have whole sections on MSDSs and warnings and educational programs for workers. And this one is missing. It needs to be included here in general but it is really serious here because the workers are being and the small ma and pa shops, everybody else is being misled by FDA's stand that says this stuff is safe. I mean, that is a big problem. You are going to need an interagency hubbub about that because the stuff is not safe to inhale. I think we can

all agree with that. Maybe not ChemRisk but everybody else. Okay? Whether it causes bronchiolitis or not, it is not safe to inhale and that has got to go on those boxes.

MR. SARGENT: I guess a comment to the comment to the comment. Ed Sargent. I will let go that the --

DR. LENTZ: Please identify yourself.

MR. SARGENT: Ed Sargent, Redstone Group. The hazard communication issues on this definitely aren't covered very well in this document at all. And there has been a lot of discussion about labeling and there are requirements under the Globally Harmonized System of Classification and Labeling Hazardous Chemicals, which has been adopted throughout the world, except for the United States and Canada. But there is a Notice of Proposed Rulemaking or -- no, Advanced Notice of Proposed Rulemaking for adoption under the OSHA Hazard Communications Standard. I think

OSHA has to hurry up on that but they haven't finished that yet.

But you ought to look at the GHS as well, not just HazCom because HazCom is probably going to be different down the line.

And you need to look at the cutoffs for percentages for various agents in terms of requirements for labeling and classification, those cutoffs. There are concentration cutoffs in mixtures and they depend upon the degree of hazard. And there are different cutoffs for different hazards. So you have cutoffs for sensitization, for irritation, for acute toxicity, etcetera. And I think you need to look at all of those in this document.

I think it would be very, very helpful to workers if you did that.

DR. LENTZ: Thank you. Your comments on the hazard communication and the GHS are especially well taken, especially given that OSHA is near completion of its hazard communication standard.

You have another question, Mr. Harnett?

MR. HARNETT: Peter Harnett. I am not going to comment on comments.

What I was curious about on the tox front is that I noticed the dosing was typically was around 100 parts per million and numbers like that.

Often with tox and testing of animals, humans, if we could do it, is that there is often a threshold below which you don't create a human health effect. And what I have noted has been done in the NIOSH REL draft is that the lower extrapolation has been done in a linear fashion, consistent with a radiomimetic model.

So there are other things that could be at play that toxicologists discuss, such as hormesis but I wonder if anyone has found disease at five parts per billion as an eight-hour exposure and 40 hours a week. It just seems uniquely low. And although it is

not NIOSH's purview or OSHA's purview, there will be a huge change in this the way business is done as homeowners realize, and again I don't have the sampling data to back this up, but that they are being exposed to say 25 ppb when they melt butter in multiple skillets in their home.

So if someone could react to that, I would be appreciative. I commend NIOSH in so much of the work that they have done but I do think that these numbers appear to be unusually conservative and lower than they should be.

COMMANDER MCKERNAN: Thank you very much for your comment. And if you do have any data, I hope that you consider putting it into the docket.

On behalf of the entire diacetyl, 2,3-pentanedione --

DR. EGILMAN: I have some data on that point.

COMMANDER MCKERNAN: Then please

submit it in the docket.

DR. EGILMAN: Okay.

COMMANDER MCKERNAN: I did want to mention on behalf of the team that we really enjoyed the exchange today. I think it has been a fruitful public meeting. You have given us a lot to think about, to seriously consider. We greatly appreciate all of the comments that were made.

I do want to remind folks that our docket will be open for public comment until October 14th and the team looks forward to those comments. We hope that you continue to review the criteria document and submit comments. I will turn it back over to our moderator.

DR. LENTZ: Okay. Thank you, Lauralynn. And I would like to acknowledge the efforts of the team, not only this morning and this afternoon in giving their presentations and responding to your issues, but also for the last several years, the

diligence that they have put forth on this effort to create this draft document.

This is an iterative process and certainly the public forum here to discuss with you the concerns and issues with this document is in fulfillment of our objective for transparency and part of our consistent review processes.

So again, we do appreciate this and our goal is to make this the best product that we can to provide the best guidance that can be of utility and based on sound science as well.

Again, this is only another step in our process. And as Lauralynn indicated, the docket will be open through October 14th. All of your comments will be compiled. Please submit them in writing, via any of the mechanisms that were described in the *Federal Register Notice*. Those comments again will be compiled, shared with the peer reviewers and the peer reviewers will have additional time

to review the document and provide their comments as well.

Each one of these comments will be taken very seriously and addressed in a companion document that I can't say whether it will be as large as the criteria document but in some cases they are. It is a companion document addressing all the comments. So that is a sizeable effort in itself.

So again, I would like to acknowledge the team. In the front two rows, too, we have many of the NIOSH senior staff members and other authors who contributed to this document. And there were countless others, too. But again, you as stakeholders play an important role in this, too. And we appreciate that role.

So with that, we will conclude this public meeting but continue the public review period through October 14th. Thank you.

(Applause.)

(Whereupon, at 2:48 p.m., the foregoing public

meeting was concluded.)