UNITED STATES FOOD AND DRUG ADMINISTRATION

Closer to Zero Action Plan: Impacts of Toxic Element Exposure and Nutrition at Different Crucial Developmental Stages for Babies and Young Children

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

MR. KAWCZYNSKI: Hello, and welcome to the Closer to Zero Impacts of Toxic Element Exposure and Nutrition at Different Crucial Developmental Stages." Hi. I'm Mike Kawczynski, and along with my co-moderator, Jessica, we will be running today's show. We have a great agenda.

So just a few little housekeeping maneuvers, this is a live event being broadcast all around the country and around the world. So if there is any technical issues that we do run into, you'll see us possibly jump in to address them. But outside of that, we expect this to run pretty, pretty smoothly.

But with that, I'm just going to hand it right off to my colleague, Jessica, to kick this off. Jessica, you ready?

GREETING AND HOUSEKEEPING ITEMS

MS. ROWDEN: Yes. Great. Thanks, Michael. As Michael mentioned, my name is Jessica Rowden, and I will be serving with Michael as co-moderator for today's meeting. Michael is behind the scenes ensuring a smooth moderation and I'll be working with

our moderators and presenters to keep us on track and on time so we can cover all of the great content that we have for today.

So just to reiterate the purpose of today's public meeting is to get stakeholder input regarding the plan scope. So we plan to discuss foods commonly consumed by babies and young children and the impacts of toxic element exposure to different crucial developmental stages and the interaction of the nutrients and nutrient status as co-exposures to toxic elements on growth and development.

So today's meeting is really meant to be the start of a conversation on these topics. We expect this meeting to be the first of several regarding the action plan. So we hope that you'll find the presentations and information shared today helpful and interesting and that this information can help to facilitate ongoing discussions.

So just a few quick notes before we get started. The agenda and all of the speaker biographies are posted on the FDA website. This meeting is being transcribed and also recorded, and we

will post that to the meeting website after the event. The recording should post within a week, and the transcript takes typically a little bit longer, so within the next few weeks.

So now I'd like to turn our program over to our host, Kellie Casavale. She's a senior nutrition advisor with the Office of Nutrition and Food Labeling here at FDA CFSAN. In addition to her work in that officer, she supports cross-center and cross-departmental collaborations, particularly related to the Dietary Guidelines for Americans and Maternal and Child Populations.

Kellie will also serve as one of our moderators later today during one of our panel sessions. So Kellie, I'll hand it over to you.

MEETING OVERVIEW

DR. CASAVALE: Thank you, Jessica. I'm Kellie Casavale, and it's my pleasure this morning to get to kick off the exciting agenda we have today. This morning we will have opening remarks from Dr. Janet Woodcock, Dr. Susan Mayne, Dr. Pamela Starke-Reed and Dr. Conrad Choiniere.

After our opening session, we will have two panels. Each panel will include four presentations followed by a moderated discussion. The first panel is on the impact of toxic element exposure at different crucial developmental stages for babies and young children, and it will be moderated by Ms. Karlyn Middleton.

Our second panel will bring perspectives on the role of nutrition in Closer to Zero, and I will moderate that panel discussion. Now we'll round out our day today with an open public comment session moderated by Ms. Jessica Rowden, who you had the pleasure of already meeting today.

Now without further ado, it's my delight to introduce Dr. Janet Woodcock. Dr. Woodcock began distinguished service to FDA in 1986 with the agency's Center for Biologic Evaluation and Research, and in 1994, Dr. Woodcock was named director of the FDA's Center for Drug Evaluation and Research, overseeing the center's work that is the world's gold standard for drug approval and safety. And after decades of contribution and a very distinguished public health

career, this past January Dr. Woodcock was named acting commissioner of food and drug.

Following Dr. Woodcock will be Dr. Susan Mayne, director of the Center for Food Safety and Applied Nutrition at FDA. Dr. Maybe leads the center's development and implementation of programs and policies related to the composition, quality, safety and labeling of food, food and color additives and cosmetics. CFSAN also oversees diet and health initiatives which include fostering the development of healthier foods and ensuring that consumers have access to accurate and useful information to make healthy food choices.

Following Dr. Mayne will be Dr. Pamela Starke-Reed from the Agricultural Research Service in USDA where she is the deputy administrator for nutrition, food safety and quality utilization of agricultural products. Dr. Starke-Reed previously served at the National Institutes of Health as deputy director of the Division of Nutrition Research Coordination and at the NIH National Institute on Aging as director of the Office of Nutrition. Notably

Dr. Starke-Reed has also previously been a biologist here at CFSAN.

And finally, I'm pleased to introduce Dr. Conrad Choiniere, the director of the Office of Analytics and Outreach at FDA CFSAN. Dr. Choiniere provides executive leadership for a broad portfolio of scientific and regulatory functions including risk and decision analysis, social and behavioral sciences, epidemiology, biostatistics and informatics, education and outreach and food defense. Dr. Choiniere chair's FDA's toxic elements working group which prioritizes the agency's efforts to reduce exposure to lead, arsenic and other heavy metals from foods to the greatest extent feasible.

Now I will turn the program over to Dr. Woodcock, with Drs. Mayne, Stark-Reed and Choiniere to follow. Dr. Woodcock?

OPENING REMARKS

DR. WOODCOCK: It's my great pleasure to welcome you to today's important public meeting on the FDA's Closer to Zero action plan and to express my gratitude that you're participating. Your input is

essential to our ability to develop and implement responsive and effective policies.

The Closer to Zero action plan sets forth the FDA's commitment to reduce exposure to toxic elements in foods that are commonly eaten by babies and young children to the lowest possible levels. It's long been an FDA priority to protect babies and young children from the harmful effects of contaminants such as lead and arsenic. We know they're especially susceptible to these dangers because of their smaller body size, metabolism and the fact that they're developing.

Our plan outlines a multiphase, science-based, iterative approach to achieving our goal of getting levels of toxic elements in foods closer to zero over time. The plan has several stages with both short- and long-term goals for achieving continued improvement. While we've already begun work on the plan, it's also important to note that the FDA's testing has shown there's no immediate health risk to children from exposure to toxic elements at the levels currently found in food.

Indeed the plan is designed to address the potential health concerns of toxic elements in foods but to do so while taking into account the environmental and other realities surrounding this issue. Those realities include that toxic elements that can be present in foods including arsenic, lead, cadmium and mercury occur in our air, water and soil and, as such, there are limits to how low these levels can be.

Our goal therefore is to reduce the levels of these substances in foods to the greatest extent possible while making sure that these changes do not inadvertently result in significant reductions in the availability of (indiscernible) rely upon for their children. In this regard, it's an issue and approach that aligns with and is reinforced by the FDA's important work on maternal and child health and nutrition which is another key priority of the agency.

We know that the impact of even small changes in nutrition security across the population can have enormous impact, especially when it involves mothers and their young children. that's why we're

working hard to help create more healthy food choices and foster innovation and competition to make these choices more accessible and provide consumers with the information to help them more easily adopt a healthier diet and lifestyle.

The action plan is also part of a broader effort being undertaken by the federal government to reduce exposures to toxic elements across the board. At the core of this effort is the president's taskforce on environmental health risks and safety risks to children which coordinates the federal government's efforts to explore, understand and act to improve children's environmental health.

A number of our sister agencies at HHS and across the government play an important role in this work. For instance, the CDC recently updated its blood lead reference value as part of its childhood lead poisoning prevention program which works to strengthen blood lead testing reporting and surveillance and connect exposed children to recommended services sand targeted population-based interventions.

In just a moment, you'll hear more details of this comprehensive plan from my colleagues. But first let me add one final important point, and that is one of the most important aspects of this plan is ensuring that we hear from all of you. It's essential we engage with a broad cross-section of stakeholders with different backgrounds and expertise. Contributions from stakeholders have already played a key role in developing policies that have led to meaningful reductions on exposure in lead and arsenic.

But we have more to learn. That's why today's public meeting is a critical component of this action plan. It's just the first of what we anticipate will be several public meetings on this critical topic and it's just one way that we will engage and collaborate with stakeholders to ensure that we hear a full range of experiences and opinions to inform our work and help us implement strong and effective policies.

I want to thank you again for your participation today. We look forward to your input and to working with you as we fulfill our mission to

deliver on the promise of science to protect and promote the health of the American public. Thanks very much.

DR. MAYNE: Thank you, and thanks to all of you for joining us today. As already mentioned, protecting one of our most vulnerable populations, babies and young children, is among the FDA's highest priorities. This isn't a new priority for us. This has long been an important issue for the FDA, and we have been continually taking actions.

This includes advancing research through developing methodologies to accurately test for levels of contaminants at increasingly lower levels, determining reference levels to estimate exposure and largescale surveillance of the food supply as well as taking regulatory action when levels are high. We have been working on this for decades and our previous actions in research monitoring, work with stakeholders and setting of action levels has resulted in significant progress in reducing children's exposure to lead and arsenic from foods.

Our work to reduce exposure to lead from

food began in the 1970s with efforts to reduce the use of lead solder in cans. Also lead in gasoline was phased out which was an important step as lead in gasoline contributed to significant levels of air pollution and contamination of crops. These two actions resulted in dramatic declines in lead exposure from food by the mid-1980s. Since then, the average daily dietary exposures to lead for one- to three-year-olds has decreased 97 percent from 43 micrograms a day in 1980 to 1 microgram a day 2014 to 2016.

For inorganic arsenic levels in infant rice cereal, the primary dietary source of inorganic arsenic for infants and toddlers, decreased 29 percent between 2012 and 2018. These levels started to decline even before we started to propose an action level. We began to see progress as we shared our testing data with stakeholders to make them aware of the issue and encouraged them to make improvements in their food products, and we saw further reductions in the period between issuing the draft and final action levels from 2016 to 2020.

Although these gains are significant, there

is more work to be done, and combining our efforts with stakeholders will create further meaningful reductions in exposure to toxic elements from food.

Ideally there would be no toxic elements in the foods eaten by babies and young children. In reality though, because these elements occur in our air, water and soil, there are practical constraints to how low these levels can be even when applying current best practices in mitigation techniques. Our goal of moving closer to zero reflects the reality that fruits, vegetables and grains do take up toxic elements in the environment as they grow.

It is crucial to ensure that measures we take to limit toxic elements in foods do not have unintended consequences like eliminating from the marketplace the nutritious, affordable foods that many families rely on for their children or increase costs in ways that could limit availability or that efforts to reduce the presence of one toxic element in a food inadvertently increase another.

Further we want to ensure that consumers aren't completely cutting out certain foods that are

rich in essential nutrients needed for proper growth and development to avoid already low levels of toxic elements in food. For this reason, we are providing consumer education on reducing toxic element exposure through a varied diet. For example although we have set action levels of inorganic arsenic in rice cereals and have recently worked with certain manufacturers to issue recalls, fortified infant cereal is an important source of iron.

We therefore combine our research and regulatory efforts with information for consumers on how to reduce exposure to arsenic through varying grain-based infant cereals to ensure an adequate iron intake for their babies and young children.

This is why we need the Closer to Zero action plan. The plan will help us move closer to zero exposure to toxic elements from foods by taking significant steps to help reduce the levels of arsenic, lead, cadmium and mercury in foods commonly eaten by babies and young children to the greatest extent possible and providing advice to consumers about what they can do to provide children a diet that

promotes and supports healthy development.

This plan builds on the progress we have made to date and outlines a science-based, iterative approach to achieving our goal. The plan includes advancing research and evaluating changes in dietary exposure to toxic elements, setting action levels with input from stakeholders, encouraging industry to adopt best practices to lower levels of toxic elements in agricultural commodities and products and monitoring the progress of levels of toxic elements in foods over time.

This plan also highlights our commitment to ongoing compliance and enforcement activities such as FDA's monitoring of the food supply by testing of baby foods and inspections to ensure that manufacturers meet their requirements under the Federal Food, Drug and Cosmetic Act.

Reducing levels of toxic elements in foods is complicated and multifaceted. Our stakeholders, including parents and consumer advocacy groups, public health professionals, the food industry, regulatory partners, academia and other stakeholders are all

vital to our efforts and we are committed to engaging with you throughout the process.

We plan to have more opportunities for active participation and collaboration in the future throughout this process. Today's meeting is just the first of these opportunities where we will discuss the regulatory and scientific issues that must be addressed for successful implementation of Closer to Zero.

Unfortunately we can't just immediately remove toxic elements out of foods. But we have seen that with scientific advances, environmental policy shifts and partnering and collaboration with stakeholders and consumer research, significant reductions have been, can be and will continue to be made.

Thank you for your time today. With that, I will turn it over to Dr. Pamela Starke-Reed from USDA's Agricultural Research Service for her remarks.

DR. STARKE-REED: Good morning. Thank you for the kind introduction and the opportunity to share USDA's contributions to addressing this important

public health goal. The USDA greatly appreciates FDA's collaborative approach to reducing exposure to toxic elements from foods.

I am Pam Starke-Reed. I'm the deputy administrator at USDA's Agricultural Research Service, ARS for short. I oversee nutrition, food safety and product quality new uses program areas. I am also the USDA science team lead for our food and nutrition priorities.

At USDA, we welcome FDA's leadership on the Closer to Zero initiative that will be discussed today, and we look forward to partnering with FDA on this vital effort.

USDA is focused on ensuring all Americans have consistent access to the safe, nutritious, affordable food essential for health and that U.S. farmers, ranchers and foresters have the tools, information and support they need to produce a safe (indiscernible) and abundant food supply.

All agricultural production starts with processes that, even in organic production systems, can result in the uptake of harmful substances such as

cyanide, heavy metals and arsenic into crops, plants or livestock. Changing agricultural and food processing systems may reduce this uptake. But it will never be completely eliminated with this approach alone.

To get closer to zero, an entire change to the food system approach that includes looking at soil, planted crops and entire ecosystem intersection is essential.

FDA's Closer to Zero initiative will provide the critical framework that must be done to reduce the content of heavy metals in all our foods, but particularly in foods consumed by infants and children, our most vulnerable group. There are many components included in these efforts and FDA has provided a clear roadmap that contains four steps: evaluate, propose, consult, finalize.

USDA has a wealth of expertise we can share with FDA to advance the first step, evaluation. We can provide the research, scientific findings and consumer communications FDA needs for developing regulations that will mitigate the risk of hazards of

heavy metals in foods and food products.

Several USDA agencies will be contributing to these efforts. The Agricultural Research Service, USDA's largest in-house scientific research agency, can conduct research to understand the risk of consuming toxic elements within the context of a healthy diet.

At ARS, we study how plants uptake heavy metals from the soil, from the cellular metabolism of plants to entire production systems so that we can find ways to mitigate heavy metals in foods to the greatest extent possible.

We also study the health risks of food contaminants within the overall matrix of the diet and food. Absorption of heavy metals in the human body is linked to a range of factors that affect their accessibility and transport and potential interactions and effects can depend on individual health factors that vary from person to person.

Right now there is limited research on these issues and well-designed studies are essential for developing risk/benefit assessments and mitigation

strategies for everyone in our society.

In ARS, these challenges give us opportunity for conducting research in plant and animal genetics, breeding and production management and finding new strategies and information that will help breeders, producers and consumers reduce the risk of consuming toxic elements.

USDA's National Institute for Food and Agriculture, or NIFA, which supports USDA's external scientific research conducted through our nation's land grant universities and other organizations, will also provide critical support for Closer to Zero efforts.

NIFA has a vast partner and stakeholder network that can collaborate in developing and disseminating targeted communications on how pregnant women, nursing mothers, infants and young children can reduce their exposure to toxic elements in food.

Its investments in agricultural research, education and extension can also be leveraged to develop data-driven approaches which reduce toxic elements in the production of critical food products.

Communication experts can design messaging that will not result in unintended consequences such as eliminating foods that have significant nutritional benefits or reducing one toxic element in a diet while increasing another.

NIFA's expanded food and nutrition education program, the first U.S. nutrition education program for low-income populations, and other partnerships with land grant universities and cooperative extension agencies will enhance its effectiveness in developing culturally and contextually appropriate messaging.

These messages will emphasize the benefits and risks of eating certain foods during critical life stages and how to reduce the risk associated with their consumption.

The USDA's Food Safety Inspection Service, or FSIS, will be another critical Closer to Zero partner. FSIS's mission is to ensure that the food supply is safe and nutritious, whether it is produced in the United States or imported from international trade partners. FSIS already monitors meat, poultry and egg products for metals and other environmental

contaminants.

As Closer to Zero expands its focus, FSIS will be providing essential oversight for assessing potential metal contamination in meat, poultry and egg products and will continue to coordinate closely with FDA if elevated levels of a concerning substance are detected in these foods.

This will ensure that new guidance and regulations that result from Closer to Zero activities are maintained and do what they are intended to do, protect the health of U.S. consumers of all ages.

Finally USDA's Food and Nutrition Service, or FNS, provides leadership in ensuring that children and low-income people have access to nutritious food and information that can guide healthy food choices. FNS recognizes that heavy metals in food is a concern to people who depend on federal nutrition assistance programs to feed their families.

As part of their overall mission, FNS encourages consumers to follow a healthy dietary pattern which is important at every stage of life and can have positive cumulative effects. The benefit of

a balanced diet can help maintain any adverse effects from consuming an excess of any one food regardless of whether the food contains unsafe contaminants.

As the work in Closer to Zero advances, FNS will continue to coordinate with its FDA partner to ensure that USDA nutrition assistance programs, policies, guidance and education are informed by current food safety regulations and guidance. These activities will play a vital role in Closer to Zero's endeavors to help consumers reduce their risk of consuming food contaminated with metals.

This is the first of several meetings to obtain stakeholder input in Closer to Zero's plans and progress. A second stakeholder public meeting is planned in the early spring on food production chain and delivery programs.

In conclusion, let me say I think the time is right to tackle these hard and complex issues and find resolutions that will enhance consumer safety and confidence in the U.S. food supply.

USDA is looking forward to building on our existing strong and effective collaborations with FDA

and other partners to find and implement solutions to ensure a safe, healthy, equitable, accessible and economical food supply for everyone in the United States. Thank you very much.

SETTING THE STAGE: THE CLOSER TO ZERO ACTION PLAN

DR. CHOINIERE: Thank you, and hello. My name is Conrad Choiniere. I am at the Center for Food Safety and Applied Nutrition, where I direct the Office of Analytics and Outreach and help spearhead the agency's efforts to reduce lead and other toxic elements in the food supply, and welcome to our first public meeting to discuss issues related to our Closer to Zero action plan.

In April of this year, we released Closer to Zero, our plan for reducing exposures to contaminants such as lead and arsenic from foods from babies and young children.

Although it will be difficult, if not impossible, to get to a point of zero exposure, we believe there are steps we can take to reduce levels of contaminants in foods and thereby reduce exposures among the very young.

Through a cycle of continual improvement, we will evaluate the science related to exposures and impacts on development, establish levels for contaminants that can help reduce exposure from foods and work with industry and other stakeholders to identify and implement best practices for managing and reducing levels of contaminants, all while actively monitoring to ensure compliance and assess progress.

From our data, which I'll share with you in a moment, it's clear there isn't one single food or food group we can point to that results in exposure to these contaminants. In general the level of each of these contaminants in any single food is low.

However overall exposure adds up because many of the foods we eat contain these contaminants in small amounts. This is not to say that we should not be concerned. On the contrary, for the contaminants we are discussing today, we have not identified safe levels of exposure for developmental outcomes.

Contaminants such as lead and arsenic, cadmium and mercury are in our air, water and soil. Fruits, vegetables and grains rely on the air, water

and soil to grow and to take in nutrients. But as they take up nutrients, they also take up contaminants. As a result, many of the nutritious foods that we eat and that we feed our children contain some lead, arsenic, cadmium and mercury.

But we want our children to eat a variety of nutritious foods because, as we all know, good nutrition has an important role for ensuring proper development, and that's why we're here today, to talk about the crucial points in children's development where exposure to contaminants and nutrition have greatest impacts on healthy development.

Since we announced Closer to Zero, we received numerous questions related to the scope of the plan. The title of the plan itself includes the term baby foods. But in the description of the plan, we use the term foods consumed by babies and young children. So what ages should we be targeting and what foods?

To answer those questions, we need to better describe the term baby food, especially when talking about exposure to lead, arsenic and other toxic

elements and their impacts on developing brains and other organs and systems.

For many of us, when we hear the term baby food, we think of those foods in the jars, those foods that are marketed for babies, marketed for infants or labeled for infants. But many of us know, those of us who've been around babies, our kids, our grandkids, siblings, cousins, we see that they eat more than those foods that come in specially labeled jars.

What are babies and young children eating? In the next few slides, I will share data taken from "What We Eat in America," the dietary intake component of the National Health and Nutrition Examination Survey, which is commonly referred to as NHANES.

This study is conducted as a partnership between the U.S. Department of Agriculture and the Department of Health and Human Services. The study collects data from a representative sample of the U.S. population about what they have consumed in a two-day period and it provides useful information about what we are eating and what we are feeding our children.

This bar chart shows an analysis of that

"What We Eat in America" data of the food groups and total daily food intake for babies or infants, those that are less than one year old. Our analysis focused specifically on infants and young children who did not consume any human milk in that two-day period where they completed the study.

We focused on these children in particular because we were doing an exposure assessment we published in 2018, and we don't have levels of contaminants in human milk. So we excluded those infants that consumed human milk from our analysis.

Nonetheless, the data that I show here includes 69 percent of those that were less than one year old at the time of the survey, and among those, 87.7 percent of the total dietary impact is from food marketed for infants. This includes those jarred baby foods but it also includes infant formula.

Broken down further, 12.3 percent comes from the jarred foods or packaged foods and 75.4 percent from infant formula. Other food categories such as beverages, dairy, fruits, vegetables, they make up a much smaller portion of the total diet at this age.

As we look to the one- to two-year-olds, we see that foods marketed for infants make up only 3.3 percent of total dietary intake.

At this stage, children start to consume a wider variety of foods such as beverages which includes bottled water, dairy, which includes cow's milk and cheese and other dairy products, fruits, which includes fruit juices, grains such as bread and baked goods and vegetables, which also includes juices.

For the three- to four-year-olds, the foods marketed for infants, babies make up even less of the total dietary intake, only 0.4 percent. Intake of mixtures which are entrees that contain a little bit of meat, grains, vegetables such as pizza or tacos make up a large percentage of the diet.

So now that we've looked at what children consume, we need to ask ourselves, well, what foods are contributing to exposure to the contaminants we're talking about today such as lead. To answer that question, we relied on our Total Diet study.

The Total Diet study is a study that FDA has

been conducting since the 1960s. It has evolved over the decades. But a key goal of the study is to assess levels of nutrients and contaminants in a representative sample of the U.S. food supply. Our current Total Diet study collects samples in grocery stores from regions across the United States at different times of the year over a two-year period.

We prepare the samples and then analyze them to assess levels of contaminants as well as other analytes. Knowing whether a contaminant like lead is present in a food or not and knowing the levels of lead in a food is not sufficient for us to understand the risk from consuming that food. We must take that information and combine it with information from other sources about how much of a food is eaten and then we can fully understand exposure.

In the next few slides, I will share some information from an exposure assessment we completed in 2018 where we used data from the Total Diet study and we combined it with the intake data that we just showed you from "What We Eat in America." We were then able to estimate lead exposure from foods

consumed by babies and young children.

For babies less than one year old, and remember we are excluding those that did not consume human milk, we found that 83.3 percent of dietary lead exposure comes from foods marketed for infants, those packaged baby foods as well as infant formula.

In this category, the breakdown is 47.3 percent of lead comes from the packaged foods and 36 percent of lead comes from infant formula. The other food categories make up a much smaller portion of the diet and also a much smaller portion of total lead exposure.

For one- to two-year-olds, we see that baby food, those packaged as baby food or marketed for babies, and infant formula contributes 5.3 percent of lead exposure. At this stage, children consume less than those types of foods and start to consume a wider variety of foods. Thus those other categories contribute to a greater percentage of lead exposure.

And for three- to four-year-olds, again we see that lead exposures are coming from grains, fruits, including fruit juices, dairy and mixtures,

and this includes, as I mentioned before, foods like pizza and tacos. And this is mainly due to a higher consumption of foods in these food groups.

The food categories concerning most of the lead exposure for older children, those that are not shown on the slide here, those that are five to six years old and seven to 17 years old, continue to be dairy, fruits, grains and mixtures. The contribution to lead exposure from mixtures and grains increases with age and the contribution from fruits deceases with age.

In general our Total Diet study data show that most foods do not contain detectable levels of the contaminants we are discussing today. For example of the nearly 3,000 Total Diet study samples used in this analysis, almost three-quarters of them had levels of lead below our ability to detect lead.

However the key sources of lead exposure are not necessarily the foods or food categories with the highest lead concentrations. In most cases, the key sources of exposure are the foods with the highest levels of consumption. For children older than one

year, the food categories contributing most to lead exposure are grains, fruits, dairy and mixtures.

But when we tested foods within those categories such as milk, yogurt, fruit juices, white bread and tacos, we found levels that were below five parts per billion. So they have low levels of lead but they are important sources of lead exposure due to high consumption.

So when thinking about exposure to lead, it's important to put it into context by comparing that level of exposure to some reference value. For lead and developmental outcomes, as I mentioned earlier, we have not identified a safe level, a safe level that we can use as a reference. There's no what we call toxicological reference value.

However FDA has developed an interim reference level for lead exposure from food. It's not a safe level of exposure. But it's a level that we developed that's based on CDC's reference value for identifying children with elevated blood lead levels.

To arrive at our interim reference level, FDA estimated the amount of lead that would need to be

ingested through food that would result in reaching CDC's blood lead reference level. FDA then applied additional safety and uncertainty factors to arrive at a level of lead exposure that could have a contribution to elevated blood lead levels.

From our estimates, most children's exposure to lead from their overall diet do not exceed the interim reference level. However we are aware that for some children in the study, lead exposure from food over that two-day period may have contributed to elevated blood lead levels.

The Dietary Guidelines for Americans provides recommendations for the American diet. It's a cornerstone of nutrition policy and it's based on robust science. The most recent edition was published in December of last year and it includes advice for those under the age of two years old, and this is the first time it's done that since the 1980s.

Recommendations for children mirror the advice from the five food groups for adults with some key differences that account for the importance of nutrients for child development. A challenge is

achieving those nutrient requirements within the limited calorie needs of young children.

At first, infants eat only a few calories from foods other than human milk or infant formula. And it takes time for the amount and variety of foods to build up to a complete diet. Children require a wide variety of food with a focus on food sources of nutrients essential to growth like iron and zinc.

Currently many children between the ages of one and two years old overconsume refined grains and under-consume whole grains. They should consume more vegetables, more whole fruit and less fruit juice. They should consume more seafood in place of meat and poultry. However foods that provide nutrients can also be sources of contaminants.

The process for uptake of nutrients in grains, vegetables and fruits is similar to the uptake of contaminants from the air and water and soil. So we should think holistically here. Exposures to nutrients and contaminants are not happening in isolation. They are happening in combination both in individual foods and across the combinations of foods

eaten over time. That's why nutrition is a key factor in our Closer to Zero plan.

While nutrients support growth, contaminants can work in the opposite direction. So understanding the interplay of nutrients and contaminants can help us address the impacts of exposures.

Nutrition is not only about the food. It's also about the nutrient status of the individual. Children without adequate body stores of nutrients can be at a greater risk of harm from lead, arsenic and cadmium and mercury exposures.

Fortunately the opposite is also true. Children with adequate nutrient status and physiologically better prepared to ward off effects of these contaminants and we will hear more about these issues today from our panelists.

Now although this Closer to Zero action plan is prioritizing babies and young children, we know that the health impacts from these exposures are not limited to these subpopulations.

The agency is working to reduce toxic element exposure for all ages and protect all

consumers from associated health risks including neurological effects, cancer and other chronic diseases.

Today our goal is to share data, information and perspectives to help inform our decisions related to the scope of Closer to Zero. What factors related to development and nutrition we should consider when identifying appropriate actions and action levels for foods.

We have brought together experts in toxicology and nutrition to hear from them about issues related to exposure to toxic elements and nutrition at crucial ages of development that can help us prioritize our efforts and inform the development of our plan moving forward.

Thank you again for your participation in our public meeting today, and I look forward to the discussion.

(Break)

MR. KAWCZYNSKI: All right. Welcome back from break. We are now going to go to Session 1, "The Impact of Toxic Element Exposures at Different Crucial

Developmental Stages for Babies and Young Children." Our moderator for this session is Karlyn Middleton. Karlyn, let's take it away.

PANEL 1: THE IMPACT OF TOXIC ELEMENT EXPOSURE AT DIFFERENT CRUCIAL DEVELOPMENTAL STAGES FOR BABIES AND YOUNG CHILDREN

MS. MIDDLETON: Good morning. I am Karlyn Middleton. I am a toxicologist and the chief of the Contaminant Assessment Branch in the Division of Risk and Decision Analysis, Office of Analytics and Outreach at FDA's Center for Food Safety and Applied Nutrition.

I'm very excited to moderate this morning's Panel 1 discussion which is focused on the impact of toxic element exposure at different crucial developmental stages for babies and young children.

FDA would like to understand how babies and young children are exposed to these toxic elements, specifically arsenic, cadmium, lead and mercury, and how exposure to these toxic elements affect development. This information will be important when considering action levels for foods consumed by babies

and young children.

As a reminder, the purpose of today's public meeting is to engage with stakeholders like yourselves and invite input on various topics pertaining to FDA's Closer to Zero action plan. We encourage you to submit any written comments to the docket, and if you have any questions, please submit them to the email address closer2zero@fda.hhs.gov.

So for this session we are fortunate to have with us four very accomplished panel members. Each member will give a ten-minute presentation and then the presentations will be followed by a moderated question-and-answer portion.

So the Panel 1 members are Dr. Laura Dishaw, toxicologist at the U.S. Environmental Protection Agency; Dr. Sean Deoni, director of MRI research, Department of Pediatrics, Memorial Hospital of Rhode Island; Dr. Margaret Karagas, professor and chair, Department of Epidemiology, Geisel School of Medicine at Dartmouth; and Dr. Jennifer Lowry Sample, pediatrician with PediaTox, LLC.

So our first speaker is going to be Dr.

Laura Dishaw. She will be discussing windows of sensitivity during development. Dr. Dishaw is an EPA toxicologist in the Center for Public Health and Environmental Assessment, or CPHEA. Her work focuses on developing human health assessment products including integrated risk and information systems and integrated science assessments. She's also involved in development and implementation of systematic review tools and processes within CPHEA.

She received a BS in biology from Le Moyne College and a PhD in environmental toxicology from Duke University where she studied the toxicity of organophosphate flame retardants. So welcome, Dr. Dishaw.

DR. DISHAW: Thank you. So today I'll be talking to you about windows of sensitivity during development. My hope with this talk is that I can give some background and introduction that will provide some more context for the later speakers that we have today.

So as Karlyn indicated, I'm from -- I work for the EPA in the Center for Public Health and

Environmental Assistance and the views expressed in this presentation are mine and do not necessarily represent the views or policies of the agency. So I do not have any disclosures at this time.

So first I'm going to give an overview of development, this complex set of processes, the rapid changes happening over a relatively short amount of time and the coordination of the timing and the location of these changes is very important to ensure that development occurs normally. So the figure below is showing a timeline of the nervous system which I'm using as an example of developmental processes and the complexity. But the general idea applies to other organs and systems.

So one of the first things I wanted to point out, and it's part of the reason why I picked the nervous system, is to look at the timeline. So here it starts at the very beginning, at fertilization. But it's a very extended process and actually development continues -- of the central nervous system continues into early adulthood.

So while we often can think of development

as being kind of limited to gestation or early postnatal development, it can -- it's not always just limited to that time period. So early on we have a rapid proliferation of cells. These -- in the central nervous system, these cells will begin to migrate to where they eventually want to be, and once they reach that point, they'll start to differentiate into specific cell types that have a very specific purpose.

Nerve cells will start to form complex junctions with neighboring nerve cells, and these junctions are called synapses which are important for transmitting nerve signals throughout the nervous system and then the myelin cells provide support and act as insulation almost for nerve cell conduction.

There's also programmed cell death. So actually during early development you produce more cells than you need. And then as development occurs, there's a normal programmed cell death or pruning of these cells to form connections, and these are very important for the function of the nervous system.

So developmental toxicity happens when exposure to a toxin disrupts normal developmental

processes. The disruption can result in death, changes in growth, something like an unusually small or unusually large baby, structural changes such as birth defects and functional changes which are just everything may look normal, but when in terms of function things have changed. And these often will -- may not be apparent until there's some sort of challenge to the function. An example of a functional change might be something like a learning disability or deficits in memory, things like that.

So it's important to remember that, depending on the timing, multiple systems can be affected by a single exposure just because of the complexity of what's happening during development, especially for early development when there's so much going on. But there is potential for widespread effects of an exposure. It's also important to remember that, particularly with functional effects, adverse changes in development may not be apparent until later in life.

So other aspects that are somewhat unique to development is that children are not small adults. So

there are a number of differences that can make it so that even given the same environment as an adult, children may have higher exposures to something that's present in their environment.

So there are differences in behavior, in etiology that can affect their level of exposure. Behavioral differences, the two pictures on the right are of my daughter when she was about one year old and her demonstrating some of these behavioral differences.

So hand-to-mouth behaviors, anything who's been around a young child knows that they love to stick everything in their mouths. It doesn't really matter what it is. It can be hands. It can be toys. It can be old Cheerios that they found under the couch. This is all actually very normal behavior in young children and it's one of the ways that they kind of learn and explore their environment. But it can increase their exposure to things.

There's also a condition called pica that can happen with older kids that are past that normal age of exploration with their mouths where there's

intentional ingestion of nondietary items which can also affect exposure to things.

There's also physiological differences. Children have higher ingestion -- when you control for body weight, children have higher ingestion of food and water, higher rate of respiration and higher surface-to-body ratio, and all of these things can mean whatever's in their environment, they could have higher exposures.

There's also differences in how they may uptake, absorb, metabolize or excrete things. Two examples are just the gastrointestinal tract and the blood brain barrier are more permeable in young children. With ingested lead, children have a four to five times greater absorption when compared to adults.

There's also potential for indirect exposure with transfer from the mother via placenta, so exposure, if the mother is exposed to something, it could have an indirect exposure to the child in-utero or if the mother breastfeeds, that could be transferred through breast milk. And depending on how long, how persistent something is in the body, it can

have -- the exposure doesn't have to happen when the mother is pregnant or breastfeeding.

We also have -- so now going on to windows of sensitivity, these really are just period of time that biological processes are particularly prone to being affected by environmental influences. And so if an exposure occurs during a window of sensitivity, there's an increased risk for an adverse outcome. And these can result in adverse outcomes to shorter exposure or to levels of a particular toxicant.

The figure to the right shows some of the general windows of sensitivity during gestational development. Remember that although, you know, I'm using this as an example, it's not limited necessarily to gestation. And as you can see, there are -- all the major organs and systems are affected. And depending on when the exposure occurs, there's potential for more than one system to be affected.

So the timing of exposure can affect the types of adverse outcomes as well. In this figure we see the yellow bar on the left. That's usually associated if something happens then, it's more so

associated with the death of the embryo. The red bar shows the time there's higher risk for major structural changes, like major birth defects because this is when the structures tend to be developing whereas the fuchsia bar shows where there's likely to be more minor or structural or functional changes. So understanding the critical windows is very important for understanding the critical life stages for a given toxicant and how to develop strategies for risk mitigation.

And lastly, just a quick thing on how they're identified, it can be difficult. Because of the multiple and overlapping windows of sensitivity, it can be hard to nail things down. Also within humans, we often have limited information on exposure timing from epidemiological studies, a potential for confounding because we are exposed to a lot of things in our environment.

There's also variability within and across species. So animal studies are helpful because it controls the timing, frequency and duration but doesn't necessarily directly translate to humans. And

within a human population, there can be variability. And so thank you for your time.

MS. MIDDLETON: Thank you, Dr. Dishaw. Our next speaker is Dr. Sean Deoni, who will discuss environmental influences on early child brain development.

Dr. Deoni is an MRI physicist by training and director of MRI research, Department of Pediatrics at Memorial Hospital of Rhode Island. Dr. Deoni obtained his PhD in physics and medical biophysics from the University of Western Ontario and was a doctoral fellow at the Center for Neuroimaging Sciences, King's College, London and Oxford University.

Over the past decade, Dr. Deoni has built one of the largest pediatric neuroimaging research programs in the world focused on understanding how genomics and environmental factors including infant nutrition, sleep, activity, social equity shape easy brain development.

This work extends around the globe with active studies throughout the USA, North America,

Africa and Southeast Asia. The goal of this work is to improve the neurodevelopment outcomes in all children. Welcome, Dr. Deoni.

DR. DEONI: Great. Thank you. Thank you very much, and thanks again to Dr. Dishaw for that really great introduction.

So I'm going to kind of build on that in a little way and really kind of dive into some of the neurodevelopmental aspects that Dr. Dishaw kind of laid out introduction there.

But before we kind of delve into the real data, I just want to sort of start off by really grounding us a little bit. We talk a lot, and we hear a lot about the first thousand days of development and how that first -- that early period of life is so fundamental in sort of setting off trajectories of overall health that will set us up for the remainder of our lives.

But what does that really mean? And so I like starting off with this picture which is really the postnatal portion of the first thousand days. This is my older son, Stephon, who is just welcoming

home his newborn sister. And my son was about two years of age when he welcomed home Neela.

So this is that first postnatal portion of those first thousand days, right, the first two years of life. And you can think about the amazing things, you know, that Dr. Dishaw just sort of talked about in terms of development that's going to happen over this time period, right? She's going to learn to crawl, take her first steps, take her first words, make new friends, learn how to manipulate her brother to get whatever she wants, learn how to manipulate her parents to get whatever she wants. So amazing, amazing things are going to happen behaviorally and cognitively over the next two years as she grows up to be like her old brother in this photo.

And so as a neuroimaging scientist, we're really interested in what's going on perhaps under the hood, as it were, in terms of brain development. And so just as a qualitative example, this is actually images of my daughter Neela across those first two years of life from three months of age up until age two.

And what you can see is there's a tremendous change in overall brain structure and appearance, right, and that's not surprising given again those behavioral and qualitative changes that we've seen.

So for example, you know, looking at the cortex or around the surface of the brain, the outer portions of the brain, you can see how that's become far more convolved and convoluted as well as the neural density has increased. Certainly you can see the volume has changed. It's gone up to about 80 -- increased by about three times, 300 percent, reaching about 80 percent of the adult level volume.

But we also see just that appearance of the white matter, that bright stuff in the center. And all that kind of relates back to that picture that Dr. Dishaw showed you of those neurodevelopmental and neural and chemical processes. That white matter is really driving that myelination that she was talking about. And these are important and critical functions of development.

And this sort of draws again on that same slide, but now getting a sense of those processes as

they occur over those first two, in this case, out to three and four years of age. What you can see is that those major brain developmental processes are reaching their peak and almost reaching adult levels by that age two or three, right, so those first thousand days.

You're reaching about 90 percent of your overall myelination. Your cortical maturation is at about 80 percent of adult level volumes. Your total brain volume is about between 80 and 90 percent of adult brain volumes at that end of age two.

And so when you think about developmental -- critical developmental period, this is what drives that, right, the idea that we have a lot of change happening over those first two years of life and this is thus a very critical window for intervening or indeed a very sensitive window for environmental impacts.

And not only is that true on a structural level, which we're showing here, but we can look at that also with respect to functional maturation. So these are now looking at functional networks within your brain that again start off very isolated and

discrete as a neonate, as a newborn but become more convolved, integrated and interdigitated as we get older. And that's really what's driving all of those behavioral changes, those cognitive changes that we see in children. And again these are sensitive to those structural changes that we were just talking about.

And these occur in a very standardized and specific way. We have sort of these core brain networks and center brain regions, your brain stem, your spinal cord, your cerebellum that begin to develop.

Then that moves on into your ability to understand and integrate receptive language, hear language and understand it, your fine motor control, your gross motor control, your ability to speak as well as your ability to integrate visual functioning. so these are all kind of sequenced across those first two years of life and come on in sequence. And so impacting those early brain maturing networks, that core network will have knock-on effects as we go along.

And so now thinking about how does that child learn and grow within their environment, each of these aspects are critical for driving these individual changes.

So be it your in-utero environment, your postnatal environment, be it breastfeeding and early nutrition as well as air quality and environmental exposures to heavy metals, et cetera, that will be talked about throughout today.

But really kind of diving into this now with that sort of understanding that this early period, these first thousand days are such a critical period of early brain development, such a rapid period of early development and therefore sensitive period of early brain development, we can begin to look at things like, for example, the impact of nutrition.

And so this is looking -- doing a pretty largescale study of about 500 kids that have been followed from birth, in this case, up until about age five or six matched for as many of those socioeconomic demographic and social demographic characteristics that we could get our hands on, but really looking at

the impact of early nutrition, be it exclusive breastfeeding, so this is breastfeeding out from birth until at least three months of age and then different types of formula.

Normally we would only look at a single type of formula and do a comparison back to, say, breastfeeding. This is actually breaking this down into the three main formula brands, the three major formula brands and you can see it's sort of a systematic change in that early myelination pattern, so thinking back the importance of myelin that Dr. Dishaw was mentioning and that we saw in those images, that qualitative white matter development all being impacted by the early nutrition over those first three months that have long-term impacts.

And not only is it impacting brain development, but indeed if we look at cognitive development, so this is looking at cognitive scores or maturation scores in terms of overall cognition, say analogous to IQ in an older individual but also looking at verbal functioning and nonverbal functioning, we can see that there are significant

differences, and they relate back to those brain maturation differences.

So those early nutritional needs not being met, for example, by some of the formulars or not necessarily being fully met leading to long scale both brain maturation changes but then having knock-on effects into cognitive changes.

And just for reference here, what we'd really like to see is that an average child on here would have a value of about a hundred as they go out in age with a standard deviation of 15. So children between 115 and about 85 would be considered typically developing.

So we can see that some of these formulas are not quite achieving that. And perhaps most depressing and distressing is that this green formula, this formula number one, and I do apologize for the spelling error here, but that's actually the formula that is part of the WIC program in Rhode Island. So those sensitive children that are already facing some other forms of adversity now also receiving adversity from a nutritional aspect as well. So that's kind of

looking again at nutrition.

We can also look at, for example, the impact of environmental exposures and in this case looking at lead exposure, looking at the differences between both high lead, so the former threshold for lead exposure in Rhode Island, that's at the five to ten milligram per decaliter level, but then even looking at children with low lead exposure.

And you can see as we go along that there is very much a dose-dependent effect from no exposure to sort of an elevated exposure, that one to five microliters up to that sort of higher lead level. And again those early changes over the first year or so really having a knock-on effect to that overall cognitive development as well as being significant as we follow these kiddoes out and so recognizing there that these changes, although they are happening early on, are having prolonged, persistent and consistent effects into later childhood. So they're not sort of normalizing with age, as it were.

This is becoming a real problem over the last couple of years as we've entered into the COVID

pandemic and a lot of challenges have been faced by parents both with respect to early nutrition as well as home and housing status.

And for example just looking at trends over our own studies over the past decade, we see that things are kind of normalized in, as I say, sort of that hundred plus or minus 15 level. But when we look at children over the last year, we start seeing them drop down rather significantly.

This is all children from about zero to three years of age, if we focus in specifically on the children who were born during the pandemic and therefore are more sensitive to those nutritional needs or those early environmental exposures, you can see that hat last dot there just being well outside of the norm, looking at about a 33-point drop. And so that's pretty significant when you're talking about child development. You'd be hard-pressed to find an impact of that magnitude elsewhere.

So again kind of reiterating the impact that these -- the insecurity and the environmental changes that have occurred over the last 15 to 18 months is

having on these children and again emphasizing that this is predominately in those really younger kids, those children under two years of age.

So again kind of bringing home some of the same points that Dr. Dishaw made that the first thousand days of life are a period of very rapid and therefore sensitive development, but that they do lay the foundation for lifelong patterns. And so alterations early on are going to lead to larger scale alterations later on. It's kind of misaligning your satellite dish. A small difference at your house is going to have a large difference in space.

Certainly the plasticity and environmental sensitivity of the developing brain is a double-edged sword. So it allows us to change things but it also makes you very sensitive and those early delays that we have may not show up until several years later, again a point that Dr. Dishaw was making. And all of this coming back to that exposure of those heavy metals, poor water quality, poor air quality, suboptimal, et cetera, all having an impact on those fundamental processes.

So with that, I'll hand off. But thank you very much.

MS. MIDDLETON: All right. Thank you, Dr. Deoni. Our next speaker is Dr. Margaret Karagas, who will discuss work done in the New Hampshire Birth Cohort Study describing early diet and association between diet and biomarkers of metal, metalloid exposure in the first year of life.

Dr. Karagas is the James W. Squires professor and founding chair of the Department of Epidemiology at the Geisel School of Medicine at Dartmouth College. She currently leads an ongoing New Hampshire birth cohort study of over 2,500 maternal-child dyads whose households are served by a private, unregulated water system in New Hampshire, a rural state with elevated drinking water arsenic.

Through the study, she and colleagues have identified the importance of diet as a primary exposure route for arsenic, in particular rice and rice products commonly served to infants and young children, as well as the impacts of trace elements including toxic metals and metalloids and nutrient

elements alone or as mixtures on child growth, neurodevelopment and immune function. She received her PhD from the University of Washington. Welcome, Dr. Karagas.

DR. KARAGAS: Thank you so much. It's a pleasure to be here, and I just want to thank the meeting organizers for the opportunity to participate in this very important meeting.

Today I'm going to talk about work we've been doing to fill critical research gaps and address fundamental questions relevant to the Closer to Zero initiative. First is simply to shed light on the questions what do babies eat and, secondly, how do -- how does what they eat contribute to their toxic metal and metalloid exposures and ultimately how does this impact their health.

We've been doing a study of the general population of the U.S. enrolling pregnant women from prenatal clinics in New Hampshire first in a region that we knew had higher well water levels of arsenic, the red dots being above 50 micrograms per liter and then the yellow dots with wells above 10 microgram per

liter which is the current drinking water standard for arsenic. We've been enrolling over 2,500 pregnant women. We're following their infants and children to capture their diets, along with many other aspects of their life experience and how those factors influence their health.

And from these data we've been able to look at babies' diets and what do babies eat. And as we know, they eat foods that can be high in toxic metals and metalloids. Babies tend to eat simple diets, a lot of the same foods. The most common food, first food, has been rice cereal, which we know can contain toxic elements such as arsenic.

And in our study, the vast majority, 80 percent of infants, were introduced to rice cereal in the first year of life. And in estimates done by one of our former postdocs, Courtney Carignan, eating just a few servings of rice cereal equated to infants who are fed formula mixed with water that contained 10 micrograms per liter of arsenic. Again, that's the standard.

Somewhat surprising to us was by one year of

age, over 50 percent of infants were eating some type of rice product and then when we drilled down a little more deeply, we found that about a third of them were eating rice snacks.

And then when we tested those rice snacks, we found that some of them contained high concentrations of arsenic, including inorganic arsenic, above the guideline value of 100 micrograms per kilogram. And this is a graph from the 2016 FDA report just to remind us that infants and young children are consuming these foods and are the highest consumers of these foods during this critical window of development when they are most vulnerable.

So as we know now, baby foods contain not only arsenic, but lead, cadmium and mercury and it's not only rice. It's other foods as well. And this congressional report tells us what is in the food we feed our babies by measuring the levels in baby foods, and our lab has done some of this work too.

What we've been focusing on is what is being absorbed and getting into the babies' bodies. We determined this by testing urine, blood and other

tissues. So we're finding that as infants transition from an exclusively breastfed diet, so in our study measuring urine at babies who are six weeks of age to solid foods by one year of age, that arsenic, mercury, cadmium and lead are all increased.

So this pattern mirrors what we know based on the measurements in the baby foods. And higher body burden of arsenic is not just found among infants who eat rice. The graphs here which aren't being shown very clearly indicate that formula-fed infants on average have higher arsenic in their urine than babies who are exclusively breastfed and these graphs are indicating that, yes, babies' urinary arsenic will increase with the amount of rice and rice products they consume.

But it's also, and you can't visualize this well, is related to the amount of fruits and vegetables. And in this final figure was the good news that urinary arsenic in infants does not seem to be related to consumption of other types of cereals.

So as we know, there are many vitamins and minerals that are necessary for good health, like

selenium and zinc. Arsenic, cadmium, mercury and lead, shown here, circled in these red circles, they do not have any known physiologic essential function in the body and there is no known safe level to our knowledge.

We and others have found direct health effects on children's brain development outcomes, immune function such as susceptibility and infection and development of other immune-related conditions like food allergies and asthma as well as growth patterns that may lead to childhood obesity and cardiovascular diseases. So these metals and metalloids may cause a myriad of health effects that manifest both in childhood and throughout life.

Our studies also look at how these metals and metalloids impact health; that is, what are the underlying biologic changes or mechanisms by which they might cause adverse clinical outcomes. And we've observed changes to the microbiome and the epigenome, which you've probably heard about, and are now looking at children's response to vaccination, which of course is a topic currently on our minds.

But in general what we find is dose response patterns which means refining relationships at very low levels. Our plant physiology colleagues including a former postdoc, Tony Signes-Pastor, have done studies to determine how to minimize arsenic exposure from rice.

We know concentrations of arsenic and other elements vary in rice plants and they vary around the world with some low levels found in certain places in Africa. We also know that the arsenic accumulates in the husk and in the bran. So removing those parts will lower levels of arsenic. And of course we can rinse our rice and studies done by Dr. Signes-Pastor and Dr. Andy Meharg show that percolating rice with arsenic-free water will reduce concentrations, but I will add that this is not how most people cook their rice.

We're also cognizant that concentrations of these metals and metalloids will likely be impacted by climate change. Rice grown in flooded paddy fields tend to have higher arsenic and water demands of plants could increase as temperatures increase and

that could affect concentrations. And then as our water supplies become more depleted, farmers may turn to growing rice more in dry fields which tend to have higher cadmium levels.

So I'd like to end by thanking my colleagues and the families and staff of the New Hampshire Birth Cohort Study. It takes a village and the generosity of many to conduct research with many people of many disciplines and background and perspectives. I've italicized the names of some of our current and our former postdocs who make our work possible.

And in closing, a recent New England Journal of Medicine article sent to me by my colleague, Dr. Carolyn Murray, who leads our community engagement and research translation core, mentions the aphorism that we heard. Children are not little results, and suggests this should be amended to children are not little adults, but they are future adults. Thank you very much.

MS. MIDDLETON: Thank you, Dr. Karagas. Our final speaker is Dr. Jennifer Lowry Sample. She will discuss common sources of arsenic, cadmium, lead and

mercury and how it enters into food and water as well as adverse health effects from exposure to these toxic elements.

Dr. Sample is a pediatrician and medical toxicologist who is currently in private practice. She obtained her medical degree at the University of South Dakota School of Medicine. Her pediatric, medical toxicology and clinical pharmacology training was completed at Children's Mercy Hospital in Kansas City, Missouri, where she practiced for over 20 years.

During that time, she was chair to the council on environmental health for the American Academy of Pediatrics and served on multiple committees including the EPA's children's health protection advisory committee and the CDC's lead poisoning subcommittee. She currently consults on pediatric environmental health issues including as a current consultant for Gerber. Welcome, Dr. Sample.

DR. LOWRY SAMPLE: Thank you very much for the introduction and to the organizers for inviting me to speak today. I'm going to change the way of discussing things a little bit. As a medical

toxicologist as opposed to doing research, I actually see children with exposures. And I want and was asked to speak specifically about the heavy metals themselves and their toxicity and where we might find them. So I'm going to go in alphabetical order and talk about the four different metals that we are -- that are currently under review by the FDA. And so here we'll start with arsenic.

As previously mentioned, arsenic is found in rice and seafood as the most commonly ingested foods known to be contaminated with arsenic. As mentioned before, inorganic arsenic is more toxic than organic and as just described, the rice plant absorbs more of the arsenic from the soil. And depending on where it's grown, the amount varies in the U.S. and across the globe.

Much of the arsenic that is present was used as pesticide many years ago and it stays in the soil and then gets incorporated into the plant. There have been numerous evaluations of the NHANES data to look at these heavy metals. In one particular assessment, they found that arsenic concentrations in urine

increased 14 percent with each quarter cup increase in cooked rice consumption in children.

So currently the FDA, and with the help of obviously some of the researchers that you've previously heard from, they found that higher concentrations were found in infant/toddler foods compared to adult foods.

And because as a result of those findings, the FDA did suggest a voluntary approach to levels below 50 micrograms per kilogram. Unfortunately this is a level that was even higher than most of the food products that adults eat in that same study. And so we know that we can do a better job in getting arsenic levels out of foods for children.

In regard to its toxicity, as a medical toxicologist, I've taken care of people who have intentionally ingested high levels of arsenic. And in high acute doses, it can cause multiorgan system failure and ultimately death. It's also classified as a human carcinogen. We know that it can increase -- have an increased for spontaneous abortions, stillbirth and preterm birth in these higher levels of

arsenic exposures, and there is some data to suggest that it can happen in chronically lower levels of arsenic as well.

Specifically though as we talk about children and the exposures that they have in regard to arsenic ingestion, it has been associated with generalized fatigue and malaise. Ingestions or exposures early in infancy or childhood has been shown to cause a disease called bronchiectasis in early adulthood. It has been associated with decreased intellectual function and hepatic function, as well as causing skin disorders.

Moving on to cadmium, cadmium usually is not found by itself out in nature. It's usually a byproduct of other metals such as lead. So when lead ore is mined, cadmium usually comes with it. And so oftentimes when you have a lead exposure, you'll also have a cadmium exposure.

The most common place that cadmium is found is in cigarette smoke since it's part of the tobacco in a cigarette. But children are more likely to be exposed by foods. It's usually found in leafy green

vegetables, potatoes, legumes and grains. It also is a known human carcinogen and, in high doses, it can cause bleeding with vomiting and diarrhea as well as renal failure and death.

We know that chronically low dose in children, it has been associated with learning disability if you have higher -- and it's been associated with a higher urinary concentration found in children.

Lead is probably what we know most about. It is ubiquitous in the environment including in soil and water. The most common sources that children get exposed to lead is actually in their home from -- in homes older than 1960 or that were built before 1960 that it was found in lead paint. But we also know that it's in the soil and water. And then it can actually have a natural uptake by plants.

So it can enter the food supply by the animals eating plants or it can also be animals themselves may have lead in it and then when we eat the meat from the animals, we can get lead. And then it can also be found in manufacturing processes of a

number of different foods.

As currently mentioned throughout the morning, we know that the FDA -- that CDC has recently decreased the reference level from five micrograms per deciliter to currently now it's 3.5 micrograms per deciliter. In looking at what the current reference level for lead in food though, it's three micrograms per day. Unfortunately it's based on the CDC reference of five. And so it may need to be decreased again if we're going to be using reference levels as the criteria and for using it as a reference level in foods.

I also want to point out that there is an FDA water limit of five parts per billion for bottled water versus the EPA's proposal through the lead and copper rule to 10 parts per billion.

Unfortunately none of the studies have assessed lead levels in children less than one year of age. They're all of kids older than that. And we have to remember that children under one year of age, as has been previously discussed, if they're not breastfeeding, they're drinking formula and that

formula is made with lead -- or excuse me, made with water that may have lead in it. And they don't get lead levels in children clinically until they're one year of age. And so we've missed a large amount of time when that exposure could have taken place and really a missed opportunity to remove lead from their diet.

This graph is a little bit hard to see. But it shows basically the difference between lead -- the effects of lead in children versus effects of lead in adults. But we know that there is sufficient evidence now that lead levels below five micrograms per deciliter and even as low as two micrograms per deciliter can have effects on the nervous system. It can decrease the IQ of children. It can decrease the academic achievement and decreases cognitive measures and can have a higher incidence of attention-related and problem behaviors in children.

Lastly I want to talk about mercury. Mercury is a naturally occurring ore with cinnabar and it's also used with fossil fuels and contaminated with fossil fuels that can happen when mining, smelting and

industrial discharges. Really what happens is it gets into the air and then it contributes to local and global contamination as it comes down into the environment and then into the waterways.

And then that result is then there's methylmercury is accumulating in the food chain and progressively bioaccumulates. And in humans, methylmercury passes through the placenta and can concentrate in the fetus and is transferred to human milk as well.

And I just put up the graph here that the FDA and EPA have put together to show what seafoods should be eaten by pregnant women and children. We know that mercury can cause adverse effects for the central nervous system, and in acute high exposures, that can lead to coma and death. It's a potent teratogen as we know from (indiscernible) exposures many decades ago. It can cause a decrease in IQ with an increase in maternal exposure. And there have been inconsistent results in regard to motor, attention and verbal test results.

So in summary, food is a common exposure for

heavy metals in children given their presence in the environment, and we really need to concentrate going forward to having allowable concentrations in food and water that need to account for all different sources, the additive and synergistic effects from all these neurotoxins as well as the different exposures at critical stages of development. And thank you very much for your time.

MR. KAWCZYNSKI: All right. We are now going to go into our moderated Q&A portion of this first panel. So let's get all of our panelists all up on camera, and I will hand it back over to Karlyn Middleton. I can't even talk today. Here we are. You ready? Here we go. And there they all are. Perfect. Take it away.

MS. MIDDLETON: I just want to say thank you to all of the panelists for providing such insightful presentations, and you can find more information about these panelists and the great work that they do in the bios document on the FDA Closer to Zero public meeting event webpage.

So like Michael said, we'll move into the

moderated question-and-answer portion. There are a few questions we would like our panelists to answer. Some are directed to the group, and some to specific panel members.

The presentations that we've discussed cover some aspects of these questions. However the Q&A session will allow us an opportunity to elaborate more on these topics. So the first question is a group question. So we would like to hear from each panel member.

And the first question is to reduce exposure to toxic elements, Closer to Zero plans to set action levels for foods commonly consumed by babies and young children. In developing action levels for arsenic, cadmium, lead and mercury, what are the most important factors to be considered for babies and young children related to the crucial most sensitive adverse effects from exposure to these chemicals?

And let's start with Dr. Deoni, and then Dr. Dishaw, Dr. Sample and then Dr. Karagas.

DR. DEONI: Okay. Yeah. I mean, that's a great question. I think, you know, with respect to at

least the neurodevelopmental outcomes, which I'm probably most suited to talk about, the challenges that we have for setting sort of safe levels and understanding thresholds is that we don't really know what those safe levels and thresholds are for neurodevelopmental impacts.

You know, obviously around things like lead, and many of these there's been large, long-scale longitudinal studies that have been done. But for a number of them, there simply haven't been, and certainly thinking about things like nutrition and whatnot, there's just not a real great sense of knowledge and particularly within this early infant timespan.

When we think of most of the lead exposure literature on neuro and cognitive outcomes, most of it's been done in older populations, adolescents, et cetera. And so that's in a neuroimaging type aspect and the cognitive aspects aren't quite as well known.

So I think there's a lot to be learned on that aspect as to how do we understand and tie up those what we think are safe levels and how there's

long-term impacts on some of these very fundamental neurodevelopmental processes. I'd leave it there and pass off to the next speaker.

MR. KAWCZYNSKI: And just a reminder to everyone that is viewing this, you can submit questions to our closer2zero@fda.hhs.gov. And you can see that at the bottom of the screen in our Q&A slide. All right. Take it away.

MS. MIDDLETON: Thank you, Michael. Dr. Dishaw?

DR. DISHAW: Hi. Sorry. I'm a little discombobulated because I lost my audio briefly at the beginning of the Q&A session. I missed most of what Sean said. But yeah, I think the -- hold on. Can we come back to me? I'm sorry.

MS. MIDDLETON: Sure. No problem. Dr. Sample?

DR. LOWRY SAMPLE: Yeah. I think as the FDA reviews all of the data and as we try to get to the right levels, I alluded to some of that in my talk in that, you know, we are looking at the metals in isolation and we really, really can't do that because

children are not just exposed to one. They're exposed to many. And we don't know if there's an additive versus a synergistic effect with those. And so I think it's important to look at everything together as well as the ages at the critical stages of development that the exposure could occur.

MS. MIDDLETON: Thank you. Dr. Karagas?

DR. KARAGAS: So thinking about the most sensitive adverse effects, and to address your question, we've been focusing on the three major outcomes, growth and other cardiometabolic outcomes, as heart disease is a leading cause of death and early risk factors such as childhood obesity have been on the rise.

Secondly, we've been focusing on immunity since infections are still the leading cause of morbidity and mortality in children worldwide and allergies and asthma has also been on the rise.

And finally, you know, as has already been highlighted, the neurodevelopmental outcomes are so crucial since their impacts are so costly in terms of healthcare and special education as well as loss of

productivity and of course for the children themselves and their lives.

Another important factor that's been brought up is to recognize that not all families have the same access to food and food choices. So it's very important that we address the foods all families eat, including those that are distributed by the federal programs and food pantries and such. And then those families, and I think Sean brought this up, who experience the high stress, poverty or violence might also be more vulnerable to the health impacts of the toxic elements such as lead.

And just one last point that I wanted to bring up with respect to this is that since I study arsenic so much, that -- and this was brought up by Jennifer about species. You know, we tend to most worried about inorganic arsenic and we're not as worried about some of the other forms of arsenic that are not metabolized like arsenobetaine which is found in seafood and fish.

But there are other forms of arsenic found in our foods, and we're just not certain about those

health impacts. We haven't been monitoring them as much. But they could metabolize or in themselves be toxic. So I think that's just one thing that I'd like to bring up in the discussion here.

MS. MIDDLETON: All right. Thank you. Dr. Dishaw?

DR. DISHAW: Were you coming back to me?

MS. MIDDLETON: Yes.

DR. DISHAW: Sorry. All right. So yeah, I mean, I don’t think I really have too much to add to what the other panelists have said.

I think one of the most important things from my perspective is really, as Dr. Sample already said, is understanding what kind of the total exposure is and how there may be additive effects of multiple exposures and, you know, that may affect what the levels are set at.

MS. MIDDLETON: Thank you. The second question is directed to Dr. Deoni and Dr. Sample. But other panel members, feel free to respond after if you have any thoughts on this question.

The question is given there are several

stages of development from the prenatal period through adolescence, what are the crucial stages most vulnerable to adverse effects from toxic elements. And if you can touch on arsenic, cadmium, lead, mercury that would be great --

DR. DEONI: Yeah. That's a really great question. So I think, you know, as I say, we kind of focus in obviously on that early -- those early stages, right, thinking through fetal development where you have a huge proliferation of neurons, synaptogenesis going on very rapidly into early, early infancy where you have myelination taking off being a neurodevelopmental process, synaptogenesis and synaptic pruning happening.

But then, you know, it's not like you get to age two and that's the end of it, you're just riding, you know, a rollercoaster that's already been set up and you're just riding the rails for the rest of your life, right? Clearly there's a lot of other stuff that occurs. And so certainly the next major point, inflection point where you have a lot of remodeling happening is early adolescence, right, so going from

nine, ten, eleven years of age into early adolescence, 13, 14 years of age.

And then there you're not only bringing in environmental aspects that you have, the adversity aspects and whatnot that you might be dealing with, but then you have hormonal changes and whatnot both on males and females.

So you know, it's a continuum of changes, right? And certainly when you look at, say, brain development, again coming back to the neuro point, you have these developmental processes that are going on that are waxing and waning with age.

Like I say, these sort of peak periods of fetal, infancy, middle childhood, certainly adolescence and pre-adolescence but then even into your 30s, 20s and 30s where you begin to inflect and begin sadly a slow, long decline into old age. So those of us who are over that 35-year window, tragically I am definitely part of, following that hopefully slow and gradual decline.

So you know, you can't just sort of isolate it and say, well, it's only going to affect our

infants or pregnant moms and whatnot. So these things are impacting across the lifespan.

DR. LOWRY SAMPLE: So I really can't add much more to that because that was a great summation. I do want to add though that when you look at the developmental stages, what else is important is the type of foods and the type of exposures that they're happening.

As I mentioned for water with lead, when you look at the Flint exposure that they had with water contamination of lead, none of those studies really looked at children under the age of one. And it's those children that are going to have the higher exposure to water compared to older children because of the water used for infant formulas.

As I mentioned, we also don’t get our lead levels clinically until they are one year of age, and what we've missed is that whole year of life and knowing what that exposure could have been. And so we really do need to think about that in regard to their exposures.

MS. MIDDLETON: All right. Thank you. Are

there any other thoughts on this question? If not, then --

DR. KARAGAS: I think I'll comment just a minute, just to reiterate this point that Jennifer brings up. We don't tend to focus on children's diet very young, at least epidemiology studies haven't been, you know, before one and what are children getting exposed to in their diet.

So I do want to highlight that point. There aren't a lot of good instruments. You tend to have to do the full diaries. And it's complicated. And we are starting to look more and more at these windows of exposure which, as everyone's highlighted, is so important. And the methods are getting better to enable us to do that. The modeling and the statistical approaches are improving.

So we can do this now better than we have been able to before. But we will need large sample sizes, and epidemiologists always say that. We need larger studies. But I just wanted to make that point. Thank you.

MS. MIDDLETON: All right. Thank you.

DR. DISHAW: Yeah. I think just kind of building on kind of what some of the other people have said, you know, it's very complicated to try and identify what the crucial stage is.

But if we can start to narrow that down and figure out what levels of exposure are likely to cause effects at a crucial stage, because that tends to be the most sensitive, we can also be protective of other stages. So even though, you know, the developmental window, you know, there may be multiple stages, that can help and be protective of others.

MS. MIDDLETON: Thank you. Question three, so question three is directed to Dr. Karagas and Dr. Dishaw. So exposure is a function of both the levels of the contaminant in the food and food intake, for example, the frequency or the serving size.

Beyond food labels labeled for babies and young children, food intake for different types of food will vary widely for babies and young children. additionally FDA surveys indicate that some foods have higher levels of toxic elements than others; for example, inorganic arsenic in rice, lead in carrots

and sweet potatoes, cadmium in spinach. Therefore identifying and prioritizing which foods to focus on can be challenging.

From your perspective, what might be the key challenges to prioritizing which foods or, you know, which toxic elements to focus on or action levels or other regulatory (indiscernible) -- and we can start with whoever wants to go first. Maybe Dr. Dishaw?

DR. DISHAW: Yeah. So I guess probably from my thought, the key challenge is probably just going to be how variable it's likely to be.

So there's likely to be variability in kind of what types of foods people are eating, what children are eating or the amount that they're eating, depending on kind of geographical location as well as cultural backgrounds. So rice might be more common with people in certain areas or certain cultures. You know, I never ate sweet potatoes until I moved to North Carolina, and now I eat a lot of sweet potatoes. And my daughter eats more sweet potatoes than I probably ever did growing up.

So that's -- there's going to be a lot of

variability. And I think that's going to be challenging from the perspective of trying to determine what the -- how to focus and what the action levels should be.

MS. MIDDLETON: Dr. Karagas?

DR. KARAGAS: Yeah, I agree. This is a huge challenge. You know, it's not just one food. It's not just baby food. Babies are going to be eating adult foods. So we need to take into account foods that are not marketed to young children, which opens up quite a can of worms, I guess.

And as I mentioned, you know, babies have pretty simple diets and they can eat a lot of a small number of foods. So I think we're going to want to figure out how to keep the fraction of foods they consume that contain these toxic elements to a minimum and then as well as minimizing the toxic elements in the foods and the food constituents.

So that rice and other products that contain these toxic -- these additives and supplements and things like brown rice syrup, and that has that outer bran layer still on it or bran, are things that are

higher in some of the toxic elements, they can sneak in -- you know, they're used in snack bars and energy bars.

So we're going to have to not think of just whole food but also what is being added to foods that are commonly consumed by babies and young children. So I think, you know, as the FDA is doing, prioritizing on the common foods, I think that makes a lot of sense and then continuing to monitor and I think that aligns with your plan and makes a lot of sense. So I'll be looking to see how FDA views what the challenges are.

MS. MIDDLETON: All right. Any other thoughts around this from the team?

DR. LOWRY SAMPLE: I was just going to add, and I've mentioned this before, looking at -- if you were just to look at lead, you'd also have to look at cadmium because, again, sometimes they are mine together.

Cadmium is one that just kind of hops onto the other metals. And so you're going to get a combined exposure. And if we look at them in

isolation and we know that lead decreases IQ and has attention deficit disorder association and we look at cadmium and cadmium has similar learning difficulties associated with it, they don't happen in isolation. They happen together. And what we don't know is if it's additive.

So do you have just a little bit more of a deficit or if it's even synergistic, if one plays off the other and then causes more of a problem. So while looking at each individual food is important, we have to look at the foods and what is actually contained in them and look at the combined effect of the heavy metals together.

MS. MIDDLETON: All right. We have another question. This is the last moderated question, and it's another one for the group. And it's related to some things that you all mentioned throughout the discussion, research needs.

There are numerous studies that evaluate effects related to toxic elements in adults. However studies investigating effects in babies and young children are more limited. Looking to the future,

what are the key data gaps or research needed to address the impact of babies' and young children's exposure to toxic elements? I'm going to start with Dr. Karagas and then Dr. Sample, Dr. Dishaw and then Dr. Deoni.

DR. KARAGAS: Well, I think it's important to recognize that collectively we have learned a lot already. So I think once you -- the FDA sets the action levels, we may not have all the answers.

And so I think that's part of the Closer to Zero paradigm and that we'll need ongoing investigations to understand and refine the study, the dose response relationships to understand the impacts of the low levels of exposure, in particular among our vulnerable populations. So by the life stages, sensitive windows, things like interactions with stress and, as Jennifer has highlighted and others, the effects of cumulative exposures and mixtures.

So those are going to be ongoing questions that I don’t think we'll have the answers to completely and that we'll still have to refine our knowledge over time.

DR. LOWRY SAMPLE: Yeah. I don't have much more to offer than what I've already said. I think part of the problem also is that these metals are in our environment.

There's no way, especially when we talk about soil, water -- well, there are ways to obviously rid them of the metals. But that is a huge undertaking and very expensive and really not feasible. And so we look at the foods that are grown in these types of soils or with this water and what we need to do then is figure out really in the manufacturing process is there a way to actually remove them from them or do we have to find other sources and other places to grow the food so that they don't have these heavy metals in them.

Unfortunately that's why it goes back to the paradigm of Closer to Zero. We'll never get to zero. And that is unfortunate, but it actually -- unfortunately it's the way it is. And so we'll do the best that we can. but I don't -- as I said again, we're not going to get there all the way.

MS. MIDDLETON: Dr. Dishaw?

DR. DISHAW: Yeah. I think that covers it pretty well. I'm not really an expert in heavy metals in terms of I don't have a really in-depth knowledge of what the current evidence base is. So I can't necessarily speak specifically to what the data gaps -- the specific data gaps might be.

But just in general, having mechanistic information can really be helpful about those different mechanisms of toxicity and that can really be helpful for narrowing down specific crucial windows of sensitivity.

MS. MIDDLETON: Dr. Deoni?

DR. DEONI: Yeah. Perfect. So yeah, I think, you know, again, not a lot to add onto what the others have said. I think, you know, in one way, as I think Dr. Karagas mentioned, is that a lot of -- these things are packages, right? It's very seldom that you have one exposure without other exposures going along with it.

So, you know, understanding how those are additive or cumulative I think will be important. how they wax and wane with age I think is a bit of a --

you know, a bit of a gap. In one way, I'd like to almost flip the question a little bit and say, well, what does the FDA need, right? What would you act on? Because we can do studies. You know, we can publish all sorts of studies doing almost anything. But if it doesn't carry the weight or answer, you know, a very specific question, was it worth doing in the first sense. So it's almost sort of what's needed.

But I think the challenge will begin to isolate the impacts to the individual elements within the broader context that the child is growing up in, understanding how much that effect size is. So is it worth putting a large amount of money into reducing lead? I think we saw that there was, right? So that's an unquestioned one.

But as you go down that list, where does that cost-risk and cost-benefit ratio begin to cross over. So I think there's a lot of gaps there. But I think, as was mentioned, we also know a lot as well.

So it's now kind of really sort of trying to tease out what's desperately needed to make decisions and drive policy and then how can we go and

effectively and accurately provide that information.

MS. MIDDLETON: All right. Thank you. Okay. So we've reached the end of our moderated portion of the session. It looks like we have a few more minutes. So we would like to include for discussion at least one question taken from the Closer to Zero mailbox. As mentioned earlier, if you have questions, please submit them to closer2zero@fda.hhs.gov.

So let's see what we have. All righty. There is a question about the differences in ways to test for toxic elements in the body, the urine versus the blood.

DR. LOWRY SAMPLE: So as a toxicologist, when we see patients come in and they question whether they've had an exposure, there are a number of different ways that we can test for them. The first is blood. Blood is more of a substance that we'd look for an acute exposure.

So for example, if they were exposed to mercury recently and they want to assess for organic mercury, we would get whole blood to look for that.

Urine is probably the most common way to assess it, and it's a much better way for looking for chronic exposures. So in inorganic mercury, lead, cadmium, we actually have levels that we would use to actually look to see if any treatment needs to be done using urine.

The last one is probably as common or is becoming more common is hair. Again, that's more of a chronic exposure because hair grows at a certain rate over time and we can actually then look at when an exposure might have occurred.

But there's a high risk for environmental contamination using hair. So it has to be -- the results have to be taken kind of with a grain of salt as we can know that if it was ingested and taken into the person versus an environmental contaminant of the hair itself.

MS. MIDDLETON: All right. Thank you. Any other comments? We do have another question. All right. There's a second question from the mailbox. A participant would like to hear more about arsenic and its impacts on immunity and whether there are studies

related to this that can be referenced.

DR. KARAGAS: Yeah. Thank you for the question. It's an area that I've been especially interested in, and I think we're all interested in it right now because children, they go to the doctor because they get infections. But we aren't always focused on that.

And immunity and inflammation are such important pathways, you know, talking about Dr. Dishaw's mention of mechanisms. There's a common pathway for really most of diseases, cancer, heart disease, metabolic diseases as well as infections and allergies and asthma. So it is an important pathway and that's why we've focused on it.

So we've looked at infant infections over the first year of life in relation to arsenic. And we've also looked at the mechanistic pathway, so looking at, as I mentioned, the microbiome, so the gut microbiome that gets colonized, and talking about the first thousand days of life, we come out relatively sterile and then we colonize based on whether we're vaginally delivered or C-section-delivered and then

through breastmilk through formula.

So those really important first steps start to form our human microbiome that we need for immunity and to prime our immune system. So that's one of the early mechanistic changes that we've looked at in relation to multiple elements and the interactions between toxic elements and nutrient elements. So thank you for that question.

MS. MIDDLETON: All right. Thank you. I think we're near time. So that concludes the Panel 1 session. I would like to thank you all, thank the panel members for a great discussion and taking the time to participate and sharing their knowledge with us.

Information from the session will be incredibly useful as we move forward with the Closer to Zero action plan. So thank you all again for participating today. Now I will turn it over to Michael who will take us to a break.

MR. KAWCZYNSKI: All right. Again, thank you so much. You guys all did a great job. And yes, we are going to take a 20-minute break. So, and we

will reconvene at around, let's see here, around 12:30. So at this time, enjoy your break.

(Break)

MR. KAWCZYNSKI: All right. Welcome back from that short little break into Session 2: "The Role of Nutrition in the Closer to Zero Initiative." The moderator for this session is Kellie Casavale. Kellie, take it away.

PANEL 2: THE ROLE OF NUTRITION IN THE CLOSER TO ZERO INITIATIVE

DR. CASAVALE: All right. Thank you. I'm Kellie Casavale, a senior nutrition advisor in the Office of Nutrition and Food Labeling at CFSAN, FDA, and I am glad to be kicking off our afternoon panel session today on the role of nutrition in Closer to Zero. We've already heard today in the first panel a lot about the essential stages of growth and development for children and the detrimental impact exposures to heavy metals and metalloids can have.

So specifically Closer to Zero focuses on four: lead, arsenic, cadmium and mercury, and the initiative is focusing on exposures through food to

drive those down over time. So naturally nutrition is an important and a highly relevant area. Closer to Zero incorporates the topic of nutrition from a number of perspectives, as Dr. Choiniere introduced this morning.

And during today's panel, we will explore some of those areas in greater depth, specifically the key stages of child development from a nutrition perspective, the role of an individual's nutrient status on their susceptibility to the effects of heavy metals and metalloids and interactions between nutritional aspects of food and arsenic, lead, cadmium or mercury.

We know from decades and decades of science that healthy dietary patterns help promote health and reduce the risk of diet-related chronic disease. We have the benefit in the U.S. of having the Dietary Guidelines for Americans, a cornerstone of our country to promote health through food-based guidance supported by rigorous science.

And in December of last year, with the release of the 2020-2025 edition of the Dietary

Guidelines, we now have more robust information than ever on the essentiality of healthy eating to support child growth and development.

I can't say enough how excited I am to have our panelists. We have a nutrition panel here today with us to discuss this very, very important topic. So as a reminder, the purpose of this public meeting is to engage with stakeholders and invite input on these various topics that are pertaining to Closer to Zero. We encourage submission of written comments from the public to the docket, and also want to remind those of you watching that we do have an email address that's open if you have questions during this panel that you can submit, and we'll try to answer those if we're able to, and that is closer2zero@fda.hhs.gov, so C-L-O-S-E-R-2-Z-E-R-O@fda.hhs.gov.

All right. So let's get started. It's my pleasure to moderate this afternoon's panel discussion. We are fortunate to have with us today four very excellent speakers who will serve as our panel. We really greatly appreciate their time to share their knowledge today. Our panelists here today

are Drs. Heather Hamner, Karen Peterson, Xiaobin Wang and Kasia Kordas. And you can find more information about the panelists and their bios at the FDA Closer to Zero public meeting event webpage.

So without further ado, I'd like to introduce our first speaker, Dr. Heather Hamner. Heather is a Health Scientist in the nutrition branch of the Division of Nutrition, Physical Activity and Obesity in the National Center for Chronic Disease Prevention and Health Promotion at CDC.

On the maternal, infant and toddler nutrition team, Heather leads efforts on early child nutrition focusing on ensuring children have optimal nutrition and feeding practices in the first two years of life.

This work has included research on food composition patterns and nutritional status of young children, working with partners to advance education and training of healthcare providers and working with federal partners to advance efforts related to early nutrition. All right. I'm going to turn it over to Dr. Hamner.

DR. HAMNER: Thank you so much for having me. So today I'm going to talk about nutrition during the first thousand days. This time period sets the foundation and is critical for health and development. I have no disclosures to report.

The first thousand days is a continuum beginning at pregnancy and ending at the child's second birthday. While good nutrition is essential throughout the lifestyle, it's incredibly important during these first thousand days for maternal health, child survival, growth and neurodevelopment and it lays the foundation for overall health and wellbeing throughout life.

During the thousand-day period, growth rates and brain development are at their peak. Nearly 80 percent of brain development happens during the first thousand days. Some vitamins and minerals are particularly important to support the high rate of growth and brain metabolism during this time. Nutritional deficiencies can have severe and significant consequences.

Nutrients are essential for child growth and

brain development. I've listed multiple here. But I'm going to only highlight three: folic acid, iron and iodine. Folic acid is needed before and during early pregnancy to prevent serious birth defects of the brain and spine. Iron is needed to help transport oxygen in the blood, and iodine is an essential component of thyroid hormones which are the key drivers of metabolic activity.

A lack of these nutrients can have long-term impacts. One example is iron and iodine deficiency which are associated with poor birth outcomes, physical growth, impaired cognitive and motor development and poor qualitative or quantitative and language ability.

Different foods and beverages can provide essential nutrients for child growth and development. Some foods are good sources of multiple nutrients. I've provided a lot of examples. But I'm only going to highlight two: seafood and fortified infant cereals, both of which are bolded here on the slide.

Seafood can provide omega-3 and omega-6 fatty acids, iron, iodine and vitamin D. Fortified

infant cereals are important sources for both zinc and iron. In general, fortified products can be an important vehicle for specific micronutrients. Even with a varied diet, there are going to be some vitamins and minerals that may still require supplementation.

For example, for infants who are fed human milk or a mix of human milk and infant formula, vitamin D is needed beginning shortly after birth. During infancy, from birth through the first year, breastfeeding is the best source of nutrition for most infants and it gives babies the healthiest start to life by supporting strong immune function and protecting infants from infections and illness. Breastfeeding reduces the health risk for both babies and mothers.

The U.S. Dietary Guidelines for Americans recommend that babies are fed only human milk for about six months with continuation of breastfeeding for up to one year of age or longer as desired as complementary foods are introduced. Dietary patterns that are established in infancy and early childhood

can set the foundation for healthy eating habits. Recognizing the importance of this time period, in 2020, the U.S. Dietary Guidelines for Americans released a comprehensive set of recommendations for children birth to 24 months of age.

I will highlight a couple of these recommendations. At about six months of age, children can begin eating nutrient-rich, complementary foods to help fuel their growth and ongoing brain development. Giving children foods with a variety of tastes and textures can help them develop their fine motor skills, chewing skills and learn to expect and like a variety of food.

Importantly the nutrient requirements relative to caloric requirements of young children is high. So there's little room in the diet for high-calorie, non-nutrient-dense foods. This means there's no room in the diet for foods or beverages with added sugar. Additionally, this is the time period in which taste preferences are being formed. So exposure to overly sweet foods could predispose children to these tastes.

So I've provided a general overview of why nutrition in the first thousand days matters. Now I'd like to talk about the state of nutrition in the U.S. and really focus in on birth to two years.

Breastfeeding rates remain low in the United States. While many infants start with exclusive breastfeeding, we see that most are not meeting recommendations in the first year. Twenty-five percent of infants are exclusively breastfeeding at six months, and 35 percent of infants are breastfed at 12 months.

Although I am not showing the data here today, there are disparities in breastfeeding rates. Working to reduce or eliminate these disparities can have important health benefits for both babies and mothers. Now the recommendation is to introduce complementary foods around six months of age. Introducing before four months of age is earlier than children are developmentally ready.

However nearly one in three infants are introduced to complementary foods before four months of age and this percentage varies across the United

States, as can be shown in this map. What this means is that infants are being exposed to foods at a very early age and this has implications when we start thinking about the kinds of foods they're consuming, how much and the nutrient content.

Food groups can provide different nutrients for young children, which makes it important to know what foods children are eating. Earlier I pointed out that there are some foods that provide multiple key nutrients, like seafood. Seafood can provide vitamin D, iron, iodine and essential fatty acids.

However what you can see here is that six percent of children 12 to 23 months of age consume seafood on a given day. The Dietary Guidelines encourages the consumption of seafood options that are lower in methylmercury as one way to meet the protein need for young children.

Overall the Guidelines have recommended dietary patterns that encourage choice and diversity of nutrient-dense food within these larger food groups. It provides flexibility in the foods that are chosen to help ensure that a variety of foods are

provided. Food group consumption patterns can also differ by milk status.

This slide is showing the percentage of children six to eleven months of age and the food groups that they consumed on a given day. What you can see is that for infants who are fed infant formula -- that's the blue, crosshatched bars -- and those who are fed human milk -- those are the solid blue bars -- there are some differences when it comes to the different foods that they are consuming.

An example is protein. Over half of infants who were fed infant formula consumed protein on a given day compared to about a third of infants who were consuming human milk. This is important to consider when we're thinking about children's nutrient needs and how they might differ based on what kind of milk they are drinking. The risk of inadequate intake among infants consuming human milk is higher for iron, zinc and protein.

The first thousand days is a key time period that can have significant impacts on growth and development. As these discussions progress, there are

some additional factors to consider. First it's recommended that infants have one source of nutrition for about the first six months. Exclusive breastfeeding is the recommendation. But many infants rely on infant formula or a mix of infant formula and human milk.

From a nutrient perspective only, the nutrient profile of both human milk and infant formula play a key role in an infant's nutritional status. Second, balancing nutrient needs with ensuring a variety of food exposures while still reducing harmful exposures is important. Iron-fortified infant cereal is an example of this. It can help provide the iron that the infants need during this time period.

But choosing a variety of infant-fortified cereal is important to reduce the risk of exposure to arsenic. Metrics for assessing dietary variety, not only alignment with the Guidelines, should be an important tool.

Third, the what and the how are both important. The Dietary Guidelines provided recommendations on what to eat. But this is also the

time children are learning how to eat. They're exploring foods and beverages and transitioning to the family diet. They're learning to bond with caregivers, develop fine motor skills and learn to accept and try new foods.

Lastly, balancing meeting dietary requirements with other aspects like personal preference, traditions, lifestyle, culture and budget are all important. The Dietary Guidelines provided a roadmap. But it is not a one size fits all. There's flexibility and choice in the foods and beverages that make up these patterns.

Taken collectively, there are opportunities for federal agencies and other organizations to work together to support dietary advice and guidance while still ensuring a strong nutritional foundation for mothers and infants. Thank you.

DR. CASAVALE: Great. Thank you, Dr. Hamner. Thank you so much. All right. So we're going to move on to our second panelist. Our second panelist today is Dr. Karen Peterson, the Stanley M. Garn Collegiate Professor and Chair of the Department

of Nutritional Sciences at the University of Michigan School of Public Health, and she holds joint appointments as Professor of Environmental Health Sciences and Professor of Global Public Health as well.

From 2011 through 2019, she directed the NIEHS EPA-funded project titled "Children's Environmental Health and Disease Prevention" and currently she serves as associate director of the NIDDK-funded Michigan Nutrition and Obesity Research Center.

Her research focuses on the role of early life diet and toxicant exposures in the development of obesity and metabolic risk, cross-sensitive periods in the life course. She also has evaluated numerous population-based interventions to promote healthy lifestyle behaviors and reduce obesity and chronic disease risk in low-income and Latin women and children.

All right. I'm going to turn it over to you, Karen. Thank you.

DR. PETERSON: Wonderful. Well, thank you

very much, Dr. Casavale and to the organizers of this conference. And it's really a privilege to be here to launch up -- this incredibly important initiative. So I want to thank you all for that. So today it's really my great pleasure to talk about our research which is focused in on a number of toxicants.

But what I'll talk about today is the role of early life lead exposures and the potential for a diet to mitigate some of the effects of those exposures on children's health and their cognitive outcomes in the context of our ELEMENT birth cohorts which are based in Mexico City. I have no conflicts of interest and I've listed my current funding here which is from the National Institutes of Public Health.

So a number of speakers in the morning, including Dr. Dishaw, really provided an ideal basis for this slide which highlights the frameworks that guide our research. So there's three that I'd like to highlight. And what I'd like to do in this talk and as part of our panel is set our sights not only on early life lead exposure but the implications across

the children's life course.

So the early origins hypothesis emphasizes that environmental and nutrition exposures both before and shortly after birth do influence the developmental plasticity and this in turn can alter susceptibility to the emergence of chronic disease in later life including adulthood.

The EPA's life stage exposure framework is an important complement I believe to the early origins hypothesis. And this emphasizes that exposures not only during early life but also across sensitive periods of development can have health effects. And then finally life course epidemiology I think brings another really important perspective which is that we want to consider exposures.

So in this I'm including both toxicants, in this case lead, and diet during sensitive periods in children's development but also across generations could interact to increase a person's risk of chronic disease or adverse neurodevelopmental outcomes. So let's look under the hood a little bit.

So Dr. Karagas mentioned this morning the

study of epigenetics as part of one of the underlying mechanisms that we need to think about in this work. What is epigenetics? Briefly it could be considered the study of heritable, potentially reversible changes in gene function that occur without a change in the sequence of DNA.

So epigenetics can include the study of changes in cell number, proliferation and size, altered metabolic function of organs as well as the list of epigenetic mechanisms you see listed here which I won't go into in this talk. But I did want to highlight DNA methylation.

This is an epigenetic mark that we have found useful in our research primarily due to the ease of measurement in certain tissues such as blood. One other aspect of epigenetics I want to highlight, so this is a really classic figure from a very classic, and I would say seminal paper by Rob Waterland and Karin Michels in 2007, and what it does is focuses our attention on the first, say, 300 to 400 days of the first 1,000 days as a time period when epigenetic marks can be established and can be influenced by diet

and toxicants or other exposures such as stress but also points to the importance of later stages in terms of understanding epigenetic so-called propagation or aging.

So enough of the under the hood part. I'd like to talk about our work which is in the ELEMENT cohort in Mexico and the ELEMENT cohort stands for Early Life Exposure in Mexico to Environmental Toxicants. So we've heard a lot about different sources of exposure. And Mexico, and I think we need to keep in mind that Hispanics are the largest and the largest growing minority population in the U.S., with its extensive lead ore deposits and widespread use of lead-glazed pottery, has a unique history of exposure.

Like the U.S., but later, Mexico introduced unleaded fuels and then ultimately phased out leaded gasoline in 1997. So why am I bringing this to bear in a session that really is on considering toxicants in infant foods. As we know, lead has a long half-life. It is stored in mineralizing tissues such as teeth and bones for up to 25 years.

So among the potential nutrients that we

wanted to consider in the ELEMENT cohorts that were originally launched by Dr. Howard Hu and Dr. Mauricio Hernandez Avila at Harvard School of Public Health and the National Institute of Public Health of Mexico, we decided to focus on calcium supplementation.

So the first cohort was a randomized controlled trial of calcium supplementation at about the level of the DRI. It was 1,200 milligrams during lactation to see whether this would prevent mobilization of lead that had been stored in bone in the mothers when they were, you know, in their childhood.

Cohort 2 of the three cohorts was an observational study to analyze how lead was mobilized during pregnancy as a result of normal bone resorption and turnover and that allowed us actually to track neurodevelopmental outcomes as the children entered into childhood.

And then finally Cohort 3 was a randomized controlled trial again of calcium supplementation again at approximately levels of the DRI during both pregnancy and lactation. And then subsequently in

2008, we pooled mother-child pairs from these three cohorts and what we wanted to do was study the perinatal lead exposure, so during pregnancy and in the early postnatal period.

And we linked those to polymorphisms of genes that are relevant to cholesterol metabolism and examined their influence on neurodevelopment and behavior in childhood. And as you'll see here from these sets of articles which is just a selection, we were able to relate early lead exposures and childhood blood lead exposures to neurocognitive outcomes.

And I do want to highlight one of the papers was actually done by Dr. Kordas, and she reported that a dopamine receptor, DRD2, gene polymorphism was related to neurocognitive development in preschool years in children in the cohort. So what does this mean in terms of real-world practice and impact?

So let me highlight just a few of the findings that were ultimately incorporated into the CDC's 2003 Guidelines for Identification and Management of Lead in Pregnant Women and Lactating Women in the United States. First we found that bone

lead was not only associated with neurodevelopmental outcomes, but also lower birth weight and infant weight and length, that the contribution of mother's blood lead during pregnancy and then in lactation to breastmilk was associated with higher infant blood lead levels.

Mother's prenatal plasma and blood lead and bone lead were associated with lower cognitive development of children at the end of the first thousand days at 24 months but also at six to ten years of age. And then finally calcium supplementation, so there's some good news here, did reduce mother's blood lead levels and bone resorption.

So what we turned our attention next to in the Children's Environmental Health Center over the last decade was the longer term effects of early lead exposure on growth and on the tempo of maturation and to consider whether the mechanism was via epigenetic changes.

So I'm going to highlight just two sets of findings here. First is that we did find that early life lead exposure, whether it was indicated by

mother's bone lead, which would be an indicator of cumulative exposure in the womb, or early life lead exposure from one to four years of age, was actually negatively related to adiposity into adolescence and specifically lower body mass index, lower waist circumference, which does have implication for cardiometabolic risk, lower skin folds and lower body fat in adolescence, and at the same time, that mother's blood lead levels during pregnancy were related to delayed menarche in girls as well as bone lead and then early childhood lead being related to delayed pubertal onset in girls indicated both by breast development and by pubic hair development. However we did not find any effects on the tempo of sexual maturation in boys.

So one last look under the hood then if we want to think about avenues whereby lead is affecting neurodevelopment and outcomes that are relevant ultimately to cardiometabolic health and understand the implications potentially of a healthy diet in altering those exposures, did we find any evidence that lead was affecting candidate gene DNA

methylation. And the answer is yes, to some extent we have some evidence.

We found that at birth, and I won't go through all these studies, that cord blood lead was actually related to DNA methylation of IGF2, which is an imprinted gene, which means that it is not going to change in later life. But importantly we also found that early life lead exposure was related to epigenetic changes as late as adolescence during puberty.

So we found that prenatal lead exposure was related with LINE-1 DNA methylation. So this is a global indicator of DNA methylation. And at the same time, that mother's first trimester diet in pregnancy associated with that DNA methylation was in turn related to delayed menarche.

Currently we're looking at what we call epigenome-wide studies and have found that lead exposure in birth, early and late adolescence, that lead exposure in-utero is related to methylation of hundreds of what are called CpG islands in the gene, in the DNA and also that prenatal lead exposure is

related not only at that time period but to DNA methylation and hydroxy DNA methylation of genes that are known to be associated with prenatal lead exposure as late as adolescence.

And very recently, Christine Rygiel in our group published data suggesting that this DNA methylation affected by lead exposure ultimately could be mediating the relationship between lead exposure and infant neurodevelopment.

So there's lots more I would love to talk about. I'm sure all of us would. But let me just emphasize points that have been really underscored by other panelists. Foods we know are sources of micronutrients, these can affect the bioavailability or mitigate the effects of toxicants. And lead's impact can be influenced not only by calcium but also iron, zinc and antioxidant vitamins and phytochemicals.

And as we look I think to strategies to reduce exposure for children and strategies to mitigate that exposure, I think we really have to think about nutrition during pregnancy and lactation

and then keep our eyes on not only neurodevelopment but also effects on growth, tempo of maturation and the development of cardiometabolic risk.

So in closing I would like to thank our very large team of collaborators, my primary partner who is Dr. Martha Tellez Rojo at the National Institute of Public Health, the trainees in our group and of course the mothers and children who have participated for almost 30 years in this study. Thank you.

DR. CASAVALE: Thank you so much. All right. Wonderful. Thank you. All right. We're going to move on to our third speaker for our panel today. And our third speaker is Dr. Xiaobin Wang. She is the Zanvyl Krieger professor and director of the Center on the Early Life Origins of Disease at the Johns Hopkins University Bloomberg School of Public Health and School of Medicine.

Xiaobin is a physician scientist who established the Boston Birth Cohort when she was a pediatrician at Boston Medical Center. The Boston Birth Cohort consists of about 8,600 mother-child dyads of a predominantly urban, low-income, black and

Hispanic population in Boston, Massachusetts.

As a principal investigator of many large-scale NIH-funded studies in the Boston Birth Cohort, Xiaobin has led multiple institutional, transdisciplinary teams to investigate psychosocial, environmental, nutritional, genomic, epigenomic and metabolomic factors and gene-environmental interactions during crucial developmental windows including preconception, pregnancy, infancy, childhood and adolescence.

Her work aims to elucidate the root causes and biological pathways underlying high-impact pediatric and adult diseases and advance early risk assessment, early prediction and early prevention of disease. Dr. Wang?

DR. WANG: Thank you so much for the kind introduction. Good afternoon, everyone, and I'm so delighted to be here, and I also greatly appreciate all the previous panel speakers for their excellent presentations.

So in the next ten minutes, I would like to share with you what we have learned regarding in-utero

co-exposure to maternal circulating micronutrients and toxic metals on child's multiorgan health outcomes. So here's my disclosure, and I have no conflicts of interest pertinent to this presentation.

First, I am giving you a quick overview of the Boston Birth Cohort. It was initiated in Boston, Massachusetts when I was a pediatrician at the Boston Medical Center. So this cohort has been funded by the NIH for the past 20 years. It currently consists of over 8,600 mother-infant dyads who are enrolled at birth and followed consecutively up to 21 years.

So this is a predominately urban, low-income, racially diverse population. So in the Boston Birth Cohort, we have used a multimodality for data collection including standard questionnaire interview, REDcap survey, in-person study visits and measurements, electronic medical records, biospecimen collection from both mom and the baby. So in the following I'll present some relevant findings from the Boston Birth Cohort.

So this slide tries to address the first question we have which is how common is in the in-

utero exposure to heavy metals in this population. So here's what we learned. First of all, we found that mercury and lead are 100 percent detectable in paired mom cord blood samples.

So our data indicate that maternal source of mercury and lead can readily cross the placental barrier and leading to fetal exposure. We also demonstrated that the fetus can bioaccumulate mercury. So what this implies is that babies were already exposed to toxic metals even before born. So the next question is what is the nutritional level in this population?

So here I just used folate as an example. So the top panel is the folate distribution for the Boston Birth Cohort. And the bottom panel is from the NHANES. So you can see the distribution looks pretty similar. And what is implicated is that the folate distribution is quite variable. And so there's women who have insufficient folate, some in the optimal range and there's also many who have excessive levels.

So an important question I think today we're all asking is what are the multiorgan health effects

of those early life exposures? So in this slide, I summarize what we learned regarding in-utero exposure to heavy metals and their impact on children both in terms of physical health as well as the mental health.

As you can see, the early life exposure can affect a child's physical health like overweight, obesity, elevated blood pressure and precocious puberty. So the early life exposure can also affect a child's mental neurodevelopmental outcome including ADHD and autism as examples.

So from a life course perspective, one can imagine the effect of children will become young adults and future parents. Those chronic conditions likely continue to affect them and perhaps future generations, leading to intergenerational amplification of morbidity and mortality.

So in this slide I'll show you one concrete example. In this study, we examined the interaction between maternal folate and the lead levels on child's risk of obesity. So in this study, we made two important observations. First, if you look at the left panel, we found that those response association

between maternal blood lead level and the child's risk of obesity, as circled in red, even at very low levels of lead, we still observed a dose response relation.

So our study actually supports the CDC's recent guideline to further lower the lead cutoff from 5 to 3.5. If you look at the right panel, the yellow line indicates children of mom with low folate levels and the lower line that's the blue line indicated children of mom with adequate folate level.

So this figure indicates maternal adequate folate is protective against the obesogenic effect of lead in-utero lead exposure. So what is the potential implication of our findings? So as highlighted by this JAMA Network editorial, here is just a quote, "The adequate prenatal folate levels might serve as a complementary intervention strategy among populations affected by lead exposure." This study "opens the door to new questions about whether adequate folate intake might modify the adverse effects of other chemical exposures."

So to answer that question, this study further examines whether folate is protective against

the obesogenic effect of mercury. So as shown in the red box, indeed we found that maternal adequate folate may also counteract obesogenic effect of mercury exposure.

This study takes it one step further to address the question whether maternal folate counteracted the impacts of in-utero co-exposure to multiple toxins such as lead, mercury and cadmium on childhood obesity. So using Bayesian kernel machine regression, we showed that folate can indeed counteract the combined effect of exposure to this metal mixture on childhood obesity.

So here we have two lines. The red line represents the group with low folate. So here we can still see a clear dose response relationship between toxic metal mixture and child obesity. The blue line represents the group with adequate folate where we can see that the dose response relationship was almost eliminated.

So beyond the folate, I would like to echo previous panelists; that is, other micronutrients may also be beneficial under a different scenario. For

example in our recent study on the impact of in-utero exposure to metal mixture on childhood blood pressure, so we found the protective effect of manganese which can counteract cadmium's toxic effect on blood pressure.

In closing, I applaud FDA's Closer to Zero initiative. It is an important step to minimize dietary source of toxic metal exposure among young children. It opens the door for many future initiatives to improve maternal and child health.

I'll end my talk with a few quotes from this American Journal of Clinical Nutrition editorial: "Foods are vessels of essential nutrients as well as toxic environmental contaminants." "More research is warranted to better understand the impact of the complex interplay between nutrients and environmental chemicals on maternal and child health. Screening of prevalent environmental contaminants in mothers before and during pregnancy can inform individual risk assessment and the development of targeted nutritional interventions and environmental abatement."

I would like to thank you for your time and

attention. I will stop here. Thank you.

DR. CASAVALE: Thank you, Dr. Wang. Wonderful. And now for our last presentation before our panel discussion, so last but not least today I'm happy to introduce Dr. Kasia Kordas, Director of the Master's in Public Health concentration in epidemiology, Associate Professor of the Department of Epidemiology and Environmental Health and co-director of the Community for Global Health Equity in the School of Public Health and Health Professions at the University of Buffalo.

Kasia is an environmental epidemiologist with interdisciplinary training, research and leadership experience that combines global health, nutritional sciences, environmental health and human development.

Her research program investigates the effects of complex chemical exposures and toxicant diet interactions on the health and development of urban children, and I'm particularly excited that she works in the area of dietary patterns. So with that, I'll turn it over to Dr. Kordas.

DR. KORDAS: Thank you so much for this introduction. Thank you for the invitation. And I'm so happy to be contributing to this important conversation.

So I will talk about toxic element exposure in children and the relationship with diet and nutritional status. And while I will talk a little bit about my own research, my job here is to be summative and provide an overview. Here are my disclosures, and I have no conflicts of interest to declare.

So I want to start by pointing out and acknowledging, I think everybody has already done a great job of pointing to this, that the relationship among diet, metal exposure and nutritional status is complex. And this means that foods and diet are sources of toxic elements.

And when children consume diets that have these elements, they will absorb more metals into their gut or by their gut and therefore will have higher metal concentrations in their body as reflected by biomarkers of exposure in blood and urine. This is

moderated by nutritional status of the children.

So if children have nutrient deficiencies, there may actually be increased absorption of metals. On the other hand, food and diet are sources of protective dietary components of beneficial nutrients. After all, that's why we eat food. We want the nutrients. And some of these nutrients can contribute to lower absorption of metals at the gut level or can contribute to detoxification of metals in the body and therefore can contribute to lower metal concentrations in children's bodies. Again this can be moderated by nutrient supply or nutritional deficiencies in children.

So typically, and this has been mentioned several times already, but I think it's important to drive this point home. When we measure toxicants in foods, many times we measure them individually. And we think about these toxicants and their effects individually. But foods are a source of mixture. There's mixtures of metals. There's multiple metals either in individual foods and certainly in the diet as a whole.

And so we need to think about these exposures of mixtures because they together may result in more adverse health effects than individual metals. And this is important to think about as we set guidelines and recommendations.

Luckily foods are also mixtures of nutrients and these nutrients can have multiple benefits, both at the level of absorption, detoxification, as well as the previous speakers have already mentioned, moderating some of the toxic effects of metals. And I want to give you an example of what this looks like in one of our studies.

This was conducted by my former graduate student, Gauri Desai, and we were looking at estimate blood lead concentration in relation to food intake in 12- to 24-month-old children from the NHANES. And we wanted to look at different food groups, including milk and breakfast cereals as well as vegetables and even fruit drinks.

And here what we were looking at is reported intakes by the parents, not by the children, and compared zero intakes to children falling into

increasingly higher reported intakes of these different foods. And so for example, what we see for milk is that compared to children who didn't consume any milk, children who fell into the highest consumption group had lower estimated blood lead concentration. We see the similar result for breakfast cereals.

But on the flipside, when we looked at starchy vegetables, so root vegetables, we see that compared to zero reported intake, children who had higher intakes had higher estimated blood lead concentration. And the pattern is again very similar for fruit drinks which includes 100 percent fruit juices.

And so here is an example of how foods in children's diets can both be sources of metal exposures as we see here, but may also result in lower blood lead concentrations through higher consumption. And that is likely through the provision of nutrients that may counteract the absorption at the gut.

So I also want to talk about how different examples of how nutrients and toxicants interact in

the body. And I will start with the absorption at the gut, and we'll talk about lead because that's probably the best known example. So what's happening here is that we have an absorptive cell in the intestinal wall, in the small intestine. And to absorb iron, we have a mechanism called the divalent metal transporter 2.

But going back to this idea that nutritional status moderates some of these interactions and relationships, when children experience iron deficiency, the body responds by producing more of these transporters to give itself more opportunity to fish iron out of the body. And lead is actually a great opportunist. It doesn't have its own transporters, and it will use existing mechanisms to get into the body.

So in iron deficiency, it will have more opportunity to get into the body. And there's good evidence that children who have iron deficiency have higher blood lead concentration. Lead also uses intestinal transporters, and that's one of the I think mechanisms behind the findings that Dr. Peterson

talked about but also perhaps the mechanism for the findings that I showed you with milk intake a couple of slides ago.

It's important to note that there are different components or different nutrients in the diet. And so lead forms complexes with phosphate and carbonate and that makes lead less available to the absorptive mechanisms and these ligands decrease the bioavailability of lead.

Finally it's important to also note that fasting contributes to higher lead absorption. And so longer intervals between meals or going without meals is also detrimental to children. Once toxicants get into the body, there's also an opportunity for interactions.

And here I'm going to switch to arsenic and talk about the fact that multiple types of nutrients have been associated with higher inorganic arsenic methylation. So nutrients such as folate, vitamin B-6 and B-12, cysteine and methionine, all of which participate in the carbon cycling, the one-carbon metabolism are related to arsenic methylation.

Arsenic is methylated twice in the body and especially the doubly methylated arsenic is thought to be less toxic than the inorganic arsenic or singly methylated arsenic.

And so we think that these nutrients contribute to the detoxification of arsenic in our bodies. In cells, arsenic, cadmium and lead are linked to higher markers of oxidative stress. Toxic elements have been shown in animals to affect antioxidant enzyme activity by lowering it. But on the flipside, vitamin C and E inhibit reactive oxidant species and participate in chelation of metals.

Nutrients such as manganese, selenium and zinc, as well as copper, form part of antioxidant enzymes and therefore there's opportunity at the cellular level for these nutrient-toxicant interactions to occur.

And again going to the bone, which Dr. Peterson has already mentioned, arsenic, cadmium and lead are all deposited in bone. And we really don’t have very good evidence in children. there's more in adults, but not in children of how nutrients may

interact with toxic elements in the bone.

One study that has been published shows that a vegetarian diet in children are related to higher bone resorption. And so as bone is remodeled and there is resorption, there's more opportunity for these toxic elements to be potentially pulled out of bone.

So to show you an example in our own data is we're looking here at the association of toxic elements arsenic, cadmium and lead in relation to 8-OHdG which is a marker of oxidative stress in schoolchildren in my study in Uruguay.

And what we see here in green is that for children who are consuming low levels of vitamin C, there is a positive association with oxidative stress whereas for children consuming higher levels, that oxidative stress association doesn't seem to be there and is actually negative.

And so again going back to a summary, these complex interactions have implications for how we think about setting guidelines and how we think about relationships between toxic elements and food and

child health. I already talked about opportunities for dietary nutrients and nutritional status to affect what the levels of these toxic elements may be in the blood. But there's also opportunities for nutritional status and deficiencies as well as nutrients to have effects on child health. And again it's important to recognize, as has already been mentioned by speakers in the previous panel, that there are other sources of exposure both in early life and concurrently.

So to quickly summarize, in the context of low level exposure, which is probably the situation that's faced by most of the U.S. population, diet may be a source of exposure to toxic elements. Nutrients may counteract the absorption of toxic elements at the gut or help eliminate them from the body.

By acting on many of the same cellular and organ systems, nutrients and toxic elements both impact child health. And dietary exposures need to be treated as mixtures as we think about setting guidelines. So thank you, and I want to acknowledge my collaborators, and I'm happy to have further discussion.

DR. CASAVALE: Wonderful. Thank you, Dr. Kordas. So as we are bringing in our panelists for the nutrition panel today, I just want to start by thanking everybody for your wonderful presentations and taking your time to talk with us today. I'm really looking forward to the Q&A session we're about to have now.

And just as a reminder for those of you who are observing through the YouTube link, if you'd like to send an email through to the email address at Closer to Zero, you're able to do that. And if we're not able to answer it today, please also send us comments through the docket.

All right. So we have our wonderful panelists here, and I also have some wonderful questions for all of you. And so I am going to start with one background question. And this came up during your presentations. We heard you talk about adequacy a lot. And for the group that's here for this meeting, I thought it would be really helpful to hear some discussion particularly maybe from you, Heather, to start us off about what are we talking about when

we talk about nutrient adequacy and how does that relate to eating food.

DR. HAMNER: Great. Thank you. So I think that that's a really good point. And the Dietary Guidelines have used the dietary reference intakes as a way to really kind of think through the foods and the food patterns that can help those populations achieve adequacy when we're thinking about a dietary reference intake.

However as we really focus in on that birth to 24 months, that was harder to identify some of those food patterns to really make sure that they could meet all of those nutrients. And that's why there was a reocurring theme that every single bite counts for those young kids. Those foods need to be really nutrient-dense when we're talking about complementary feeding because there's just not a lot of room when it comes to calories to have that added sugar or other pieces.

So those foods need to be very nutrient-dense. And there are some nutrients that are going to be harder to meet through diet alone. Vitamin D was

one of those examples, and so making sure that we're really thinking through what the foods are that kids are eating and thinking about those vitamins and minerals that may still require some supplementation depending upon some of the other pieces that they are consuming.

DR. CASAVALE: Wonderful. Thank you. All right. And our next question for our panel today, I'm going to ask this question to Xiaobin, to Dr. Wang. And this one is about vulnerable stages of development.

So today we've heard really great examples through your presentations and the earlier panel on the effects of arsenic, lead, cadmium and mercury on child development and now, through this panel, also on nutrition's role in protecting child development.

So when we're looking at both toxicology and nutrition together, what do you see as the stages that really overlap there where children are most vulnerable to both nutrient inadequacy and also the adverse effects from toxic element exposure?

DR. WANG: Well, this is a great question.

I think the previous panelists already presented many relevant information and also laid a nice foundation for addressing this question. So here I'd just like to highlight what we know. And so if we look at the entire life course starting from in-utero or the fetal period, infancy, childhood, adolescence up to adulthood, so we have evidence that environmental toxins and nutrition can affect anyone at any life stage.

However if we look more closely at each life stage and based on current evidence, I would like to echo previous panelists, the first 1,000 days are very important. Within the first 1,000 days, I would emphasize the fetal period is most vulnerable. So here I just want to give you -- just highlight a few reasons why I say that.

First of all, the fetal period is the beginning of life and it sets the stage for later growth and development and health. And second, although fetal period is relatively short, it's only nine months compared to an 80-year average lifespan, the fetal period is most amazing if you think about

it, most amazing and critical period. It starts with a single cell, a fertilized egg. Then it undergoes rapid cell division, differentiation, organ system formation and functional development.

And therefore the fetal period represents the most rapid period of the growth, development and also its most sensitive for environmental perturbations that including nutrition insufficiency as well as toxicants. And so here I'd just give you two concrete examples. One is the maternal period conception folate deficiency which as you know can lead to neural tube defect. So that's a devastating condition.

For this reason, in 1998, U.S. FDA launched a mandatory folic acid fortification program. So in our recent study we learned and although the folic acid was originally aimed to prevent neural tube defect, we found adequate maternal folate may also counteract intergenerational obesity and counteract lead and mercury obesogenic toxicity related to maternal lead or mercury exposure. So this is an added benefit which we didn't know before, now we

know.

So in short, from a toxicology and nutrition perspective, they are relevant to entire lifespan. But fetal period is most vulnerable to both nutrition inadequacy and the toxicants. I'll stop here.

DR. CASAVALE: Wonderful. Thank you. Thank you so much. So Dr. Wang just gave the great example of folate. Dr. Kordas, in your presentation, you gave a lot of different examples.

I was curious what interactions between nutrients or metals and metalloids do you feel are really best understood and specifically, as we think forward, we've been talking a lot today about what we already know, but as we think forward, are there some areas of theory or emerging science where we may learn about other nutritive components that may play a role here.

DR. KORDAS: Thank you. I think that's an excellent question. So you will notice that I spent quite a lot of time on iron and lead as well as arsenic and nutrients that participate in one-carbon metabolism. And there's a reason for that. I think

that those are the best studied examples that we have. And so I think that they are most well understood. And there's clearly more to do.

There's multiple nutrients that we haven't even really thought about. And most of our -- I think most of our research has focused at the gut or at this level of detoxification. But as we've already seen in presentations, there's more. There's tissues. There's cells.

And there's an opportunity for protection or interaction at the cellular level as well as for linking these interactions to health effects, whether that be obesity or later in life or oxidative stress or these effects, molecular effects that Dr. Peterson has mentioned which are methylation at the epigenetic level.

So I think that there's quite a bit that we know. But there's actually more that we don't. And so I think that this is very much ripe for further investigation to understand these relationships.

DR. CASAVALE: Wonderful. Thank you. And you mentioned Dr. Peterson. Dr. Peterson, in your

presentation, you mentioned antioxidants. And it led me to think that, you know, we talk -- when we talk about nutrition, we talk about the nutrients for which we have DRIs. But there's a lot of nutritional components to foods that go beyond the traditional DRIs, and that's true for whole foods as well as human milk.

And so I just wanted to ask you if there was any emerging areas related to those other components such as antioxidants that -- some nutrients are antioxidants, but there's a lot of antioxidants in these heathy foods where we also see these chemical mixtures. And where are you seeing some of the emerging science in that area that we should perhaps be focusing on and have our ear to look for?

DR. PETERSON: I think that's a great question. And some of the -- so overall most of the evidence is still coming from animal studies. And as you know, in our group, June Rippon is leading this research, but looking at whether -- it seems to be there's some evidence for I guess we'd say herbs that are added to foods, so curcumin, I think Dr. Karagas

talked about we need to really understand what is in other food products that are not -- that may be either eaten differently in different ethnic groups and are in a range of different foods that could vary by culture or tradition. And then different antioxidant components as well as phytochemicals.

So I think that list is quite complex. But there might be ways to target what we know so far based on animal studies. But then we'd probably need to go back to the TDS, for example, the Total Diet Study, and see if there would be a way to collect that information and get a better sense of how they're being consumed and then relate them to toxicants.

So just some initial thinking. But I think we have a long way to go to understand what's happening in humans, particularly in children.

DR. CASAVALE: That's wonderful. Thank you. All right. So this next question is going to be on vulnerable populations. I'm going to ask Dr. Heather Hamner to start us off there.

So Heather, as Closer to Zero moves forward, we are working to of course decrease toxic element

exposures but also their effects, and we're really taking this multifaceted approach. So we'll be doing things such as prioritizing foods for action levels, targeting messages and of course collaborating and fostering new collaborations with other federal programs and with our agencies.

So with thinking from this population-level perspective, are there groups or subgroups of children that you see that we should really be particularly concerned with because of poor nutrient status or inadequate nutrient intake that might put them at particularly higher risk for those effects from arsenic, lead, cadmium or mercury?

DR. HAMNER: Thank you. It's a great question. So I think one of the first things to think about are the people who are in all of our studies, and so making sure that we have data on individuals who may be understudied or underrepresented is really important so that we can actually make clear recommendations and have the information to support that and know really who we need to target. So I think that's one particular piece.

The second population that I think comes to mind is when we're thinking about children who are eligible for different federal programs like WIC, so the Special Supplemental Nutrition Program for Women, Infants and Children. And for those children, making sure that they are participating in that program is really important.

There have been multiple studies showing that WIC can help improve dietary patterns. But for children who are eligible but are not participating, we see differences. And that's a really important piece to think about, knowing that there are going to be dietary differences based on their decision to participate or not in a federal program.

And then the last population that comes to mind is again thinking about the consumption patterns for milk status, so for those very young infants and when we have infants who are consuming human milk or infant formula or a mix, they have different food consumption patterns. And thinking about that when we think about nutrient adequacy and where we want to really target, that's important. They also have

different feeding practices.

So infants who are consuming infant formula are more likely to start complementary foods early. And that's again we need to kind of keep that in the back of our minds as we're thinking about who to really target and think about. Thanks.

DR. CASAVALE: Wonderful. Thank you.

DR. KORDAS: Do you mind if I --

DR. CASAVALE: Yeah. Go ahead. Yeah.

DR. KORDAS: Do you mind if I add --

DR. CASAVALE: Please do.

DR. KORDAS: So one of the groups that I think we may also want to focus on are children who have just different consumptions patterns than the general population. And so in the first panel, the point was made that exposure is a function of consumption as well as the level of the toxicant in the food.

And so thinking about children with special needs or children with autism who repeatedly eat the same type of food and may therefore have very high exposure to a certain type of food and if those have

higher levels of toxicants, then they will have higher burdens of exposure. Children who have food allergies or children who are picky eaters, they have different patterns of food consumption than a typical child. And so that may be a special subpopulation that may be important to focus on as well.

DR. CASAVALE: That's wonderful. Thank you. That's really excellent. Any other additional thoughts from Dr. Wang or Dr. Peterson?

All right. So the next question is really about -- more about dietary patterns and using those to really think holistically about exposures which we heard a lot in the presentation from the nutrition panel today. So those food intake and dietary patterns happen over time. And we know that some foods have higher levels of toxic elements than others but also that low levels of exposure can be rather ubiquitous in some categories of food.

So identifying and prioritizing which foods to focus on through Closer to Zero is one challenge. So from your perspective, how could we take a more holistic approach using dietary patterns research to

better understand diets that are consumed as mixtures over time and exposures of both the contaminants but also those beneficial and essential aspects of food?

So I'm going to see if Dr. Peterson, if you can comment on that question, and then I think Dr. Kordas, with your background in dietary patterns research, it will be really lovely to hear your thoughts as well.

DR. PETERSON: Great. I'm so inspired by this question, and I keep writing notes over here next to the computer. So here's my initial thoughts. So typically in dietary pattern research we might do a method of statistical clustering called PCA and we would say in a given population, there's three or four dietary patterns. There's a healthy one, a less healthy one, which we usually call Western, and a mix.

So what I'm wondering is whether it would be useful again to take, for example, the Total Diet Survey and it looks like there's increased emphasis on regional foods and somehow constitute two or three or four different types of dietary patterns and then constitute something that comes out of the market

basket that really captures this is how people are eating these foods together. So it would be a reductive approach. But would be a place to start.

And then building on Dr. Hamner's points, I know originally the TDS I think sampled from the Continuing Survey of Food Intakes of Individuals which oversampled low-income populations and which we have used in the past when I was on the WIC food package revision committee.

So it raised for me the question about whether there's a way to also relate the market basket to lower income populations and/or, as Dr. Hamner pointed out, populations that would be eligible and/or participating in WIC or perhaps SNAP.

And then my other idea, I don't really know how to operationalize this, would be to take the WIC food package, for example, say in the under twos or the first year of life and then look at how that's being consumed in relationship to the rest of the diet.

And then of course I would want to go back to Dr. Choiniere -- Conrad Choiniere, and say, so, is

there any way we could do some downstream research using the Total Diet Survey to understand what is jointly coming from that combined diet of supplemental foods and foods that are usually consumed in lower income families. So those are my initial thoughts.

DR. CASAVALE: Wonderful. Thank you. Dr. Kordas?

DR. KORDAS: I really love those ideas, and I think it would be great to look at what Dr. Peterson has suggested. I think that in terms of diet patterns, some of the areas where we don't yet have very good evidence is -- and I think Dr. Hamner did a really nice job talking about, you know, so what are the foods that children are eating and how is that changing and it also relates back to the earlier panel where Dr. Karagas was talking about switching from formula or breastfeeding to solid foods and the related exposure levels.

So across childhood, from early to adolescence, there are changes in diet patterns. They don't remain constant. I mean, it's really important to characterize them and understand what they are.

But they don’t remain constant. And so think about how does exposure change as diet patterns change across childhood, I think that's really important.

I also like the view of dietary patterns rather than foods because thinking about foods, they change probably more daily than a diet pattern would. And so if you eat sweet potatoes, going all the way back to the first panel, eat lots of sweet potatoes and you buy them in a different place or there's some kind of a change, it's a little less stable to relate that exposure to a specific food.

But also again we eat foods. We eat whole diets, and so thinking about exposure in terms of diet quality and insufficiency and moderation as well, I think that there's a lot of questions that would need to be -- that would need to be answered. I'll stop here and let others respond or to contribute.

DR. CASAVALE: Yeah. I just want -- the point that you made, Kasia, about foods changing more often than the dietary patterns change really resonates because when we do research with very young children, we find that looking over the past 24 hours

is not as representative as looking over the last 36 hours when it comes to energy intake.

So it brought me back to facts like that that really help us to think of when we're thinking of very young children who may only have been exposed to three foods in their infancy, really thinking about dietary patterns over time helps us to better understand what those exposures are versus just cross-sectional discrete time points. So thank you for that.

So we only have about five minutes left, and I have a couple more questions I really want to hear from you guys on. So, and this next one is for Dr. Wang. So this one is on estimating the effects of both the toxic and nutritive aspects together. And so we often discuss toxicology and nutritional effects on child development independently.

But the research of this panel really brings these disciplines together. So how can these potentially counteracting effects be quantified or qualified for specific foods or eating patterns? How can we really get our heads around how to bring those

details together to take -- to inform actions?

DR. WANG: Wow, that's another great question and also a challenging question. Given we only have short time, I'll try to be brief, but just share my thoughts. Indeed traditionally toxicology and nutrition are studied separately in the context of child growth and development.

I really appreciate the organizers of this workshop to bring experts from both aisles together. So this is truly a catalyst opportunity to stimulate our thinking and to come out with some innovative ideas. So from both scientific and the translational perspective I think it's truly significant and important to have a better understanding of the toxin-nutrient interaction.

So I think from today's panel presentation, it's at least we have evidence suggesting that the foods and the toxins are indeed interacting. And so down the road, regardless of whether you are a toxicologist or a nutritionist, when you examine toxicology facts, you need to think about nutrition because nutrition could modify. And as a

nutritionist, when you think about, oh, what is the dose response, what is the optimum nutrition range or value or intake, you also need to consider individual exposure.

Maybe different exposure warrants different type of nutrition with different level of nutritional level, at least as we demonstrated in the Boston Birth Cohort. And so I think this actually going forward, first of all, the two aisles come together.

Secondly, we need a multidisciplinary team, and thirdly, we need key data elements in order to study this. And interim exposure, we're no longer just happy with nutrition or toxin. Both need to be measured. And in terms of the outcome, not only do we need to study the short term, we also need to study the long term because, particularly for chronic disease, we demonstrated for obesity, diabetes, hypertension, cancer, we didn't demonstrate but the future studies likely will demonstrate.

So for those long-term outcomes with long latency, so we do need longitudinal studies. So if we're specifically interested in the vulnerable

period, the critical period, then the longitudinal birth cohort study will be the best bet. So I'm going to stop here and have my other panelists to weigh in.

DR. CASAVALE: All right. Other thoughts? All right. We have one more minute. So I'm going to use that minute, and I'm going to take a question that we got from the email.

And this question says can you please address the perceived discrepancies between Dr. Peterson's report of delayed menarche, breast development, et cetera, in girls associated with metal exposures and Dr. Wang's presentation mentioning precocious puberty for girls as an outcome of metals exposure. It might take more than a minute to answer.

DR. WANG: Karen? Karen, would you like --

DR. PETERSON: I'll go very briefly. So our results are really confined to looking at very early lead exposure. So specifically we were looking at bone lead. So that is an indicator of sort of sub chronic in-utero exposure to the fetus and then in one of the studies we also looked at cumulative lead exposure from one to four years of age. So it was

very particularly related to lead exposure.

And I think I would turn it over to Dr. Wang, who spoke more broadly about other metals exposure. The others -- the contexts are different. So I think the Mexico City population may have different countervailing factors, protective and counter protective factors than the Boston Birth Cohort. That might be another thing to think about. It is a fantastic question, I have to say though.

DR. CASAVALE: Go ahead, Dr. Wang.

DR. WANG: Do I have time or are we done?

DR. CASAVALE: Yes. Go ahead.

DR. WANG: Okay. Ten seconds. First of all, besides the fetal period, I think the adolescent period, just from a pediatric period, it's another critical period. It's the transition from children to adulthood. And it has tremendous implications for future reproduction, for cardiovascular health, for bone health, for a whole range of health, mental health, physical health.

So if we think about early life exposure either to metal or maybe in the future we study other

toxins, at least for lead and mercury, we know they are endocrine disruptors. Just from a biological perspective and from a biological plausibility perspective, those are endocrine disruptors. And puberty is very much driven by endocrine -- it truly is a tremendous activity during puberty.

So I would say this is a very, very important topic. If there is opportunity, I think definitely we should pursue this line of investigation.

DR. CASAVALE: Wonderful. Thank you so much. Well, I can't thank the panel enough. I really enjoyed having a panel discussion with you all today and for your willingness to participate and get our minds turning to think about bringing nutrition and toxicology together at this first meeting.

Michael's going to take us to a quick break before we come back to hear oral testimony and then we'll close out today with some remarks from Dr. Conrad Choiniere. Thank you so much.

DR. KORDAS: Thank you.

MR. KAWCZYNSKI: All right. Thank you.

Thank you so much, panel. That was phenomenal. And at this time, we are going to take probably about a 15-minute break. So we will be right back.

(Break)

MR. KAWCZYNSKI: Hi, and welcome back from that short little break. We are now going to go into our open public comment section of the meeting, and I will hand it off to my co-moderator, Jessica. Jessica, take it away.

OPEN PUBLIC COMMENT

MS. ROWDEN: Great. Thanks, Michael. Yes, so as Michael mentioned, we're here for our public comment session. So we're here to listen to stakeholder perspectives and reactions on topics related to Closer to Zero. I want to welcome all of our public comment presenters. Thank you for taking the time today to prepare your remarks and offer public comment.

This afternoon, we have a number of folks who are ready to give comments. Please ensure that you're all situated so that you're ready to give your comments when your name is called. I will call each

of you individually by name, and you will have three minutes to present your remarks. Please be respectful of time. If you do go over the three minutes, you'll be asked to wrap up and submit your full comments to the docket.

Joining us for this segment, we have a panel of FDA subject matter experts who are present to listen to the comments offered. I'll turn it over to them to introduce themselves, first starting with Dr. Conrad Choiniere.

DR. CHOINIERE: Hello. Dr. Conrad Choiniere, and I direct the Office of Analytics and Outreach at the Center for Food Safety and Applied Nutrition at FDA.

DR. CASAVALE: Hi. I'm Kellie Casavale. I'm senior nutrition advisor in the Office of Nutrition and Food Labeling at CFSAN, FDA.

DR. SOUTH: Good afternoon. My name is Paul South. I'm a division director in the Office of Food Safety at FDA's Center for Food Safety and Applied Nutrition.

DR. DENNIS: Good afternoon. I'm Sherri

Dennis. I'm the director of the Division of Risk and Decision Analysis in CFSAN. Thank you.

MS. ROWDEN: Thank you all. At this time, we're going to be turning off our cameras, and we're going to be starting the public comment process. Our first public commenter is Charlotte Brody, from Healthy Babies Bright Futures. Charlotte?

MS. BRODY: Thank you. As you said, I'm Charlotte Brody, a registered nurse and the national director of Healthy Babies Bright Futures.

Last year more than 3.6 million babies were born in the United States, an average of 9,877 babies every day. The FDA Closer to Zero plan must be designed so it progressively gets the level of toxic elements closer to zero for all these babies and to do so as quickly as possible. Almost half of these children, 49 percent, are babies of color.

Closer to Zero must recognize both the toxic burden and the dietary differences for these babies and their others and set action levels that protect the most vulnerable child of color and, by doing so, protect all children.

In September, JAMA Pediatrics published a study of the blood lead levels of more than a million young U.S. children. More than half of the children tested had detectable levels of lead in their blood. The study also confirmed past findings. A young child is more likely to have elevated blood lead levels if they live in pre-1950s housing or live in poverty or live in a predominantly black ZIP code. Many children live with all three threats and may also not have the nutritional status that mitigates exposures.

Closer to Zero must fully protect them. While we don't have the same kind of test results for other toxic elements as we do for lead in young children, studies of women of childbearing age warn of the disproportionate prenatal exposures and disproportionate levels of heavy metals in breast milk. Published analyses of CDC biomonitoring show that compared to white women of childbearing age, black women have higher concentrations of lead and mercury, Hispanic women have more mercury, inorganic arsenic and cadmium and Asian women have higher concentrations of lead, mercury, inorganic arsenic and

cadmium.

Dietary preferences contribute to these disparities and strengthen the case for Closer to Zero setting action levels that fully protect the children that are most exposed in-utero and from non-food sources and from the aggregate exposure to multiple toxic elements as well as other neurotoxic chemicals.

One of President Biden's first executive orders directed all federal agencies to develop policies to address the disproportionate health and environmental impacts on disadvantaged communities. Closer to Zero should be a stellar implementation of that EO. The 9,877 babies starting to eat solid food every day isn't just a number, and Closer to Zero shouldn't be a bureaucratic, slow-moving, academic exercise. These are real children that are being threatened by a harm that FDA has the authority to minimize.

Healthy Babies Bright Futures encourages you to swiftly and substantially lower the levels in the foods babies eat and create brighter, healthier futures for more babies including, and especially for

babies of color. Thank you.

MS. ROWDEN: Thank you, Charlotte. Our next public commenter is Samuel Cohen, from the University of Nebraska Medical Center.

DR. COHEN: Thank you. My name is Sam Cohen, and I'm professor in the Department of Pathology and Microbiology at the University of Nebraska Medical Center. I appreciate the opportunity to make comments here.

First of all, I'd remind everyone that this morning Dr. Woodcock indicated in her introduction that current foods in the United States are really safe. Others indicated that we needed to have a balanced approach and to be careful not to sacrifice good nutritional options in the process of trying to lower toxic levels.

For example, seafood, a good source of nutrition, as we were told earlier this afternoon, is very high in arsenic. For another example, large epidemiology studies in the U.S. and Japan have shown no evidence of increased cardiovascular disease or cancer in individuals with rice exposure.

In fact, in one study from Japan, there was a decreased risk of cardiovascular disease with increasing rice consumption. I just want to encourage the group doing this review to critically and carefully review the science. The speakers this morning emphasized utilizing mechanisms to enhance our understanding of other various adverse events. Especially important is to consider the importance of thresholds for the effects being evaluated and the substances being assessed.

As an example is arsenic. Basic chemistry, biology and epidemiology strongly supports the presence of a threshold. For cancer, the threshold is around 100 parts per billion in drinking water. Drawing straight lines from high exposure effects to possible effects at low exposures is biologically inappropriate and grossly overestimates risk. It is critical going forward to not inappropriately frighten the public. Thank you.

MS. ROWDEN: Thank you for your remarks. Our next public commenter Aparna Bole, from the American Academy of Pediatrics.

DR. BOLE: Thank you. Good afternoon. As was said, my name is Dr. Aparna Bole. I'm a pediatrician in Cleveland, Ohio, and I'm here today on behalf of the American Academy of Pediatrics, a professional organization with 67,000 pediatrician members across the United States.

I currently serve as the chair of the AAP's Council on Environmental Health and Climate Change. The AAP appreciates the opportunity to provide input at today's public meeting on this important children's public health issue. Exposure to toxic metals such as lead, inorganic arsenic, cadmium and mercury is harmful to the developing brain and has been associated with developmental and behavioral problems even at very low levels.

There is no known safe level of exposure to these metals for children. Exposure to toxic elements has a disproportionate effect on infants and toddlers because their brains are rapidly developing, especially during their first 1,000 days.

Children consume more water and food as a proportion of their body weight than adults, meaning

they have both higher exposure to these elements than adults and also are more susceptible to their harmful effects. The AAP is concerned by the toxic metals currently found in baby and toddler foods which are elements from the water and soil used in agriculture and from other sources.

To best protect children's health, we must prevent their exposure to toxic metals from all sources, including food. The FDA has a critical role to play in reducing levels of toxic metals in baby foods and we are grateful that FDA has launched this important work. Interagency collaboration will be critical to the success of FDA's action.

In particular, USDA administers key federal nutrition programs such as the Special Supplemental Nutrition Program for Women, Infants and Children, WIC, the Supplemental Nutrition Assistance Program, SNAP, and other programs, and the potential impact to those programs and the families they serve should be adequately considered.

The AAP is encouraged by the FDA's Closer to Zero action plan and appreciates the agency's

commitment to a science-driven, transparent and inclusive process that engages many stakeholders. We also appreciate the agency's attention to addressing potential unintended consequences of measures to reduce toxic metal exposures.

Any final comprehensive policy approach must address these issues holistically. A comprehensive response should consider effects on parental options and purchasing behavior. For example, if policy changes designed to promote safety in packaged baby food inadvertently drive parents to exclusively use homemade baby foods, we know these (indiscernible) have lower levels of toxic metals and in some cases may not be nutritionally adequate.

This broad stakeholder engagement would also help prevent unintended consequences for federal nutrition programs an ensure that all families have equitable access to safe and nutritious foods.

The AAP has called for greater efforts by policymakers and industry to reduce toxic elements in the food supply, promote effective risk communication with the public and develop and implement policy

changes to reduce exposure.

While the Closer to Zero action plan is a welcomed step, it is essential that this work proceed expeditiously. We urge the FDA to adopt a more aggressive timeline for finalizing action levels and reducing exposures as quickly as feasible. Thank you.

MS. ROWDEN: Thank you, Aparna. Our next public commenter is Max Shterngel, from the Office of Attorney General, State of New York.

MR. SHTERNGEL: Good afternoon. My name is Max Shterngel. I am an assistant attorney general in the Office of New York State Attorney General Letitia James.

Four weeks ago, our office led a coalition of 23 attorneys general in submitting a petition to FDA urging the agency to take a number of actions to help protect children from toxic heavy metals in baby food in the near term. My remarks explain how our petition is consistent with and supports the goals of Closer to Zero.

Some initial observations: first, FDA has recognized that ingesting lead, inorganic arsenic,

cadmium and mercury in food at an early age is associated with adverse health effects including neurodevelopmental challenges. Second, the baby good industry generally responds to FDA guidance identifying limits for such contaminants. Third, it is appropriate to consider whether proposed FDA guidance limits are feasible.

Our office supports the risk-based approach of Closer to Zero. FDA projects that by 2025, it will have finalized action levels for lead and possibly for inorganic arsenic and may have proposed action levels for cadmium and mercury. These future actions will help protect babies born a few years from now. But that timeline begs the question what can FDA do in the short term to reduce heavy metals in baby foods.

With the babies and parents of today firmly in mind, our petition urges FDA to take three concrete steps as soon as possible to fill the gap while the Closer to Zero plan is pursued.

First FDA should by April release interim proposed action levels for lead, inorganic arsenic, cadmium and mercury. To do this, we urge FDA to adopt

a method to benchmark interim guidance levels to the baseline performance already being achieved by the best performing manufacturer within each relevant market segment and to revisit and revise the interim levels periodically. Our petition includes a detailed discussion of this method. This commonsense measure would drive innovations in the supply chain and in manufacturing practices and spur a race to the top throughout the baby food industry in months, not years.

Next our petition asks that FDA reevaluate its 100 ppb action level for inorganic arsenic in infant rice cereal. Given FDA's prior findings that a lower limit would reduce health risks, the agency should further protect babies through this action.

Finally we urge FDA to provide clear guidance to baby food manufacturers that finished product testing should be performed as a preventive control under the Food Safety Modernization Act. This practical approach will help the baby food industry and suppliers adapt to whatever action levels are eventually adopted under Closer to Zero.

If FDA guides all companies now to match the best performers in limiting heavy metals and to test finished products, industry will be primed to meet FDA's health-based guidance limits. FDA believes in a new era of smarter food safety and agrees that the youngest Americans need the most protection from heavy metals in food.

We applaud FDA for placing the baby good industry on the Closer to Zero path. The actions sought in our petition enable this to be achieved more swiftly and broadly by promoting healthy competition and innovation. Thank you.

MS. ROWDEN: Thank you for your remarks. Our next public commenter is Betsy Ward, from the USA Rice Federation.

MS. WARD: Thank you. My name is Betsy Ward, and as president and CEO of USA Rice, I'm here representing the U.S. rice industry.

Rice is the only ingredient in baby food that already has an FDA action level on contaminants, specifically arsenic despite rice being just one of the many foods we feed our infants and children. The

U.S. rice industry takes arsenic in rice issues very seriously. We've spent millions of dollars researching mitigation strategies and we've shared all of our research findings with the FDA.

We support FDA's Closer to Zero initiative and in particular the agency's reliance on scientifically rigorous data collection and analysis to drive regulatory decisions, the same process the agency used to establish the action level for rice. Arsenic is a widespread and naturally occurring element that exists in rocks, soil, air and water and is taken up by everything that's grown in the ground and/or uses water, including fruits, vegetables and grains.

But we certainly understand consumer anxiety related to infant foods and heavy metal exposure. However a fair amount of confusion stems from inaccurate reporting and false equivalencies, which, when repeated enough, stand in for fact.

For example, when discussing arsenic levels in rice, not everyone takes the time to explain the important difference between organic and inorganic

arsenic. Exposure to high levels of inorganic arsenic can have negative health effects and it's why FDA set a very low threshold of a hundred parts per billion inorganic for rice used in infant rice cereal.

We are proud of the fact that based on FDA data, the overwhelming majority of U.S.-grown rice and certainly all rice used in infant cereal has met the levels set by FDA so that rice can continue to be used as a healthy ingredient in infant cereal.

As we've studied this issue, the rice industry has been responsible and transparent and we have achieved significant reductions leading to rice used in infant cereals consistently testing below the established action level. However, as I said, it's not just rice that children are eating and the lack of attention to other ingredients used in infant foods creates serious difficulties for our industry.

For example, we've recently seen product recalls and hesitancy or refusal of same manufacturers to use rice as an ingredient even though the rice being used tested below the action level. So unless and until other ingredients used in baby food have

action levels established for any contaminants they may contain, we encourage FDA to shift its focus from end-product testing that tells an incomplete picture to ingredient testing.

We're proud that not only are the levels of inorganic arsenic in rice grown in the United States the lowest in the world according to the United Nations and the WHO, but our vigorous testing and compliance with the FDA action levels continues to lead to a downward trend in already low levels.

Thank you again for the opportunity to share our views and highlight the efforts and continued commitment of America's rice farmers to provide a healthy and nutritious staple food for both children and adults. Thank you.

MS. ROWDEN: Thank you, Betsy. Our next public commenter is Michael Hansen, from Consumer Reports.

DR. HANSEN: Thank you for the opportunity to talk about the FDA Closer to Zero program. My name is Michael Hansen, senior scientist for Consumer Reports.

Consumer Reports has been testing a variety of baby foods and fruit juices for heavy metals for a number of years. We note that in recent years, more and more studies are coming out to show that heavy metals, but especially inorganic arsenic, lead and cadmium are more hazardous than previously thought with new studies finding adverse effects, particularly neurobehavioral effects at lower and lower levels.

Consequently we think there are enough data on the toxicity of heavy metals for the FDA to set mandatory standards or limits on baby foods and fruit juices for infants and young children and so think that the timeline for the Closer to Zero program is too prolonged.

Based on CR testing, we think that FDA could take action immediately on various heavy metals in baby foods, especially fruit juices. For instance, rather than wait until April 2024, FDA should immediately finalize the inorganic arsenic apple juice action level of 10 parts per billion.

Next FDA should set a new limit of inorganic arsenic in fruit juices of three parts per billion.

Our testing of heavy metals and fruit juices published in the January 2019 issue of Consumer Reports found that the majority, 58 percent of samples were below the three part per billion limit of inorganic arsenic indicating such limit is achievable to meet.

We therefore urge the FDA to set a new three part per billion limit for inorganic arsenic that is applicable to all affected types of juice in the form of a mandatory standard or, at a minimum, an action level.

For lead, the FDA should set a mandatory standard of lead in fruit juice of one part per billion. Although there is a five part per billion limit for lead in bottled water, the American Academy of Pediatrics advocates for a one part per billion lead limit for school drinking water fountains. Our testing of fruit juices found that a majority of juice samples could meet this one part per billion limit which demonstrates that this is an achievable standard.

For cadmium, whose risks are similar to lead, FDA should set a mandatory standard of cadmium

in fruit juice of one part per billion. Our testing of fruit juices found that over 90 percent of juice samples could meet this one part per billion limit. So establishing a mandatory limit of one part per billion cadmium for fruit juice would not be disruptive.

Finally we urge the FDA to move more quickly in setting action levels or limits for a range of baby foods. In developing the action levels for lead, we note that the FDA determined an interim reference level, or IRL, for dietary lead of three micrograms per day for children and 12.5 micrograms per day for adults.

FDA's IRL was based on the CDC's blood reference level for lead of five micrograms per deciliter of whole blood. However last month the CDC lowered the blood refence level from five micrograms per deciliter to 3.5 micrograms per deciliter of whole blood, representing a 30 percent decrease.

Thus we urge FDA to revise their IRLs using the new blood reference level to roughly 2.1 micrograms per day for children and 8.3 micrograms per

day for adults prior to developing action limits for lead in baby foods. Thank you.

MS. ROWDEN: Thank you, Michael. Our next commenter is Cheryl Callen, from the Gerber Products Company.

MS. CALLEN: Good afternoon. My name is Cheryl Callen, and I'm speaking on behalf of Gerber Products Company. Let me begin by acknowledging the moderators, speakers and organizers of today's public meeting for dedicating their time and expertise to this important topic.

For over 90 years, Gerber has been providing nutritious, high quality foods for babies and toddlers, and our commitment to their health and wellbeing is unwavering. This is why we support the FDA's Closer to Zero action plan. Heavy metals occur naturally in many crops. They are taken up through the soil and water in which they grow.

As part of our quality and food safety program, Gerber sets limits for heavy metals in certain ingredients and finished foods and we work with our suppliers and growers to minimize their

presence. Our efforts include lowering inorganic arsenic in the rice used for infant cereal, seeking lower levels of cadmium in whole grains and carrots and minimizing lead that may be found in sweet potatoes.

These nutritious foods are important for a healthy varied diet. Carrots, sweet potatoes, whole grains, not to mention beets, spinach and kale which are also susceptible to heavy metal uptake. I think we all agree we want our children to learn to love these nutritious and nutrient-dense foods and a wide variety of foods overall.

Acceptance of new foods begins in early childhood, making baby food an important part of the journey. Ensuring these health foods remain a part of a varied diet for infants is essential as we work together to minimize the presence of heavy metals.

Gerber also conducts one of the largest dietary intake surveys of children from birth to 48 months of age. This is our Feeding Infants and Toddlers Study. Conducted in 2002, 2008 and 2016 with a total sample size of 10,000 children, FITS provides

a robust data set of what children are eating and their nutrient intake.

While time won't permit an in-depth discussion, FITS shows that in general the diets of infants is largely nutritionally adequate with a critical and concerning exception that almost 20 percent of older infants do not get enough iron, a nutrient essential for cognitive development in the first years of life.

FITS data also shows the importance of certain foods in ensuring nutrient adequacy varies depending on whether infants are breastfed, formula-fed or mixed-fed. In a recent paper by Finn, the impact of infant cereal consumption on nutrient adequacy highlights the potential for low intakes of iron, zinc, folate, vitamin B12 and choline for the breastfed baby not consuming infant cereal.

Gerber is committed to providing infant cereal and many grain choices and a wide variety of other nutritious foods to promote adequate intakes of iron and other essential nutrients. Finally Gerber pledges to continue our work to minimize heavy metals

in foods consumed by this most vulnerable population.

We welcome the opportunity to support the FDA in implementing their action plan and we are committed to ensuring access to important data on the food and nutrient intakes of young children to better understand how a variety of foods provides optimal nutrition and promotes a healthy dietary pattern. Thank you.

MS. ROWDEN: Thank you for your remarks. Our next public commenter is Cassie Huang, from the Environmental Defense Fund.

MS. HUANG: Hi. My name is Cassie Huang, with Environmental Defense Fund. Thank you everyone for the opportunity to speak in this forum.

EDS has a longstanding history of protecting the health and safety of young children, particularly from exposure to heavy metals. We do this in part by urging FDA to develop tighter heavy metal standards necessary for preventing contamination of food.

I'm going to tell you today about an investigation that underscores the need for more action and regulation to prevent heavy metal

contamination in baby food. Healthy Babies Bright Futures, with support from EDS, conducted a study investigating lead levels in canned pears after seeing results from FDA's Total Diet Study showing that lead in canned fruit, particularly pears, was higher than lead in fresh or frozen fruit.

Suspecting this was a symptom of a bigger problem, we bought and tested the contents and components of almost 100 containers of pears of different brands from grocery stores around the United States. We found that canned pears have up to nine times higher lead levels than other types of pears. Depending on the amount of pear assumed to be eaten by a child in a day, these high levels can exceed the three micrograms of lead maximum daily intake for children set by FDA. This is also known as the interim reference level, and it is based on CDC's blood lead reference value. CDC recently lowered the blood lead reference value and thus we expect FDA to correspondingly lower their reference value as well.

We alerted FDA of these high lead levels and they did not take action. FDA explained that their

calculation of lead in pears does not exceed the maximum daily intake for lead. In coming to this determination, FDA assumed that the lead in canned pears was the only lead ingested that day by a child.

As we've heard over and over again from scientists and stakeholders and FDA today, children are exposed to lead through many different routes. FDA cannot continue to assess risk in a vacuum, taking into account just one chemical at one time. In their lack of response to the elevated levels of lead in pears, FDA did not account for all the other ways a child is exposed to lead, which taken together may very likely exceed FDA's maximum daily intake for lead.

As EDF has recommended multiple times in the past, FDA needs to change the way they evaluate toxic chemicals' risk to health. FDA is not following through on their word to consider aggregate exposures to toxic chemicals nor are they considering the cumulative effects of lead, cadmium, arsenic and mercury together, as has been promised.

We recommend that FDA move swiftly to

investigate sources of heavy metal contamination when its own data indicates high levels and, most importantly, FDA must act to set tighter heavy metal standards in foods eaten by infants and children that incorporate our scientific understanding aggregate exposure and cumulative, additive and synergistic effects. Thank you.

MS. ROWDEN: Thank you, Cassie. Our next public commenter is Jensen Jose, from the Center for Science in the Public Interest.

MR. JOSE: Good afternoon, and thanks for the opportunity to comment. My name is Jensen Jose, and I'm regulatory counsel for the Center for Science in the Public Interest.

CSPI is one of the oldest, science-based consumer advocacy organizations that is focused on improving our food system and supporting healthy eating. In addition to representing CSPI, I myself am a parent of a one-and-a-half-year-old toddler and I have another baby on the way. So as you can imagine, this issue of nutrition and food safety is near and dear to my heart.

Nutrition is critical for the -- nutrition is critical to the health and development of our children. however there is no need for a tradeoff between exposure to contaminants and proper nutrition. Action levels should prioritize toxicity and exposure. Once set, companies can meet these action levels and nutritional demands by responsibly sourcing ingredients with lower levels of contaminants and, if needed, use a combination of other fruits and vegetables with lower contaminants that meet children's nutritional needs.

For example, carrots and sweet potatoes are commonly consumed by children under two and are high in vitamin A, potassium and other vitamins and minerals. Unfortunately baby foods containing these vegetables frequently contain higher levels of lead compared to baby foods made from other vegetables and fruits. However we do not need to have -- we do not need to set higher action levels out of fear that we will eliminate these baby foods with significant nutritional benefits.

This is true for two reasons. First,

responsible sourcing should not present a significant burden on manufacturers. Not all baby food with carrot and sweet potatoes have been found to have lead and not all carrots and sweet potatoes have excessive amounts of lead. In 2020, there were 3.4 pounds of sweet potatoes and 3.4 billion pounds of carrots produced in the United States. Companies just need the proper motivation to find safer ingredients and source responsibly.

Second, sweet potatoes and carrots are rich in vitamin A and potassium. But they're not the only available sources of these nutrients. There are very few unfortified foods that can equal vitamin A content for the vitamin A content of carrots and sweet potatoes. However butternut squash and pumpkin are vegetables that are common in commercially available baby food and are rich in sources of vitamin A. according to USDA's food data central database, those vegetables provide roughly one-third to two-thirds as much vitamin A as carrots and sweet potatoes.

For potassium, its underconsumption by infants and toddlers could pose a public health

challenge or concern as established by the 2020 DGA committee report. Fortunately butternut squash and pumpkins contain as much potassium as carrots and sweet potatoes. In addition, many fruits found in baby foods can provide similar amounts of potassium. These include bananas, peaches, prunes and apricots. FDA could work with the USDA's food pattern modeling team to explore the impact of these alternatives on typical diets of infants and toddlers.

To recap, the FDA should focus on setting action levels based on toxicity and exposure. By responsibly sourcing ingredients to meet these action levels, companies can provide nutritious, safer food for our babies. Thank you very much.

MS. ROWDEN: Thank you for your remarks. Our next public commenter is Scott Faber, from the Environmental Working Group.

MR. FABER: Hi. My name is Scott Faber. I'm speaking today on behalf of the Environmental Working Group. But I've also worked for the food industry. So I know from personal experience that setting standards to protect our babies' developing

brains from toxic metals will not increase the price of baby food.

The cost of baby food is driven by much more than the cost of raw ingredients. Energy, transportation, labor, marketing, processing, packaging, these all make up a much bigger share of the overall cost of making food and many other factors, not just the cost of making food, impact the price that consumers pay in a grocery store.

So arguments being made that higher baby food prices will result if we take steps to protect our babies' brains is simply wrong. How do I know? because the food industry made the same bogus arguments when food companies opposed efforts to protect us from pathogens. FDA didn't believe it then, and FDA should not believe it now.

The implementation of FSMA has been a great success. And guess what. Did protecting us from foodborne pathogens increase the price of food? No. Here's how else I know. When the FDA set draft levels for arsenic in infant rice cereal and apple juice, prices did not change.

But here's what else our experience with infant rice cereal and apple juice told us, that FDA should not look to current food and farm practices to assess what's achievable. To meet the levels proposed by FDA, baby food companies simply changed where they sourced their ingredients to avoid soils with high levels of arsenic. And as a result, average arsenic levels in infant rice cereal and apple juice fell dramatically by 37 percent and 63 percent respectively, again with no change in the price consumers pay at retail.

As I speak today, 10,000 babies will start to eat baby food. The timelines proposed by the FDA are just too slow to protect our babies' developing brains. Dr. Woodcock, there are immediate health risks. We must go faster, or millions of babies will be needlessly exposed to high levels of toxic heavy metals.

What's more, linking final standards to the best of what's currently available in the marketplace rather than what can be achieved if we challenge our farmers and baby food manufacturers would be a

mistake. For too long the FDA has let the baby food companies, not the FDA, decide what's safe and our babies have paid the price.

FDA must quickly set tough, enforceable standards, must require baby food companies to test finished products and must make those tests public. If a baby food exceeds the standards that protect our babies, if should not be in the market. Thank you for the opportunity to speak today.

MS. ROWDEN: Thank you, Scott. Our next public commenter at this time will be Theodora Scarato, from the Environmental Health Trust.

MR. KAWCZYNSKI: Go ahead, Jane.

MS. HOULIHAN: Okay. This is Jane Houlihan, with Healthy Babies Bright Futures. And I just want to thank FDA for prioritizing the Closer to Zero program. We really think this can play a big role in protecting babies' brains from toxic heavy metals in food.

So I'd just like to raise five brief points. One, we really think it's critical that the program's timeline be accelerated. You heard that for every day

that passes, almost 10,000 more babies begin eating solid food. Yet for lead and arsenic, your proposed final standards are three or more years from now and for cadmium and mercury, no date has been specified for final standards. So we really urge you to accelerate that timeline and get final standards in place as quickly as possible.

Second, to protect babies' brains, the standard must account for additive impacts of multiple toxic metals, what we heard so much about in the panels this morning. To date, FDA has proposed only a few standards for single metals in single foods, arsenic in infant rice cereal or lead in juice. But our 2019 study shows that a quarter of all baby foods contain all four toxic heavy metals you're reviewing, arsenic, lead, cadmium and mercury. And your own recent developmental neurotoxicity research confirms the additive impacts of these metals.

Just one example, preliminary analysis from ACT Associates shows an estimated 12 million IQ points lost among children ages zero to two and that's just from dietary exposures and just from lead and arsenic

in foods. So considering additive impacts is really going to be important.

Third, the standard needs to be proven by what's necessary to protect children's neurodevelopment and not by current contamination levels of current processing and farming methods that you heard from Scott Faber. This has all failed to protect children.

And we've seen that when you act, the food industry can respond quickly. Your Total Diet Study shows that within just a few years of your issuing draft guidance, arsenic levels dropped dramatically in both infant rice cereal and apple juice simply through changes in sourcing and farming practices.

Fourth, again, standards should be driven by what's needed to protect babies' brains and not by conjectures of supply issues or nutritional deficits because experience shows that when new standards go into place, the market adapts.

When the state of Oregon removed infant rice cereal from its Women, Infants and Children program in 2016, and this is a program available to about half of

the babies in the state, four to five alternative cereals were made readily available at an equivalent price point and there weren't reported supply issues or gaps in nutrition for babies. And this experience shows that the manufacturers and vendors can adapt to the new standards with nutritious and cost-effective alternatives.

And then fifth and finally, we completely agree with your intention to set standards for foods beyond the baby food aisle because we know that many parents serve children homemade and not store-bought food, and Conrad's data showed that really clearly. So they're pureeing or dicing whole sweet potatoes and carrots from the produce aisle or they're buying frozen.

We're currently testing almost 300 samples of store-bought baby food and corresponding homemade food and that data will be public early next year, and we're finding heavy metals at comparable levels whether the food is store-bought or homemade. So setting standards that apply beyond the baby food aisle will really be important. And really

importantly, this will also protect women of childbearing age and pregnant women as well as children.

So thank you again for the opportunity to provide comments and for this really informative session you've put together today.

MS. ROWDEN: Thank you, Jane. Our next public commenter is Theodora Scarato, from the Environmental Health Trust.

MS. SCARATO: Thank you. A growing body of research indicates that wireless microwave radiation and other types of nonionizing electromagnetic fields can impact brain development and research has also found synergistic effects between electromagnetic fields and known carcinogens as well as other toxic physical or chemical agents such as those found in baby foods, specifically lead.

As an example of this research on synergies and tumor promotion, studies that have investigated blood lead levels combined with cellphone radiation found increases in ADHD symptoms in children. Research on mother/child pairs found children exposed

to higher material blood lead levels in-utero associated with delayed neurodevelopment in relation to increasing cellphone radiation exposure.

There's also research looking at people with metal in their mouth. Research found people with mercury amalgam exposed to Wi-Fi frequencies had higher mercury in their saliva. Experimental animal studies out of Jacobs University found cellphone radiation at very, very low levels when combined with a known carcinogen far more than doubled the tumors in the liver and lung in the carcinogen-exposed mice.

Toxic and heavy

Metal exposures are likely potentiated by nonionizing electromagnetic fields because they can increase the permeability of the blood-brain barrier. Nonionizing electromagnetic fields are used to deliver drugs into the brain and in various new medical treatments, precisely because of these effects, the levels of microwave, which is wireless radiofrequency radiation, associated with albumin leakage are very, very low, far lower than FTC's safety limits which are now 25 years old.

Babies are handed cellphones as toys. Parents are unaware that cellphones, iPads, wireless baby monitors and speakers all emit wireless radiofrequency radiation that's absorbed into their bodies, their babies' bodies. They're also exposed to magnetic fields, nonionizing electromagnetic fields from various electronics in the nursey, parents holding their babies for hours while simultaneously using laptops, computers, working, cellphones resting against the baby while breastfeeding and so forth.

The safety limits for human exposure to wireless radiation were set in 1996 and no agency has done a systematic review of the research on brain development, not then nor ever. The EPA, NCI, CDC and FDA did not develop safe limits based on the data on neurological impacts and certainly not on the cumulative effects or the synergistic effects. Children are more vulnerable to cellphones and wireless radiation.

They have smaller heads, thinner skulls, more conductive brain tissue and the radiation penetrates more deeply and more intensely into their

brain centers, especially those responsible for memory. They have more active stem cells in their bodies, and research shows stem cells are more sensitive to radiofrequency radiation. And government regulations were based on an over 200-pound man's head, not a child's head and children of course will have a lifetime of exposure from before they are born, just like with other toxic agents such as in baby food.

Research on prenatal exposure in humans and animals have found behavioral impacts, hyperactivity. Animal studies have found damaged brain cells and increased oxidative stress from wireless radiation. So to protect brains, the FDA must ensure a systematic review of the research. Safety limits must consider the synergistic effects to ensure toddlers and babies are protected. And we also hope that the FDA will update its page which makes it seem like wireless radiation is safe even for children. Thank you so much.

MS. ROWDEN: Thank you for your comments. Our next public commenter is Tom Neltner, from the

Environmental Defense Fund.

MR. NELTNER: Hi. Thank you for the opportunity to talk. And I want to reiterate what Cheryl said about how good it was for FDA to hold this session. It's been six months or so since FDA started the Closer to Zero plan and it's time to keep having more of these. We need this kind of engagement. The quality of the speakers was great.

They reminded me how important it is that we address arsenic and cadmium and mercury and lead and we have to consider the cumulative effects. It also reminded us that nutrition can help soften the blow from these chemicals but that not all the kids get a proper nutrition. And FDA cannot be setting standards to protect only those kids that get all the best nutrition. They need to protect all the kids.

This is an irreversible effect on the brain. I know we heard a speaker talk before about cancer and arsenic. But what we're talking about, based on the presentation, brain development. And you only get one chance to build those brains. And because there doesn't seem to be a threshold for some of these

substances, and particularly lead and arsenic, we need to put on the shelf the word safe and talk about safer and focus on continuous improvement.

Setting a standard now doesn't keep it good for years to come. Second I want to emphasize that FDA needs to get out into the public its Total Diet Study data from 2018 and 2019 and what it was able to collect in 2020. We're working blind on this because we're not getting the best data out there.

And when we look at best practices, as Kathy pointed out, some brands, some things have very high levels. So any standard should be based on those fruits that are grown and vegetables grown with the best practices. For instance, a farm, any fruit or vegetables grown on a farm that's been treated with lead or arsenic should not be used and you have to separate those out.

Finally if FDA is going to be using cost of food, as Scott pointed out, it's got to do a thorough evaluation to show that cost is actually changed, that reformulating has made a big difference because I don’t see it in the evidence. The bottom line is we

need to be focused on safer food and continuous improvement.

We need to recognize that short-term exposures result in long-term harm and it's important for FDA to not just move forward methodically but to move faster. We can do more. We need to get these levels out. We need to see standards for arsenic, cadmium and lead and we need to get them tightened on a regular basis. It is not just a onetime event. The arsenic standards that were set back in 2014, we now know we can do better. Feasible is not just enough. Thank you.

MS. ROWDEN: Thank you, Tom. Our next public commenter is Hilary Thesmar, from The Food Industry Association, FMI.

DR. THESMAR: Good afternoon. My name is Dr. Hilary Thesmar, and I am the chief food and product safety officer and senior vice president of food safety at FMI, The Food Industry Association.

FMI is the trade association that advocates on behalf of a wide range of members within the food industry value chain from food wholesalers and

suppliers to grocery retailers. As a food scientist, a registered dietician and, most importantly, a mother of two children, this is not only a very important issue to me, but it is a priority for FMI and our members and it is critical that we get this right to assure exposure to toxic elements from foods for babies and young children is as low as possible.

The food industry considers the safety of the products they sell its top priority and FMI members remain dedicated to delivering safe, nutritious and affordable food every day.

FMI commends the FDA for establishing the Closer to Zero program and holding the first public meeting to evaluate the science and impact of toxic element exposure and nutrition and crucial developmental stages. FMI and our member companies agree that FDA is the authority on setting food safety standards and support the plan to approach this issue through an interactive process that is guided by science and input from stakeholders.

We agree the federal standards regarding these elements in foods for babies and toddlers as

well as foods of interest should be established by FDA through the evaluation of existing and new scientific data, information and resources. Food and commodity production practices, along with achievability and feasibility of standards should be considered.

We urge the FDA to devote the appropriate resources and work diligently to set action levels and to take measures to limit toxic elements in foods in a way that is transparent and engages stakeholders from the scientific community.

The food industry is committed to working through this complex issue with the FDA and we offer our support to evaluate nutrition and health concerns, food production challenges as well as best practices in sampling and testing methodologies used by the industry and regulators for monitoring levels of toxic elements in foods. Thank you for this dialogue, and we look forward to future engagement with the agency.

MS. ROWDEN: Thank you, Hilary. Our next public commenter is Molly Rauch, from Moms Clean Air Force.

MS. RAUCH: Hi. Good afternoon. This is

Molly Rauch. I'm public health policy director for Moms Clean Air Force, an organization of over 1 million moms and dads fighting to protect our children from toxic chemicals, air pollution and climate change. Thank you for the opportunity to comment today.

Earlier this year, a congressional investigation showed that there are significant levels of toxic heavy metals in baby food. And when that happened, across the country, our members were startled and deeply concerned to learn that high levels of arsenic, lead, cadmium and mercury are in our babies' food and even worse that these contaminants are basically not regulated.

Despite the fact that our food is contaminated by metals known to cause permanent harm to the developing brain, there's basically zero oversight of this problem. This is unacceptable to parents. Toxic metals harm babies' developing brains and they're reaching our babies' brains in combination with other toxic exposures from the air, water and soil and these effects are cumulative.

The reality is that this harm is irreversible and permanent and it may often be subclinical but it's still real harm to real children and it's imminently preventable. It's a top priority of Moms Clean Air Force that this kind of exposure is prevented and it's time for FDA to make that happen.

Allowing baby food companies to regulate themselves and voluntarily set their own standards has failed to protect our babies. It's kind of like asking my teenage son to voluntarily limit his time on TikTok as he sees fit. It's just not a helpful strategy. It can't be left up to the companies.

But FDA's Closer to Zero plan is just too slow to protect our babies and toddlers. It's way too slow, given what we already know. We need immediate aggressive interim standards and ambitious deadlines for FDA action. If FDA waits until 2024 or later to set final standards for toxic heavy metals in baby food, millions of babies will be unnecessarily exposed to substances known to compromise their development. Parents have a right to know what we're feeding our babies.

So that means that baby food must also be tested regularly to ensure that the standards are being met and that those test results must be made public. Products that don't meet these standards should be recalled as a health threat. And standards must consider the effects of toxic heavy metals in combination, not one by one, to protect our babies' brains.

Finally, and we've heard some about this from previous speakers, standards should not be driven by what's achievable based on current manufacturing and farming practices. We already know that those current practices allow toxic metals to readily enter into our babies' food and from there into our babies' bodies. Instead our standards must be based on what's needed to protect our babies from permanent harm to their developing brains and their other organs. As parents, we cannot settle for anything less. Thank you.

MS. ROWDEN: Thank you for your comments. Our next public commenter is Serenity Carr, from Serenity Kids Baby Food.

MS. CARR: Hi. My name is Serenity Carr. And like many of the commenters today, first and foremost, I'm a concerned parent. I also happen to be CEO and cofounder of a young baby food company called Serenity Kids, and I'm here in support of Closer to Zero.

I started this company for my daughter Della because I was disappointed with how most baby products contained sugary fruits, low nutrition grains or rice. I created baby foods made from nutrient-dense, pasture-raised meats, organic vegetables and healthy fats to help parents meet the USDA's nutrition recommendations for children under two years old. My three-year-old daughter still eats our products every single day.

Back in 2018, I learned about the risk of heavy metal contamination in baby foods and our team immediately began a quality program to help monitor and lower heavy metals through strategic supplier relationships. After all, I was feeding them to my own baby.

Back then, we were a very small company with

limited resources. But we decided that reducing and eliminating toxins was really, really important to us. So we found a way. Since there are no clear FDA standards, we used a combination of European Union and California Prop. 65 guidelines.

We have created a program that ensures that our products have as low as possible levels of heavy metals and other environmental contaminants. We carefully vet our suppliers, test all ingredients to ensure they fall within our limits and regularly test final products to ensure nothing was missed.

We also partner with Clean Label Project, a third-party watchdog that tests our products annually and helps us get better and better. It has not been easy. It's taken a ton of work, time, money, careful planning and relationship building to get to this point. We even came close to cancelling launches of key products because we had a hard time finding clean ingredients. Fortunately we have somehow always been able to succeed in the end and we're still a small company.

We believe the baby food industry needs

clear standards set quickly that are both achievable and aspirational to ensure safer products today and a consistent reduction in the levels of heavy metals in the future. Serenity Kids products are proof that it is possible.

We're prepared to share our test results, our quality program to support other baby food companies and do anything else we can do to help make baby food cleaner and safer for America's children. Thank you for the opportunity comment in support of regulating heavy metals in baby foods.

MS. ROWDEN: Thank you for your comments. Our next public commenter is Trisha Dello Iacono, from Moms Clean Air Force.

MS. DELLO IACONO: Good afternoon. My name is Trisha Dello Iacono. I am the mom to four young children and the senior legislative manager for Moms Clean Air Force. Thank you for this opportunity to provide my comments today.

Moms Clean Air Force is an organization of more than 1.5 million moms and dads across the country fighting to protect our children from toxic chemicals,

air pollution and the climate crisis. Lead, arsenic, cadmium, mercury, these are not ingredients that we want in our baby food. These harm our children's health and they cause damage to our babies' developing brains. No mother should have to worry about what she is putting into her baby's mouth day after day.

The science is clear on this. The FDA must take immediate action to remove heavy metals from our food. As a mom to four growing children, this issue hits home. I live in southern New Jersey with my husband and four children, including Josie, my youngest child who is just shy of two years old. Josie is a voracious eater who wants meals and snacks coming her way at all times.

Feeding my youngest alongside my four-year-old and two teenagers is a daily challenge and like so many parents I am often tempted to reach for what is most convenient in our kitchen or pantry. Like so many parents, I spent years assuming that baby food was safe. But now I understand that there is a shameful lack of standards to protect our babies from heavy metals in their food. This must end.

I am no stranger to the damage toxins can do to our children. in 2012, my family was poisoned by toxic chemicals due to a train derailment and massive chemical spill causing my now 11-year-old Liam to have chronic health problems. And then in 2016, Liam was exposed to and again sickened by a toxic exposure, this time, the heavy metal mercury from the flooring in his elementary school.

As a parent to a child who has suffered impacts from not one but two toxic chemical exposures, I know to take toxics seriously and so should all of us. The simple act of feeding my children is fraught with worry so long as baby food may be contaminated with heavy metals like lead, arsenic, cadmium and mercury which undermine our children's ability to thrive.

No mother should ever have to hold up a jar and ask herself how safe is this baby food. It's why we need to take action on heavy metals in baby food and it is why we absolutely need the FDA to make it easier for parents like me to nourish their babies without unknowingly putting them at risk. It's high

time we parents are given the protections from toxic metals that we think we already have. thank you.

MS. ROWDEN: Thank you, Trisha. Our next and final public commenter is Tracy Gregoire, from the Learning Disabilities Association.

MS. GREGOIRE: Hello. Thank you for the opportunity. My name is Tracy Gregoire, and I'm the health children's project (indiscernible) mission is to (indiscernible) healthy children project works to eliminate the preventable causes of neurological (indiscernible) harmful chemicals and heavy metals.

I'll start with some (indiscernible) one in five American children (indiscernible) 1 in 54 children has autism and approximately (indiscernible) in the U.S. over 7 million children, or 14 percent of all public schools (indiscernible) special education. Among these students, the most common disability category is specific learning (indiscernible) the etiology or cause of these disabilities (indiscernible) one or more factors that the National Academy of Science has (indiscernible) environmental factors and toxic chemicals contribute to over a

quarter of these disabilities.

The good news is that these causes are totally preventable. We know that food is not only a significant route of exposure to heavy metals but also a more easily preventable (indiscernible) FDA needs to focus on cumulative exposures and cumulative effects. A child may be exposed to a "safe" amount of arsenic in one food but that same child may be exposed to lead from lead-based paint or other heavy metals in their environment and in their diet.

We ask the FDA to carefully consider and account for the risk of heavy metal exposures from (indiscernible) when added to other likely sources of exposure as well as the synergistic impact of multiple neurotoxins. As you shared today, foods babies and young children eat are not just in the baby food aisle. Children eat produce and vegetables and other foods that are not from (indiscernible) baby food aisle.

Going beyond the baby food aisle also protects (indiscernible) I also appreciate the one speaker who mentioned that kids who already have

neurological disabilities like autism may have an even higher risk due to habits like eating (indiscernible) potentially increasing (indiscernible) how is the FDA going to account for these children at higher (indiscernible) neurological impacts.

How will you address other vulnerable populations such as children of color and ones that are from (indiscernible) are protected given the data that they have higher exposures to various neurotoxins from multiple sources.

Finally I want to highlight that there are viable nutritious safer alternatives to some foods like rice that are likely to have much higher levels of heavy metals. For example infants can avoid rice cereal and instead eat other nutritional (indiscernible) barley.

FDA only has to (indiscernible) pull their infant rice cereal to know that companies and the public, including moms like me, know that the exposure from rice and baby food is not worth the risk. It is better to limit or eliminate some foods than to avoid permanent harm to children's brains.

Children need and deserve FDA's leadership (indiscernible) take swift action that will truly (indiscernible) by reducing children's and pregnant (indiscernible) exposure to toxic heavy metals, we protect (indiscernible) --

MS. ROWDEN: Thank you, Tracy. And thanks to all of our public commenters today for your remarks this afternoon, and we look forward to your full comments submitted to the docket. Right now, I'd like to turn it over and welcome back Dr. Conrad Choiniere, and he will provide our closing remarks today. Thank you.

WRAP-UP AND LOOKING AHEAD: WHAT'S NEXT FOR CLOSER TO ZERO

DR. CHOINIERE: Thank you. Thank you, Jess, and thank you to the panelists that we heard from today and sharing their valuable time and expertise with us on many of the issues, or at least some of the issues that we are grappling with in Closer to Zero, particularly the windows of susceptibility to exposure as well as nutrition, critical points and ages that we need to be concerned about so that can help us and

inform us as we move forward in setting action levels for foods for babies and young children.

I also want to thank all of the commenters today that provided some comments as well as all the stakeholders that joined us in this meeting today. We weren't able to take and answer all of the questions that came into our email box. But we have them, and we will certainly look for future opportunities to address many of the issues that were raised in those questions.

I do want to reiterate FDA's commitment to this Closer to Zero plan. We are working as expeditiously as possible to lower exposures from foods to these contaminants by setting action levels as well as providing consumers with some advice about how they can improve their diets in order to be protected against these exposures.

We want to work in a way that does not lead to any unintended consequences as well as work collaboratively across all of our stakeholders so that it can result in meaningful and sustainable reductions in exposure. Many of the issues that were raised in

the mailbox as well as by the commenters we do plan to address in future meetings.

As Dr. Starke-Reed mentioned at the beginning of the meeting today, I appreciate USDA's commitment to collaborating with FDA on this important initiative, particularly to deal with some of the issues that are outside of FDA's domain, some of the -- some of the -- particularly some of the agricultural issues and we are on track to have some sort of a meeting to start talking about those in a public space in the next year, 2022.

We are also planning on having a number of other meetings, whether they're public meetings such as this one, maybe some more informal webinars as well as scientific discussions to talk about the other aspects of Closer to Zero and some of the issues that were raised in many of the questions we received today, for instance, the manufacturing processes, best practices that can be put into place that many manufacturers have already adopted.

Hopeful that we can share the information across the various stakeholders so other parts of the

industry can also adopt those practices. Again looking at agricultural practices, thinking more in depth about some of the levels of exposure. We have a meeting on December 1st actually. We are cosponsoring a colloquium with the Society of Toxicology to talk about arsenic and its role and its impacts at early ages. It is open for registration. I don't have the link here. But if you Google SOT FDA arsenic, you should be able to find that page.

I do want to encourage you to continue to submit the questions and comments that you have related to Closer to Zero. We have a docket for those questions and comments. You can continue to send questions to the email box. However it's not always monitored. So I would recommend that they be submitted to the docket so that we are sure to capture them.

So again, thank you all. this has been a great meeting. I appreciate all of the support that I've heard from all the stakeholders, and I look forward to your continued engagement as we move forward. Thank you.

MR. KAWCZYNSKI: All right. Thank you, Conrad, and thank you everyone who has joined us today. This meeting has concluded. Have a great rest of the week and a happy Thanksgiving.

(Whereupon, at 4:00 p.m., the proceeding was concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, STACIE DORSEY, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

STACIE DORSEY

Notary Public in and for the

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I, SONYA LEDANSKI HYDE, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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