Use of Orally Ingestible Unapproved Prescription Drug Products Containing Fluoride in the Pediatric Population
July 23, 2025 | 9:30am-4pm *(eastern)*

Transcript

Welcome

Susan C. Winckler, RPh, Esq., Chief Executive Officer, Regan-Udall Foundation for the FDA

Susan C. Winckler, RPh, Esq. (00:00:34):

Hello and welcome. Thank you for joining us both here in person and online. I am Susan Winckler, and I have the privilege of serving as the Chief Executive Officer of the Reagan-Udall Foundation for the FDA. We are pleased to convene this public meeting in collaboration with FDA on the use of orally ingestible unapproved prescription drug products containing fluoride in the pediatric population.

(00:00:59):

For those of you who are new to the Foundation's work, we are the non-profit, non-government organization created by Congress to help the FDA do more to protect and promote the public's health. One way we do that is by convening meetings just like this to help the agency gather information and hear perspectives from a range of stakeholders. These engagement opportunities help inform the agency's work. Of note, the Foundation does not advise the FDA on nor engage in regulatory decision-making.

(00:01:33):

Today's discussion is focused on information sharing and illustrating the many scientific, clinical and public perspectives on today's topic. We are here to engage in productive civic discourse to have a respectful exploration of various perspectives.

(00:01:53):

Before we begin, I do need to do just a few housekeeping issues. Most of our speakers and several attendees are on site here at the FDA White Oak Campus in Silver Spring, Maryland. We also have a significant number of virtual participants. Because of the size of the meeting, virtual attendee cameras and microphones will remain off throughout the event with one exception. Those of you who were confirmed in advance to present stakeholder comment will be granted access to unmute and show video during the public comment period after lunch. We are recording the meeting and we'll post the recording along with the side deck and transcript on the Foundation website next week. For our virtual participants, a link to today's materials can be found in the chat now. Those of you in the room should have received materials when you checked in.

(00:02:44):

So before we dive into the agenda for the day, I thank our colleagues at the FDA Center for Drug Evaluation and Research. We appreciate your partnership and support in planning this public meeting. In addition, I'm profoundly thankful to each of our presenters and discussants and public commenters for investing their time in preparing for and participating in this discussion. An illustration exercise like

today is only possible through the generosity and engagement of each of you. As I noted, the meeting is convened to gather information about the clinical use and safety of orally ingestible unapproved prescription drug products, tablets and drops, that contain fluoride and are intended for use in children. This is not a decision-making meeting nor is it a meeting about fluoride in water. We appreciate your participation and look forward to a thoughtful and informed discussion.

(00:03:45):

Now, let's talk a little bit about this agenda. We are going to begin with a session that explores the current scope and use patterns of these products. After a brief mid-morning break, we'll explore safety concerns and potential risks associated with these products, with a focus on oral and gut health, neurocognitive development, and thyroid function. We'll then take a lunch break and move to a critical part of our meeting, providing an opportunity for members of the public to share perspectives and experiences. When we announced the meeting, we issued an open call for public comment, inviting any member of the public to request time to speak. I am thrilled that we were able to accommodate every request to speak. We also offered those commenters the opportunity to submit a slide to support their remarks, and so you will see those when we get to that section. When we get to the public comment component, I will explain exactly how that will run, but we do not need to run through that right now.

Opening Remarks

Jacqueline Corrigan-Curay, JD, MD, Principal Deputy Center Director, Center for Drug Evaluation and Research, FDA

(00:04:50):

Let me first turn then for opening remarks from the Center for Drug Evaluation Research and particularly from Dr. Jacqueline Corrigan- Curay, who is the Principal Deputy Center Director at FDA's Center for Drug Evaluation and Research. She has been a long-time partner of the Foundation, which we appreciate and brings her unique legal scientific policy and clinical background to lead stakeholder initiatives and make tangible progress in complex policy. So with that, Dr. Corrigan-Curay, the stage is yours.

Jacqueline Corrigan-Curay, JD, MD (00:05:27):

Thank you so much, and thank you Susan, and good morning everyone. Thank you for taking the time to join us today, both in the room and online. We're very happy to partner with Reagan-Udall to discuss the use of orally ingested unapproved prescription drug products containing fluoride in the pediatric population. I also want to acknowledge some of our FDA staff. There's many who've worked and brought this meeting together, including Carolyn Wong, Dr. Jacqueline Burgette, Dr. Frederick Hyman, Tina Smith, and others. Finally, we have the privilege today to welcome the new CDER Director, Dr. George Tidmarsh, who ... Please stand up ... We're very excited to have him here and have him here at this meeting.

(00:06:10):

Our mission at FDA's Center for Drug Evaluation and Research is to ensure that safe and effective drugs are available to improve the health of all Americans, and we continuously monitor the safety of drug products sold in the United States, including marketed unapproved prescription drug products.

(00:06:27):

An unapproved drug is one that we have not reviewed for safety and effectiveness. They stay on the market because we do not take action. We are always interested in hearing from patients, families, and

the public about how drug products are being used and any safety concerns they may have, especially in children and other vulnerable populations. We understand that over time new science may warrant FDA review of the safety of the products that are on the market, and today's public meeting aligns with that approach. In May, Commissioner Makary highlighted his concerns with the safety of unapproved pediatric ingestible fluoride prescription drug products, and we are hosting this meeting to provide patients, parents, advocates, clinicians, research and others the opportunity to inform us on the science around ingestible fluoride tablets. There is no better way to do that than convening a public meeting and hearing from a wide variety of perspectives.

(00:07:27):

We are looking forward to hearing, I think, nearly 20 parents, patient advocates, clinicians, and researchers in our two panel sessions, and then we will hear over 20 in-person and virtual attendees' comments. Additionally, when we announced this meeting in June, as Susan mentioned, we opened a docket. We have over 5,000 written comments to the docket, and we want to thank everyone who submitted their comments for taking the time and sharing your expertise and passion on these products. The agency has set a goal for the end of October for completing this safety review, and your comments will be carefully read and analyzed.

(00:08:03):

Let's turn back to today's meeting. I want to provide some important background. As Susan said, we are only focusing on products that contain sodium fluoride as the active ingredient and are marketed as unapproved prescription drugs. These products come in tablets and liquids. They contain 0.25 to one milligram of sodium fluoride, usually taken once a day. They are prescribed for the prevention of dental caries and treatment of fluoride deficiency. They are currently labeled for pediatric patients over six months.

(00:08:34):

To our knowledge, the only ingestible fluoride prescription drug products currently marketed are unapproved new drugs, and as I said, those are drugs that have not obtained FDA approval. Without FDA review we cannot be sure ... Um, a little too quick ... We cannot be sure whether these drugs are safe and effective for their intended use, whether they are manufactured in the manner that ensures consistent drug quality, or whether the label is complete or accurate. Although they never received FDA approval, they have been available as prescription for a number of years, decades including, and this situation is not unique to fluoride just so you know. There are other unapproved drugs available in the US In certain situations.

(00:09:17):

You will hear first from US medical and dental organizations that recommend unapproved prescription drug products containing fluoride where topical treatment is difficult or insufficient and from others who will highlight the risks of these products. So with that background in mind, I want to emphasize what Susan noted about the scope. We understand there are many sources of fluoride, and there is sometimes confusion about what our role is here. For today, as we said, it's really just on these ingestible fluoride products. The meeting is not about the use of fluoride generally as a cavity prevention strategy, but only providing it as an oral ingestible unapproved product. We don't want to discuss over-the-counter prescription topical fluoride containing drug products or fluoride in products marketed as dietary supplements or fluoride in drinking water.

(00:10:06):

So now that I've discussed the scope, I want to set the stage a little bit for what we know about utilization of these products. Our drug use team in the Division of Epidemiology II used proprietary

databases available to the agency to assess the use of these products in the United States. The focus of their analysis was on single ingredient products. In general, they're being marketed to prevent dental caries, and as you see in the figure displayed, this is a five-year trend in outpatient prescription utilization. From '20 to '24, we see that they were most frequently dispensed to children age three to nine, accounting about two-thirds of what was dispensed of the total prescriptions. Overall we also see a downward trend in dispensing of oral sodium fluoride products from 2020 to 2024, with about a 40% decrease in prescriptions to children age three to nine or younger than three years.

(00:11:08):

The next slide focuses on who is dispensing these products, and as you can see, it's pediatricians first, accounting for about 43% of prescriptions, followed by dentists and then family practitioners, nurse practitioners, and other specialties.

(00:11:26):

In summary, the ingestible prescription fluoride products were largely dispensed to children, and the prescriptions for these products were most frequently written by pediatricians and dentists. I hope this brief background has provided some helpful context for what I anticipate will be a robust data-driven discussion we're about to have. With that, I'd like to thank you again, and I'll turn it back to Susan.

Session 1: Scope of Use of Orally Ingestible Unapproved Prescription Drug Products Containing Fluoride in Clinical Practice

Sally Greenberg, JD, Lived Patient Experience
James H. Bekker, DMD, University of Utah School of Dentistry
Bill Osmunson, DDS, MPH, Fluoride Action Network

Susan C. Winckler, RPh, Esq. (00:11:48):

Great. Thank you so much, Dr. Corrigan-Curay. So with that, let's jump into our first session. This first session is exploring the scope of use of the orally ingestible unapproved prescription drug products containing fluoride in clinical practice. Now moving to the stage are our reactor panelists. I will introduce them at the conclusion of the presentations, but what you should know is that we have invited them here specifically to be listening to the presentations and assuring that we have a robust discussion. So actually I'll have you go to the other podium. Thank you.

(00:12:31):

Our first speaker providing us the lived patient, or as we say in this case, the lived parent experience is Sally Greenberg. Sally, we welcome you to the podium, and thank you for joining us this morning to share your thoughts. You can speak from the podium or the seat, whichever you prefer.

Sally Greenberg, JD (00:13:03):

Thank you, Susan, and welcome everyone. My name is Sally Greenberg, and I am the head of a consumer organization, but I'm really here speaking as a mom with lived experience with fluoride supplements.

(00:13:22):

To start off ... Are my slides going up? Oh, oh, there they are. Okay. Let me start by saying that moms like me and millions of others rely on the experts. When it comes to kids' teeth I look to groups like the American Dental Association, the American Academy of Pediatric Dentistry, the US Preventive Services Task Force, and professional medical associations, which all support continued access to fluoride

supplements where needed. They agree that fluoridation is one of the most effective ways to prevent cavities for children, reducing tooth decay by 25%. As a mom, I worry that when community water fluoridation programs are threatened, for example, Florida and Utah, two states that have banned fluoride in drinking water, parents will need options like fluoride supplements.

(00:14:20):

In fact, my son was prescribed fluoride supplements when as a child we lived for a time in a community where we weren't sure what the fluoridation levels were. There were no discernible negative effects on his gut or his brain. He is pursuing his third degree. He just finished his first year of law school, and he has a master's degree as well. The only issue I have with him is that he doesn't call me back when I leave messages. So, as with my experience, communities that rely on bottled water or well water, fluoride supplements are a needed option.

(00:14:59):

Let me give you a very short glimpse of my family history, which makes me committed to the notion that we need fluoride supplements available to the American public. My grandmother was born in Romania, raised in the Twin Cities before water fluoridation. She lost all of her teeth and wore dentures as far back as I can remember. Both of my parents without early fluoridation, also despite brushing and flossing and lost most of their teeth by the time they reached 65 years old. My dental health with fluoridated water is far better than theirs, but dental care wasn't as advanced as it is today, and I confess to having a weakness for candy of all sorts, and that hasn't helped. But the good news is I have all my teeth, albeit my share of crowns, root canals, and a few implants.

(00:15:48):

My son at 29 years old has had the benefit of fluoridated water and fluoride supplements and advanced dental care. He has one, perhaps two, cavities total. I credit his dental health to fluoridated water and the fluoride supplements that he had access to and better dental care.

(00:16:08):

Let me close by saying that moms rely on professional medical associations and other experts who agree that FDA should not withdraw fluoride supplements. The proposal is not, as far as I can tell, backed by sufficient science. It most importantly removes parental choice, and I believe it puts children at risk who don't have access to water fluoridation. Thank you very much.

Susan C. Winckler, RPh, Esq. (00:16:35):

Thank you, Sally. Thank you, Sally. So let us now move to our second presentation, which will be from Dr. James Bekker, who's Associate Dean for Professional Community and Strategic Relations at the University of Utah School of Dentistry. Dr. Bekker, please proceed.

James H. Bekker, DMD (00:16:56):

As an educator. I've got to figure out how to use this clicker. I think I've got the right button. It's nice to be here today with so many colleagues and interested people around the country in this very important issue that we're talking about. My comfort zone is talking to a classroom, so welcome to class today. I hope we can all learn together.

(00:17:21):

Let's talk for just a minute about what the role of supplements are in creating optimal oral health. I'd like to talk just a little bit about balance. I have a couple simple illustrations that I want you to keep in your mind as we go forward.

(00:17:42):

What's fluoride? A lot of people ask about that. If you look at the naturally occurring elements, nutrients that we have in the earth, fluoride is right there. Hydrogen, silicon, sodium, magnesium, potassium, all those things that are important to us, fluoride is one of those nutrients that occurs naturally. Like all other nutrients, an optimal level is important. We've got to have a balance. We don't want to have too much, and we don't want to have too little.

(00:18:17):

When fluoride is present during tooth development, it results in stronger teeth. When fluoride is not present during development, it results in weakened enamel and weakened bone strength. When we have too much fluoride present in development, we can see fluorosis or spotting of teeth, and that's not good either. So we go back to this notion that we've got to have a balance. We've got to have a situation where the right amount of fluoride is present during development.

(00:19:08):

As we look at ways in today's world of achieving that balance, supplements play a very important role. There are areas where there's fluoride occurring naturally. We don't need supplements in those areas. There are areas where we have community water fluoridation, and we don't need supplements in those areas. But there are many areas of our country where we either don't have community water fluoridation or we don't have naturally occurring fluoride. In those places, supplements are the key to achieving that balance.

(00:19:49):

As I said, that balance leads to optimum oral health. Now, how does this work? Providers, as you saw on the previous slide, pediatricians, dentists, all kinds of professionals, doctors that interact, talk to their patients, and you determine what's happening in that community, what the level of fluoride is, and according to that specific need the provider and the patients work together to create that optimum balance. That's very, very important.

(00:20:29):

Now, let me just tell you a little bit about what has happened recently in Utah and my experience for many years as a pediatric dentist. I practiced in an area where a large part of the community had fluoridated water, but immediately adjacent in the next county there was no fluoridated water. In my experience with my patients, I had to visit with each family, each parent, and determine what their situation was and what was the most effective way of creating optimal health. For patients that were not in a fluoridated area, we would determine if there was any natural fluoride, which Utah is way down ... We don't have any natural fluoride, and we would determine the appropriate dose of fluoride for them. That is a model that's happening all across the country. Practitioners interacting with patients, parents and creating a pathway for health by determining the appropriate levels.

(00:21:43):

We have basic science studies. We have demographic studies. You can see with the National Institute of Health, many studies that have been recorded that show the benefit of this fluoride supplement role. We also have an opportunity as we look at communities that have supplements or fluoridated water in communities that we don't see the results over time. These societal impacts are very, very significant. When we don't have fluoride and when we don't have the opportunity to supplement a non-fluoridated area, there are certain things that happen that are very disturbing. We have an increase in tooth decay. That's documented. We have an increase in the use of emergency services to receive care for dental

emergencies, emergency rooms, which is one of the highest costs in healthcare options, and it doesn't solve the problem.

(00:22:53):

When you use an emergency room, you get an antibiotic and a painkiller, but you don't solve the problem. So we have an increase in that which leads to an overall increase in healthcare, as many of the significant dental problems in children come and need to be treated in an OR setting where the cost of care is so much more. So those kinds of things are increasing when we don't have the opportunity to balance, create that balance, optimal health with a fluoride supplement.

(00:23:36):

Many people will ask, what are the alternatives to a fluoride supplement? What can we do in an area where there's no fluoride in the water and where there is no naturally occurring fluoride? What are the alternatives to a fluoride supplement? That's a great question, and it's got a very simple answer. There are no good alternatives in those situations to fluoride supplements, tablets and drops, that can be used to create that optimal level of health. This is a wonderful discussion, and it has much, much impact in especially underserved populations. We strongly recommend that this be considered as a mechanism to continue in establishing optimum oral health and creating that balance in our communities. Thank you.

Susan C. Winckler, RPh, Esq. (00:24:43):

Thank you, Dr. Bekker. So let's turn then to our third presentation for this session. For that, we will hear from Dr. Bill Osmunson, a retired dentist who serves as Senior Advisor to the Fluoride Action Network. Thank you for the clicker handoff. That may be the most valuable piece of equipment in the room today. Dr. Osmunson, please proceed.

Bill Osmunson, DDS, MPH (00:25:07):

Thank you very much. It's a pleasure to be here. I'm a retired dentist of 46 years. I have a master's in public health, so I'm a wet-fingered dentist. If you feel like I'm throwing rocks at you, remember that I promoted fluoridation for 25 years. I prescribed fluoride to my children, and then I read the science. The science does not support fluoridation.

Speaker 1 (00:25:34):

... litigation. I asked EPA, I asked the CDC, I asked the FDA, and I asked all the manufacturers of the chemicals that we add to water for fluoridation, I asked them all the same question. Can you point me to safety data that will allow me to know where the safe level turns into a toxic level? What is that level? What is it? Not a single one of those organizations had an answer. None of them knew what the safe level versus the toxic level was. CDC as you sit here today is not aware of any data in the published literature that would define the tolerable upper fluoride intake for neurotoxic effects on children? For children?

Casey Hannan (00:26:42):

As a rep of CDC, to my knowledge we don't have any knowledge about that.

Speaker 1 (00:26:46):

Okay. Does the NSF have a position on what the upper tolerable daily dose of fluoride that will not cause neurotoxic effects is?

Amanda Phelka (00:26:55):

Since we have not conducted risk assessments on any of the fluoridation chemicals, we do not have a position on a daily dose that would be appropriate to prevent or to reduce the risk for neurotoxic effects from fluoride exposure.

Speaker 1 (00:27:10):

As you sit here today, you're not aware of a study that would establish the safety of prenatal fluoride exposure for the brain?

Joyce Donohue (00:27:16):

Remember, dose makes the poison. So I'm not aware of a study that right now says this dose is safe.

Bill Osmunson, DDS, MPH (00:27:28):

What I've done here is I've listed the randomized controlled trials at the top of the page of showing the benefit, and then I have a list of the meta-analysis of those randomized controls listed at the bottom of the page. There are none. That's the most important slide you can see right here. We don't have those studies. Now, we don't know what's safe. We do know that if you don't have any fluoride, you don't get dental caries. What is the so-called euphemistic optimal level? We really don't know that either.

(00:28:20):

Fluoride is a drug, not a nutrient. FDA testified to Congress on it. US Pharmacopeia has it listed. FDA, the whole list of them are all there. In fact, on the fluoride toothpaste label, it says, "Do not swallow." I prescribed them for my children. I didn't read the directions. The FDA has had a tradition, 35 companies, Drug Therapy in 1975, 50 years, there's no substantial evidence of drug effectiveness. It's all rumors and hearsay. Something's moving my slides for me. I'm recommending that fluoride be banned.

(00:29:03):

The FDA responded to the Washington State Board of Health when the Board asked if they could get approval for fluoridation of water, and the FDA responded, "If you attempt to get approval, it would be banned." What about banned is so hard for people to understand? The toothpaste label, drug facts, "Do not swallow." When I read this, I go, " A pea-size amount. My goodness." So I put a little pea-size on my toothbrush there and I said, "Oh, that much do not swallow. My goodness." But that's twice the size of the FDA's recommendation that has a half milligram. And what we have here is a quarter milligram of fluoride is what the FDA is concerned about, and that's the same amount an 11-ounce glass of water or the smallest supplement that you can prescribe. The FDA says, "Do not swallow."

(00:29:59):

Low income children experience higher rates of decay regardless of fluoridation. I plotted the 50 states on the percentage of the whole population fluoridated, and you can see here the different states. This is the percentage of the population fluoridated in each of these states. This was when I was first learning about this stuff and looking into it. Then I plotted the very good, excellent teeth in each state to see what it was. Then I plotted the double the welfare or low income population, and a couple things jumped out at me. Number one, my goodness, what I was ... Oh, I don't want that one. Okay, we'll get back here. What I was doing was comparing in my patients the good teeth with the no, well, the good teeth, but the wealthy with the poor, and it was socioeconomics. Socioeconomics. CDC NHANES, it's all socioeconomics that I was comparing, not dental fluorosis, a dental fluoride benefit. I gave fluoride the benefit in pills and in water.

(00:31:15):

Socioeconomics is more powerful. Unless we control for socioeconomics in a study, we're dead meat. Now let's look at this one. This is a very important one too. My mom, 12 years old, decay; I, 12 years old, decay; my children 12 years old decay. It's a moving target. If you start comparing these people with these people, you're gonna get any results you want. You can't compare a moving target. Keep that age straight.

(00:31:45):

Now, this is a very important one. World Health Organization data comparing non-fluoridated countries and fluoridated countries. Was it socioeconomics? Was it something else? We don't know what it was before fluoridation started. Boy, this is one sensitive little critter. So the important thing that I want you to see here is if we look at the past, we may see some benefit there. Whether it was fluoride or not, I don't know, and there's lots of debate on that.

(00:32:18):

But certainly over the last 20, 25 years, whether you fluoridate or you don't fluoridate, whether you give the supplements or you don't give the supplements doesn't make any difference. It's all hoax. It's not much stronger than bloodletting for 3,000 years based on observational evidence. We need quality research. Would that even be ethical?

(00:32:42):

Huge increase in dental fluorosis. I'm not touching this thing. It's going for me. Okay. Okay. Whoa, whoa, whoa. Okay, we're doing it. In 2000 NHANES report 40% children had dental fluorosis. In 2012, 70% had it. Now, there's different studies, and these are just sections of the country so it may not be going up that high. But remember, man, this thing, I love it, but remember it is going up. These are regulatory agencies. These are not endorsements like the IAOMT that is opposed to it or the AAIM or the ADA or those kinds of things. China. We buy fluoride from China because they don't put it in peoples' mouths and prescribe it.

(00:33:36):

Certainty of harm versus certainty of safety. Let's pretend that we are ... I'm a pilot ... Let's pretend that we are gonna go on an airline flight, and I tell you and the passengers that there's a tremendous storm out there, a typhoon we're gonna fly through. We do not have certainty that we're going to crash. Now, other planes have crashed and they've had problems, but there's no certainty that we're gonna be harmed. So how many of you want to join me on this flight? The person in the back there says, "Hang on. Are you gonna assure us that we're going to make it?" No, no, no, no. That's not science. Science is proof. I want to see dead bodies before I can tell you that there's a problem. We want safety. We don't have to have proof of harm. She says, "I'm about ready to be done." Green, Till, there's lots of them are saying there's an IQ damage lower, and that is a self-reinforcing loop in which the fluoridation lowers the IQ, and it's a problem.

(00:34:47):

We have a list of things back in 2006 of concerns of harm. We have a list even longer, and this is not the full list of harm. Each of these we need to be able to assure the public that it's safe. Thank you very much.

Session 1 Reactor Panel:

George Tidmarsh, MD, PhD, Center Director, Center for Drug Evaluation and Research, FDA
Linda Birnbaum, PhD, DABT, ATS, Duke University, National Institute of Environmental Health Sciences

David Krol, MD, MPH, FAAP, American Academy of Pediatrics
Scott Tomar, DMD, MPH, DrPH, University of Illinois Chicago College of Dentistry

Susan C. Winckler, RPh, Esq. (00:35:05):

Thank you, Dr. Osmunson. Our objective in the initial presentations was to assure that we had a variety of perspectives to illustrate. And so thank you, Ms. Greenberg, Dr. Osmunson and Dr. Bekker. We are now going to have the panel discussion and so let me first introduce our reactor panelists who we compelled to sit in front of you for a bit of this. But joining us to help with the conversation we're about to have, we have Dr. Linda Birnbaum, who is a scientist emeritus at the National Institute of Environmental Health Sciences and the National Toxicology Program.

(00:35:44):

Dr. David Krol, a pediatrician representing the American Academy of Pediatrics. And Dr. Scott Tomar, Professor and Associate Dean for Prevention and Public Health Sciences at the University of Illinois Chicago College of Dentistry. As we turn to the panel discussion, in contrast to the microphones on the podiums, these you do have to push to talk. So if you push it in, it turns red and you get your mouth close to it, then we will be able to hear you through the microphone. But to kick off our discussion, I want to take the opportunity to call on our new center director for CDER. So, Dr. Tidmarsh, you have some questions, please.

Dr. Tidmarsh (00:36:28):

Thank you.

Susan C. Winckler, RPh, Esq. (00:36:29):

It is on.

Dr. Tidmarsh (00:36:30):

Wonderful. Thank you all for being here today. Thank you panelists. Our job at FDA is to balance risk and benefit and every day we have to make that balance. And it's always a challenge... It's frequently a challenge, not always, but nothing is without risk. And you have to make sure that if there is risk, there's a clear benefit. And that analysis needs to be done with data. It can't be done with opinion and with due respect to Ms. Greenberg, it can't be done by just passion and forceful effort on behalf of your child. And I'm not demeaning your presentation, Ms. Greenberg, but our job here is to use evidence, okay? And I have this Cochrane review from 2011, but actually... And I'm happy to provide that. It basically says an analysis of 11 different studies, all with some bias showed that there was no evidence of an advantage of fluoride in the prevention of caries in deciduous teeth.

(00:37:41):

So the deciduous teeth are the youngest members of this vulnerable population. And this meeting really kicked off because of a publication in JAMA of a study that was conducted by the NIH that showed fluoridation in water caused a decrement in cognitive function in IQ. Okay, that's a huge issue. Everybody should be concerned about that. So what this is saying is that the fluoride in water was causing a cognitive decrease in the younger... When it's given to the younger children. And the randomized studies say that there is no benefit. So that's a tough thing to defend. One important thing, I'll just point out, I appreciate both Dr. Bekker and Osmunson being here today, but please look at their presentations. And with all due respect, Dr. Bekker, I didn't see much data in your presentation, whereas Osmunson, yours was chock-full of data, okay? So our job is to use data to strike that balance.

So as you look at this and form your opinion, please look at the data. So that's all I really want to say. If somebody has comments, please, Dr. Bekker, maybe.

James H. Bekker, DMD (00:38:58):

I'd love to respond. Thank you. I could not agree more that data is important. My goal was not to have you overwhelmed with slides that you were trying to assimilate. That data, that information is readily available. All across the country, we have studies going on that in supplemented areas and non-supplemented areas or children that have supplements or not have supplements, fluoridated water or non-fluoridated water, you see the results. We see the difference in counties and areas where the fluoride is available or where it is not. We see it in populations that avail themselves of supplements or do not. That data is very available. It's important to understand that so many areas where they have found that supplements are not available, the children are showing an increased caries rate.

Dr. Tidmarsh (00:40:13):

Can you respond to that, Dr. Osmunson?

Bill Osmunson, DDS, MPH (00:40:16):

Yeah, I'd like to know from the panel members, do any of you know of randomized controlled trial showing that fluoride supplements of pills reduce dental caries? There's your evidence.

Dr. Linda Birnbaum (00:40:36):

I think that we need to look at the recent Cochrane report that came out in October of 2024, which basically showed that an analysis of a large number of studies did not show... Showed a zero to 4% reduction in caries at most. That's a big change from what occurred when the public health service first recommended fluoridation in 1962.

Susan C. Winckler, RPh, Esq. (00:41:07):

Yeah. So the discussion has started, which is exactly what we wanted, Dr. Tomar.

Dr. Scott Tomar (00:41:11):

I need to respond to that. So the Cochran review that came out in 2024 was specific to community water fluoridation and in fact only added one study to what it had looked at in 2015. The bottom line though is the prevented fraction was really about the same, 25 to 30% across all the post 1965... Excuse me, post 1975 studies that were included. I mean, one of the limitations in that Cochran review that they point out is they had very stringent inclusion criteria. It had to be a cohort study where they had baseline measurement and then at least one follow-up point. But in the discussion section of that Cochran review, there's actually dozens of cross-sectional studies, which I know that NTP relied on heavily in it systematic review. But the Cochran review had dozens across multiple studies, incredibly consistent showing lower carries prevalence-

Susan C. Winckler, RPh, Esq. (00:42:07):

Dr. Tomar.

Dr. Scott Tomar (00:42:08):

[inaudible 00:42:08] to non-fluoridated.

Dr. Linda Birnbaum (00:42:09):

Can I respond?

Susan C. Winckler, RPh, Esq. (00:42:10):

Yes. Let me go to Dr. Birnbaum and hen to Dr. Osmunson.

Dr. Linda Birnbaum (00:42:15):

I was the director of the National Institute's Environmental Health Sciences and the director of the National Toxicology Program. And in 2012, I began to serve on the public health service panel, which in fact was looking at community water fluoridation. And our recommendation after that, which was published in 2015, was to lower the level from 1.2 to 0.7 parts per million. That was based on mild dental sclerosis, which was a concern. But I can tell you that my participation in that panel, I have to say, I am not an epidemiologist. I am not a neuropsychologist. I am a toxicologist who has run and conducted lots of research. And I think what I learned from sitting on that panel and looking at all the literature that had been accumulated is that the National Academies had said, we need to look at the issues of IQ deficit.

(00:43:12):

We need to look at some of the other health impacts of fluoridation. And so when that was over, I went to my National Toxicology program folks, and I said, "We need to look at this. This has to be something that is looked at carefully." And let's just say it took years to do that. And last summer, the NTP finally published its extensive systematic review on fluoride. Now, the focus was not on fluoridation and drinking water. The focus was can fluoride affect the developing brain of our children? And the answer from this systematic review was yes. That was followed up by the report that published in JAMA Pediatrics, I think it was January 6th of this year, which was a meta-analysis and combined all the studies. And I'm sorry, Dr. Tomar, most of those studies, yes, some were cross-sectional, many were in China.

(00:44:09):

But the best studies were prospective longitudinal studies, which followed the exposure early in life and then looked at the children's IQ outcome. And these studies, especially the most recent ones and the best ones, I have to say, none of them were in the United States. They were in Canada and they were in Mexico. But there were also studies in Scandinavia and Europe, and they all had the same conclusion that there is an association between elevated, especially fluoride as measured in urine, which is a better measure than drinking water fluoridation because it's a measure of total. So urinary fluoride does account for the supplements that people take.

(00:45:03):

Does account from what you get from swallowing that hopefully pea-sized amount of toothpaste that you brush your teeth with. Does account what you get from black tea. And when you look at those measures, as well as if you looked at water fluoridation as a overarching measure that people have been concerned about, what you find is there's an increased risk to the developing brains of our children.

Susan C. Winckler, RPh, Esq. (00:45:29):

And we'll hear... In session two, there is a specific section that we'll be exploring, the neurocognitive and the data there. This was really more on the scope and clinical use. Because you mentioned Dr. Tomar, I'll go there. And then I have Dr. Osmunson and Dr. Bekker.

(00:45:43):

Dr. Tomar.

Dr. Scott Tomar (00:45:45):

So first to respond to that, and you'll hear much more later today about the NTP report. And the problems with what they consider the two best studies actually used an invalid measure of fluoride intake as well as unreliable measures of IQ. And that's the best evidence they've got. The small number of studies that they considered at low risk for bias. Again, the vast majority are cross-sectional studies done in China, Iran, and India that frankly have no relevance to the levels of exposure in the United States. But I want to come back to a point that Dr. Osmunson said about the randomized clinical trials. So most of our data on community water fluoridation, and I know this focus is on supplements, but since most of his talk was really on fluoridation, I feel compelled to respond to some of those. You can't conduct a randomized clinical trial very easily on community water fluoridation.

Bill Osmunson, DDS, MPH (00:46:43):

It's being done.

Dr. Scott Tomar (00:46:44):

But we have... I know it's being done. And in fact-

Bill Osmunson, DDS, MPH (00:46:47):

Then don't say that it's not being done when's being done.

Susan C. Winckler, RPh, Esq. (00:46:49):

I believe he said it was difficult. Now ground rules, right? Absolute discourse, respectfully. Okay?

Dr. Scott Tomar (00:46:59):

So most, again, we have years of evidence from cohort studies on community water fluoridation establishing its effectiveness. There is one randomized clinical trial that's being conducted by University of North Carolina. And in fact, the only group that has tried to kill it is Dr. Osmunson's Group Fluoride Action Network.

Susan C. Winckler, RPh, Esq. (00:47:18):

Well, but the key there is that there is a randomized trial underway. And so that may provide some illumination that would be helpful. I've got a queue. So Osmunson, Bekker, Birnbaum.

Dr. Linda Birnbaum (00:47:30):

Can I just respond to that?

Susan C. Winckler, RPh, Esq. (00:47:31):

You have 27 seconds.

Dr. Linda Birnbaum (00:47:33):

That trial is not looking at in utero or infantile exposure.

Susan C. Winckler, RPh, Esq. (00:47:38):

Okay. So then that's a helpful clarification of where the trial may provide some illustration. That's helpful. Dr. Osmunson and then Bekker.

Bill Osmunson, DDS, MPH (00:47:47):

I'd like to refocus the discussion onto clinical use. Dr. Bekker, when was the last time you prescribed fluoride pills?

James H. Bekker, DMD (00:47:58):

Within the last year.

Bill Osmunson, DDS, MPH (00:48:00):

Okay. And when the patient was sitting in front of you, what are the questions you asked to determine how much fluoride the patient was already getting?

James H. Bekker, DMD (00:48:11):

Where do you live?

Bill Osmunson, DDS, MPH (00:48:13):

I live in Issaquah.

James H. Bekker, DMD (00:48:16):

No, I'm not asking you. You asked me-

Bill Osmunson, DDS, MPH (00:48:18):

I'm the question.

James H. Bekker, DMD (00:48:20):

The question was to the patient that I was sitting in front of.

Bill Osmunson, DDS, MPH (00:48:24):

Okay.

James H. Bekker, DMD (00:48:25):

I don't know about Issaquah because I don't live there. But I do know about my community and that the levels of fluoride in the different areas of my community. So I determine as a professional, working with a parent-

Bill Osmunson, DDS, MPH (00:48:40):

Okay, you ask where they live. Any other questions?

James H. Bekker, DMD (00:48:44):

Yeah, you ask about their supplement intake, if they're already taking a supplement, if they have a vitamin that has fluoride or not fluoride, any of the factors that might determine-

Bill Osmunson, DDS, MPH (00:48:57):
You ask where they go to school?

James H. Bekker, DMD (00:48:59):
Absolutely.

Bill Osmunson, DDS, MPH (00:49:00):
Okay. And do you ask whether they're swallowing toothpaste?

James H. Bekker, DMD (00:49:04):
Yes.

Bill Osmunson, DDS, MPH (00:49:05):
And how much toothpaste are they swallowing?

James H. Bekker, DMD (00:49:08):
That's a very hard question for parents to-

Bill Osmunson, DDS, MPH (00:49:10):
Did you really ask all those questions?

James H. Bekker, DMD (00:49:12):
You bet.

Bill Osmunson, DDS, MPH (00:49:13):
You did. Do you think the pediatricians ask all those questions?

Susan C. Winckler, RPh, Esq. (00:49:17):
So-

Bill Osmunson, DDS, MPH (00:49:18):
What about foods? What about medications?

Susan C. Winckler, RPh, Esq. (00:49:21):
Let's illustrate versus interrogate. Okay?

Bill Osmunson, DDS, MPH (00:49:28):
But pediatricians and dentists don't have the time.

James H. Bekker, DMD (00:49:30):

Just make your-

Bill Osmunson, DDS, MPH (00:49:31):

[inaudible 00:49:32].

Susan C. Winckler, RPh, Esq. (00:49:32):

So if I may, we do actually have a representative that the pediatricians here, so Dr. Krol, recognizing none of us are aspiring to sit in on a conversation between a pediatrician and a parent. Very helpful to think through those questions, so I appreciate that, Dr. Osmunson. But I don't think we're planning to sit there through everyone. But generally, as you think about it, Dr. Krol and representing the pediatricians, thoughts that you would share.

Dr. David Krol (00:49:58):

Yeah. Well, I think the first thing to say is that the AAP supports fluoride supplementation and recognize that it's important to assess the fluoride intake and all the sources of fluoride intake for patients. So when we are considering as pediatricians, whether we're going to provide supplementation for a patient, we do ask all the questions of access to fluoride. Do they live in a fluoridated community? Do they have well water that's naturally fluoridated? Has that well been tested for fluoride? And if it hasn't been tested, we encourage our pediatricians to get that tested and often the local health department or other agencies will do that testing. But all of that, we say in our policy statement, our clinical report on fluoride, that pediatricians should be assessing all those sources of intake of fluoride before supplementation is to be done.

Bill Osmunson, DDS, MPH (00:51:05):

Do they eat mechanically de-boned meat that has bones in it? How much fluoride are they swallowing? It's just not possible to determine how much fluoride a patient is getting from some other sources.

Susan C. Winckler, RPh, Esq. (00:51:20):

Which may not be unique to prescribing of this product versus a range of other-

Bill Osmunson, DDS, MPH (00:51:26):

It is unique because this is a drug that has a 30 to 70% of the amount of fluoride that we get is from other sources. You don't get that with other drugs, that there's naturally occurring drug from other sources.

Susan C. Winckler, RPh, Esq. (00:51:38):

Certainly an important animating factor. Dr. Bekker, you were in the queue. And then to Dr. Birnbaum.

James H. Bekker, DMD (00:51:42):

Thank you. This queue is getting... Anyway, a couple of things I just want to respond to. It's been said that we don't know what a safe dosage of fluoride is. And in my simple diagram of optimum and balance, we do know what the safe dosage of fluoride is. It's been through years and years and years of that experience in those studies. And we are now dosing and using our supplements to reach that optimum level. And a supplement is just one part, one tool in reaching the optimum level. There is no data. There is no data. Well, let me turn this the other way. Any data that refutes the benefit of fluoride

is either something taken out of context or flawed data with some kind of extreme level of fluoride that's being tested. And when you look at studies that are done with an optimal level of fluoride, there is no conclusive evidence that there is any deleterious effect at that optimum level. And that's important. The studies that people are quoting are flawed or taken out of context.

Susan C. Winckler, RPh, Esq. (00:53:14):

I think, Dr. Bekker will be helpful that in our second session there's that robust debate of what do we know of the effect of fluoride in gut and oral microbiome in neurocognitive and in thyroid? Because I will say the lawyer in me did hear there are no, and-

James H. Bekker, DMD (00:53:34):

Those kinds of statements are hard.

Susan C. Winckler, RPh, Esq. (00:53:35):

I'm not allowed to... That was driven out of me, the ability to say none, but to explore and say what is it that we might see? But thank you for teeing up the second session where we will hear the discussion of that. So I appreciate that. Dr. Birnbaum.

Dr. Linda Birnbaum (00:53:52):

Well, I guess I'm going to take you on again, Dr. Bekker or raise an issue.

Susan C. Winckler, RPh, Esq. (00:53:57):

Engage in civil discourse.

Dr. Linda Birnbaum (00:53:59):

This is civil, I hope. You talked about that fluoride is natural and you described it as a nutrient. I know of no data that says that fluoride in fact is nutritional. We have lots of natural elements. Fluoride is an element like lead. I don't think any of us would say that because it's natural, it's good to have lead or arsenic or uranium. And I could go on with some of that.

James H. Bekker, DMD (00:54:26):

There are bad ones. Yes.

Dr. Linda Birnbaum (00:54:27):

And I think that we have to... I don't know. Well, no, let me say it a different way. I think we talk about risk benefit. Maybe in some cases we have to talk about comparative benefits and comparative risks and look at both. So let's just make the assumption that we'll hear more about the neurodevelopmental effects, which in fact may be occurring at levels much lower than we'd like to believe.

James H. Bekker, DMD (00:55:00):

But higher than optimum recommended levels.

Dr. Linda Birnbaum (00:55:03):

No, that may not be the case. I think the data is suggesting it may not be the case. Do we need more research? Yes. But I could argue that we know enough now to say that fluoride is not good for the developing brain, and therefore, we should be very, very careful of its use.

Susan C. Winckler, RPh, Esq. (00:55:24):

And continuing to learn. I've got Dr. Tomar and then Dr. Osmunson.

Dr. Scott Tomar (00:55:29):

So community water fluoridation... And again, I know the focus is on supplements, but again, most of the evidence we have is on community water fluoridation, and that's mostly what the exposure was in the vast majority of studies that they're talking about. We are the only country that is questioning the safety of fluoride at this level. This has been looked at by World Health Organization, the United Kingdom, Australia, New Zealand, other countries that have had a long experience with community water fluoridation. They've looked at those same studies, have concluded that they were flawed and not relevant to the levels of exposure involved in... The levels that we're talking about, whether from water fluoridation or from supplements. I would also want to correct a misrepresentation from Dr. Osmunson's presentation where listed all these European countries rejected, rejected.

(00:56:27):

The reality is that Europe has not rejected fluorides. They don't have... There's about 12 million Europeans that get fluoridated water, but there's about 70 million that get it through salt fluoridation. They've simply chosen, and usually because of logistic reasons of small and old water systems, they've used alternative methods, the Nordic countries that had said rejected, they actually have universal dental care and provide pretty intensive community-based and school-based prevention programs, all of which involve the use of fluorides. So I just wanted to correct the misperception that somehow everybody else has rejected that they've not. We are the outlier.

Susan C. Winckler, RPh, Esq. (00:57:08):

Well, and to be clear, I think, Dr. Osmunson you noted or aspired to note that that was about community water fluoridation. And it was not about the focus of this discussion, which is the orally ingestible, unapproved prescription drug products that contain fluoride used in a pediatric population. So hence the discussion of when might this be prescribed? What is that clinical need? Obviously has to have the broader animation. But let's bring us narrow back to the question at hand. So, Dr. Osmunson and then Dr. Birnbaum.

Bill Osmunson, DDS, MPH (00:57:44):

Yes. There was a study by Zimmer, and it was about 15 years ago, and the study reported anecdotally that the dental associations in Europe no longer recommended the ingestion of fluoride. I have a friend who lives in France and he said, "Well, yeah, we have fluoridated salt, but it's not put in commercial and it's there available if somebody wants it." But it used to be about 30%. Now it's gotten down to less than 10%. So the amount of fluoride supplements that is being used in Europe is much less than it was than before. And several countries don't permit it.

Susan C. Winckler, RPh, Esq. (00:58:34):

Dr. Birnbaum and then we'll turn-

Dr. Linda Birnbaum (00:58:37):

Just to let Dr. Tomar know, and I just don't think Tomar... Sorry, I don't think you had the opportunity, but this week the European Food Safety Authority just released its report on ingestion fluoride and the levels that they have come up with that they do not ensure are safe, let's say they are lower than what WHO has recommended for community water fluoridation.

Susan C. Winckler, RPh, Esq. (00:59:08):

So continued exploration of the topic and release of the information. So I think in particular, I do want to call it that observation, Dr. Birnbaum and that it's helpful where you can call to and say, these are studies that are underway or might be further explored. Because we know when we spoke with all of you beforehand, we said, it's not only not a decision-making meeting, it's not a resolution meeting. It is an opportunity to share what are the various perspectives and then see where additional exploration would be needed. As I turn to you, Sally, I'll note, I appreciate you opening the session with a patient story as we often do in FDA activity. Just not for the data, but rather for the grounding us in why those in this space do the work to keep that patient perspective in mind and that we did not ask you for data. But do want to hear your perspective and thoughts. As parents, we make these types of decisions and we want to have information available.

Sally Greenberg, JD (01:00:22):

Yeah, that's right, Susan. Thank you. And welcome to the CDER community. We're looking forward to working with you. I think I started my remarks out saying that we rely on experts and my expert is my dentist. And so, I and many, many other thousands of moms and certainly friends of mine, talk to our dentists about the condition of the younger generation and their teeth. And what I'm told over and over again is there is a dramatic drop in the number of dental caries among my son's friends and his generation compared to my generation, certainly the generation before. So yes, fair point about anecdotes do not prove the point.

Susan C. Winckler, RPh, Esq. (01:01:13):

Absolutely.

Sally Greenberg, JD (01:01:13):

But we do rely on the experts that we work with and they are strongly supportive of certainly safe levels of fluoridation. And where fluoridation is not available in communities, the access to fluoride supplements is critically important.

Susan C. Winckler, RPh, Esq. (01:01:36):

I think I heard there too, the option component that it would be an available piece. I've got Dr. Krol, Dr. Osmunson, Dr. Bekker.

Dr. David Krol (01:01:45):

Yeah. Thank you. So I wanted to touch on... In being a reactor, I did want to react to what Sally said, and that was her comment on parents need options when there isn't fluoride available. And that goes the same for pediatricians. We need options when our patients don't have access to fluoride, so we can prevent tooth decay. And the best part for me about being a primary care pediatrician is the conversations that I have with patients. And this is an important conversation that I have with patients.

Asking those questions about access to fluoride from all the different places. We know that children don't just live at home. We know children go to school, we know children in different places, and those questions are important to ask.

(01:02:32):

And only when that conversation takes place does the decision about whether a supplementation is given. And I think that's very important. And I don't know how... I mean, the slide that showed the changes in supplementation over time, that's really hypothesis generating to me, why is that happening? And some of that may be that conversations are happening between providers and patients to try to understand that. And after that conversation, there is still a need for the provision of supplementation for some patients.

Susan C. Winckler, RPh, Esq. (01:03:13):

And so that, Dr. Krol, just so that I'm internalizing the slide, that was the initial slides showing the prescribing data.

Dr. David Krol (01:03:22):

That's correct. The one especially that showed the three to nine-year-olds was going down over time, but the other ones seemed to be relatively consistent.

Susan C. Winckler, RPh, Esq. (01:03:29):

Yes, yeah. Dr. Osmunson and then Dr. Bekker.

Bill Osmunson, DDS, MPH (01:03:33):

Two things, but number one, the reason that fluoride started supplements water fluoridation is because the sugar industry was very concerned about the increase in dental caries with sugar, and they wanted to have something to help out with that sugar intake. And so the best way to handle a disease, of course, or a problem, is to give it a drug. And if that drug causes a problem, then we need to give another drug. And if that one gives problems and then we develop another one. It makes a lot of money for the manufacturers and we help people because it's much easier to prescribe a drug than it is to say, "I think you're eating too much sugar." And one of the problems we have is there are lots of fluoride in many different products.

(01:04:26):

And so where are the labels for those fluoride? How much fluoride is in the mechanically de-boned meat? How much fluoride is... And all these other sources. If a pediatrician, a dentist, were able to say, okay, you're having a lot of this and oh, these are high in fluoride. Post-harvest fumigants, oh, interesting. You eat some of those too and you're not eating organic foods. All these different things make a difference with how much fluoride that a patient is getting. And we don't ask those questions, but we need to spend far more time on talking about our bad habits of eating sugar, of taking a bottle of Mountain Dew and giving it to the baby to go to sleep with and getting teeth rotten.

Susan C. Winckler, RPh, Esq. (01:05:11):

Oh, my goodness. Dr. Osmunson, Diet Mountain Dew to the baby or regular Mountain Dew to the baby is not going to get sleep. That will inspire the exact opposite reaction. But I understand.

Bill Osmunson, DDS, MPH (01:05:22):

Well, I have patients who gave soda pop to their babies.

Susan C. Winckler, RPh, Esq. (01:05:24):

Yeah, soda pop, just Mountain Dew happens to be profoundly caffeine-laden as my teenage children and their propensity for energy drinks. But to the illustrate... Yes, as with prescribing, I would say there are other drugs as they're prescribed that it's important to understand the context. The task for CDER is the use of these. Now I saw our pediatrician and two dentists, I think want to weigh in on the prescribing component, if we might. So I'll do Bekker, Tomar, Krol.

James H. Bekker, DMD (01:06:01):

Yeah. And I just wanted to take off on what Dr. Krol had said. Let's look at what we're experiencing in Utah and Florida where they have banned fluoride completely in the water supply. They put that forward as well, if you want fluoride, if you believe that's a health benefit, get a supplement. That whole argument in that legislation was get a supplement. We're talking about supplements here today, and we're talking about a choice and giving people a choice if they want to have that benefit of fluoride in a non-fluoridated area or where it doesn't occur naturally. The supplement is the only tool they have, and so as we consider supplements, the opportunity to have them available is a matter of people's choice. We're not forcing anyone to take them. We're allowing them to have an option and to have a choice.

Bill Osmunson, DDS, MPH (01:07:02):

What about a piece size of the toothpaste?

Susan C. Winckler, RPh, Esq. (01:07:05):

... that conversation. Right, but, Dr. Osmunson I think it actually plays into what you said of the need for robust conversation and alternatives to understand the prescribing-

Bill Osmunson, DDS, MPH (01:07:15):

The pea size of toothpaste is the same amount of fluoride., it's-

Susan C. Winckler, RPh, Esq. (01:07:16):

But I don't think we're saying that toothpaste and a tablet are equivalent in the excipients.

Bill Osmunson, DDS, MPH (01:07:21):

They are. Same amount of fluoride. Fluoride is fluoride.

Susan C. Winckler, RPh, Esq. (01:07:23):

Sorry, I'm speaking to the excipients in the other components that would be in a toothpaste are certainly different from the excipients in a tablet. You just having-

Bill Osmunson, DDS, MPH (01:07:33):

[inaudible 01:07:34]?

Susan C. Winckler, RPh, Esq. (01:07:34):

No, no, sorry. Having compounded products as a pharmacist, I'll assure you distinctly, there are different excipients to yield the paste that is in a tube, what you need to put with it than what you would do to create a tablet. There'll be some overlap, but there's a difference. I'm just saying we shouldn't equate them in a conversation that's just about the tablets and the drops. Tomar and Krol.

Dr. Scott Tomar (01:08:00):

A couple of things. And again, I feel compelled to correct misrepresentations from Dr. Osmunson.

Susan C. Winckler, RPh, Esq. (01:08:08):

Or to share a perspective that you see it differently. Okay? I understand. Let's just categorize it. You see this side of the room and he sees that side of the room.

Dr. Scott Tomar (01:08:20):

Well, without going through the history of fluorides and fluoridation, I have not seen evidence that fluoridation started it because of lobbying by the sugar industry. I totally agree that there's too much sugar in our diets. I would hope the current administration would develop a meaningful sugar policy including excise taxes on sugar sweetened beverages.

Bill Osmunson, DDS, MPH (01:08:44):

I agree.

Dr. Scott Tomar (01:08:44):

You would have total support in the dental public health community for that. But to speak to two points that were raised earlier about that this is a socio-economic status issue and not a fluoride issue. The reality is... And again, nobody would dispute that there is not an SES effect on caries. However, there's actually pretty good evidence, again, a lot of it coming from University of North Carolina showing that appropriate use of fluorides reduces those socio-economic disparities in dental caries.

(01:09:17):

So again, it's a good argument for why we should have the availability of fluoride supplements and community water fluoridation, particularly for those communities. And again, the... Okay, I won't use the word misrepresent, but the graph that was showing that there was a decline in caries going back to starting in the 30s that preceded fluoridation. I have to explain to the audience where that slide comes from. Those are data from New Zealand, it was published in a [inaudible 01:09:51] magazine called Fluoride. It publishes anti-fluoridation material, and it was actually from non-representative data for five-year-olds collected... These were kids that were showing up for treatment. So again, that doesn't represent what was going on. What was not shown was the data collected by New Zealand's Health Department over that time. They had nationally representative samples of eight and nine-year-olds, and 12 and 13-year-olds, and in fact, there was no improvement in carries until community water fluoridation was introduced, primarily in the '50s into the early '60s in New Zealand, and then another decline after the widespread use of fluoride toothpaste. So again, it was misrepresenting what the real history was of fluoride. Until we had that on the market, there really was no change in the very high prevalence of carries.

Susan C. Winckler, RPh, Esq. (01:10:42):

So Dr. Kroll, and then I'll come back, Dr. Osmunson.

Dr. David Krol (01:10:44):

Yeah, I simply wanted to touch on the fact that part of the reason we're having this conversation is because I think we would all agree that we want to try to reduce the impact that the disease of dental carries has on kids. And we recognize as pediatricians, and I imagine many of us recognize that disease is a multifactorial disease. And all multifactorial diseases that I know require multifactorial approaches to address them. And fluoride supplementation, as well as conversations about diet, conversations about hygiene are the kinds of things that take place with families in that office between pediatricians and patients, and we have to have that opportunity to continue those conversations, and have those multifactorial tools to address this disease.

Susan C. Winckler, RPh, Esq. (01:11:37):

Thank you, Dr. Kroll. Dr. Osmunson.

Bill Osmunson, DDS, MPH (01:11:39):

And I agree, we need to have a multifactored, and it takes time for the patient to have a change in their habits, and paradigm shift for all of us. So seeing the dentist, seeing the pediatrician. And I appreciate what our pediatricians do in helping to reduce dental carries, but throwing a substance at patients where the evidence doesn't show that it has continued benefit... I mean, the EPA scientists speaking through their union, because they were fired when they spoke outside their union, they spoke through their union and said that fluoride is a highly toxic substance, and it does no longer have benefit, if it ever did. That was in 2001.

(01:12:27):

And when I read that, I was just shocked. These are good scientists, and they're saying it doesn't have benefit. It's a little bit like bloodletting for 3,000 years, and people would say, "Okay, you're going to die unless you have the bloodletting." And they had the bloodletting, and they lived. They gave tremendous testimonial evidence that, "Yes, it worked." For 3,000 years. However, if they didn't live, well, that's God's will. And so what we're doing here is no different. We're going on lack of science, saying that it's beneficial, and then from there, it's a hierarchical evidence of, "Yes, it's wonderful, and it's beneficial, and therefore, now we need to do it, and we need to make sure we don't miss out on it." And that's just false. Wrong.

Susan C. Winckler, RPh, Esq. (01:13:21):

Yeah. To continue to explore. So I'm going to turn Dr. Birnbaum to you, and then have... I actually think I captured three places where you all agree. So-

Dr. Linda Birnbaum (01:13:30):

So one quick point. I really don't think that we have the data that proves supplementation by itself is advantageous or not. I don't think we can calculate a margin of safety for that drug. I can tell you, with drinking water fluoridation, which we're not talking about, with a margin of safety clearly of less than two, you would never approve that for anything but an absolutely critical drug to save lives. And I think we don't have that data for supplementation, and something that maybe needs to be looked at. But it can't be done on a population where they're already getting fluoridated water, and you would want to very carefully look at the level of urinary fluoride to account for all the other sources.

Susan C. Winckler, RPh, Esq. (01:14:18):

Which takes me to then, so you just very clearly said what I think, at some point, each one of you did, which was, we do need to continue to learn more, and to explore, and to do this. So that was one point where I think you might all at least say there is a component. The other, you all agreed we want to reduce caries, that's what this is about, is... Particularly from the dentist's perspective and with the pediatrician's support, to reduce dental caries, and to reduce the sugar in the environment.

(01:14:50):

So there were three that we were able to pull out, but you also did what we challenged you to do, which was to illustrate that there are many perspectives, and to better understand when the products are prescribed, and why, and the impact on individuals when they are. So for that, thank you for sitting in front of these very bright lights, and turning to a very intense conversation. We appreciate your investment in that. We're now going to take a 15-minute break, and we will return at the top of the hour. Thank you.

Session 2: Identifying Safety Concerns and Potential Risks Associated with the Use of Orally Ingestible Unapproved Prescription Drug Products Containing Fluoride

George Tidmarsh, MD, PhD, Center Director, Center for Drug Evaluation and Research, FDA
Valerie Heaton, Lived Patient Experience
Jennifer Webster-Cyriaque, DDS, PhD, National Institutes of Health
Purnima Kumar, BDS, MDS, PhD, University of Michigan School of Dentistry
Gary Moran, BA (Mod), PhD, TCD, Trinity College Dublin
Griffin Cole, DDS, NMD, MIAOMT, International Academy of Oral Medicine and Toxicology
Jayanth Kumar, DDS, MPH, formerly at California Department of Public Health
Susan Fisher-Owens, MD, MPH, University of California San Francisco
Kyla Taylor, PhD, National Institutes of Health
Christine Till, PhD, C.Psych, York University
Kathleen Thiessen, PhD, Oak Ridge Center for Risk Analysis

Susan C. Winckler, RPh, Esq. (01:15:22):

You are all so good at being quiet. Well, let me open session two, and let's talk about what session two will be, and we will keep moving. I hope you are all awake now. Let's move forward from the break slide. In session two, we're going to focus on the safety concerns and potential risks associated with the orally ingestible, unapproved prescription drug products containing fluoride that are used in the pediatric population. And let me prepare you for... This is a quick relay of presentations, focus talks, delivered back-to-back to highlight different aspects of the topic. And following the same approach we had in session one, we also will start with lived experience, and we will move through the presentations, and then have a panel discussion at the end. But I first want to provide the microphone to Dr. Tidmarsh for a few remarks, and then we will jump into the session.

Dr. Tidmarsh (01:16:27):

Thank you. I just want to reiterate a couple of things, and put a little bit in perspective, and add. So it's been very instructive for me, and it's thought-provoking. So one thing I would just want to make sure everybody understands, and it's been said many times, so sodium fluoride has not been approved, it's unapproved. So that means it has not gone through the rigorous FDA process to show that the benefits outweigh the risks.

(01:16:58):

So we're not talking about taking a drug off the market that was already FDA-approved. So in that context, we need to make sure there's a rigorous analysis. And so if we decide to take sodium fluoride supplement off the market, there's nothing that would prevent a group from doing the rigorous studies, bringing it back to FDA. So it doesn't mean that it's over, and I want to make sure that's really clear. And the second point I want to make is that if we decide to take it off the market, we would absolutely come to the dental and pediatric community to look at all the things we talked about, that everybody agreed on, sugar, other things in the diet, other things that can help oral care, oral health. So I just wanted to put that in perspective.

Susan C. Winckler, RPh, Esq. (01:17:54):

Great. Thank you so much, Dr. [inaudible 01:17:56]. It's one of the challenges of the regulator to navigate that environment. So thank you for that framing. So let's begin our second session. I want to invite, and in fact I will invite Valerie Heaton to the stage to share her lived parent experience. And Valerie, if I recall correctly, you practice this with your grandkids, so I think that means you will be spot on time.

Dr. Susan Fisher-Owens (01:18:23):

Okay. Hello, everyone. I'm so grateful that I have the opportunity to be with you here today. My name is Valerie Heaton. I'm from Utah. And I am here to share a few of my thoughts about my experience with administering fluoride to children, not as a medical expert, but just as a mother navigating the many choices out there for creating optimal health opportunities for your children. Let me preface my remarks with a short introduction to my family. My husband and I have nine children, and we were fortunate enough to have excellent health insurance, which provided us great medical care, and great medical care for the entire time of raising our family. When our first child was born, I was a registered nurse, and had worked at our local hospital on the pediatric, and the mother and baby units. I was determined to be a good mother, and give my children the best start in life. I breastfed my babies, and was aware that mother's milk lacked, or had low amounts of certain vitamins, and so along with the encouragement of my pediatrician and his prescription, I was able to give my first child daily doses of Tri-Vi-Flor vitamins, which included vitamins A, C, D, and small amounts of fluoride.

(01:20:14):

I felt very good about this choice, especially since we did not have community water fluoridation in our area. And I continued about this same plan for several children. At that point, my mother-in-law who owned a vitamin and herb business, and had very strong opinions about natural medicine and nutrition, became aware that I was giving my children doses of fluoride. She was horrified, and shared with me concerns, and pointed to the research she had read. She told me that it was toxic, and that I was poisoning my children, and her grandchildren. A note of interest here, I had a lot of respect for my mother-in-law. In fact, I had run her herb business for her for a couple of years while she was out of the country. And this experience gave me more knowledge about nutrition, and developed a philosophy that I carry through to this day, and that is that I like to take the best of both worlds, medical science, and natural and holistic approaches.

(01:21:35):

So mostly to appease my mother-in-law and her worries, I discontinued giving my children Tri-Vi-Flor drops, and instead, gave them Tri-Vi-Sol, which contained the vitamins only. However, at some point, I remember deciding fluoride was a wise choice for my children, and I began using fluoride again in the form of little pink or orange tablets. My children would take these according to their weight and age,

and I'm sure that I consulted with my pediatrician and dentist at this time, because I needed their recommendation and prescription to obtain them.

(01:22:19):

Now, fast-forward a couple of decades, and my children are all grown, and because I have several of my children that live near me in Utah, we gather on Sunday afternoons once or twice a month for family dinner. It's great to share stories, and among the group of 20 to 25, kids and adults, occasionally, the topic of dental health and dental injuries over the years come up. During one lively conversation, one daughter in particular was bemoaning the fact that she seemed to have at least one, and sometimes several dental caries or cavities. Each time she went to the dentist, she was told that she had soft enamel, and thus was more prone to caries.

(01:23:12):

She envied some of her siblings who had not had a cavity or filling well into adulthood, despite having the same dentist, having sealants, and regular semi-annual check-ups. As she spoke, I suddenly realized she might have been one of the children born during the period when I had stopped giving fluoride supplements, and my heart just sank.

(01:23:41):

I even apologized to her, worried that my decision back then might have led to lifelong challenges for her. This daughter, a mother of three boys, smiled, and kindly said, "Mom, you were just doing what you felt was best at the time." I really appreciated her gracious attitude. While I felt bad for my daughter, this conversation made me grateful that I had used fluoride with most of my children. My husband and I now continue to see our dentist every six months, and when they ask if we want fluoride, we accept the option of having fluoride painted on our teeth. We're grateful that our insurance covers the cost of it, because we feel that it does have value. Ultimately, I appreciate the privilege of having access to information, and having the choice of whether or not to use fluoride. Thank you for inviting me to share my experience.

Susan C. Winckler, RPh, Esq. (01:24:57):

Thank you, Ms. Heaton. And as I noted in our opening patient or parent experience with session one, it's more as an illustrative, and to keep in mind why we have these conversations. But now, we'll turn to a data presentation, or at least an explanation presentation. So we are going to hear from Dr. Jennifer Webster-Cyriaque, who is acting director of the National Institute of Dental and Craniofacial Research at the National Institutes of Health. So Dr. Webster-Cyriaque, please proceed.

Dr. Webster-Cyriaque (01:25:29):

Thank you, and thank you for having me here. Fluoride during development does mean strong enamel, and it does mean benefit throughout the person's life course, but we don't know about the risks. There are unknowns. There does need to be rigorous analysis. So what are we doing? What are we doing to address the unknowns? The potential safety concerns and risks? We've heard about the benefits, we've heard about the risks, what we need to do is focus in on the science. We've heard about that this morning. So what have we done as we continuously move to discover what is true here in the U.S.?

(01:26:13):

We held an HHS-wide round-table, it was an internal meeting, and then we pulled together a call to action, with two major points, to bolster research on fluoride safety and risks, and as we move through today, I'll give an example of several large-scale studies that we will be leveraging, and I'll also share some other ongoing efforts. The other thing is, as we get this data, we've got to share that information

so people can make a choice, that they can be empowered to make informed decisions, and that's what the research will do for us. We have to move forward with a persistent and active search through science.

(01:26:58):

So we had representatives from across HHS gathered in a round-table format last September. This was an internal meeting, and we talked about risks and benefits of fluoride in terms of where we were in the state of the science. We heard from the National Toxicology Program, and NIDCR talked about fluoride mechanisms, and role in dental disease. We talked about past efforts, what the studies are that are already ongoing, and what are the needs. But we also talked about what we need to share, what we need to share to empower the community with knowledge, and importantly, safety and efficacy, and how to get there.

(01:27:42):

So the call to action first focuses on bolstering research and inter-agency collaborations to answer questions about impacts here in the U.S., at levels of fluoride here in the U.S., at levels provided by people taking supplements here in the U.S. And also to develop comprehensive, multi-level approaches for untreated tooth decay, because fluoride is not a magic bullet.

(01:28:10):

So let's talk about the strategy. Basically, we have four strategies. One is to tap into existing public health surveillance data to leverage ongoing large-scale longitudinal studies, to encourage reuse of large data sets for new analysis, and to support investigator-initiated research, like the randomized control trial that we talked about earlier today.

(01:28:36):

So I'm going to provide four examples. The first one focused on NHANES, that asks, what are the home fluoride water levels actually here in the U.S., and the relationship to decay? I'll talk about the HEALthy Brain and Child Development Study, the NIH Environmental Influences on Child Health Outcome Study, and the Adolescent Brain Cognitive Development Study, or ABCD. And these are all NIH-wide studies, and nationwide studies.

(01:29:07):

So first, as we tap into existing public health surveillance data, and this is NHANES data. Over the past year, we conducted with some colleagues from the CDC an exploratory analysis of NHANES data to look at what the levels of home water fluoride were, what's actually coming out of the tap in over 8,000 homes across the U.S. of kids age 0 to 19. And these were randomized, so some of these were well water, some were coming from fluoridation systems. And what we know is, about 12% of homes do not have any detectable level of fluoride in them across the U.S. We know that the recommended amount is 0.7, 0.7. And we know that about 70% are homes are at that level or lower, but the mean level of fluoride in the U.S. is 0.052. That is three times below levels associated with neurocognitive risk, and four times below levels associated with dental fluorosis.

(01:30:16):

We also know that close to 2% of homes do have high levels of fluoride of more than 1.5. We also are aware that at the level two, the EPA provides warnings, and at the level four, the EPA lets people know that they should not drink that water. And so this happens on a regular basis, where the public health communities go out to people and let them know what their levels are.

(01:30:48):

So what difference does this make? And what if you're already brushing your teeth? So these kids, based on parent report, were brushing and using toothpaste. So in the 12% of homes where they didn't have detectable fluoride in the water, and the kids were brushing and using toothpaste, they had a 22% prevalence of untreated tooth decay. So brushing is not enough. The other thing that was very clear is, again, not a magic bullet, you need multiple preventive exposures. You need brushing and using toothpaste, there was home water fluoride, there was access to dental care. All of these were significantly associated with decreasing tooth decay. Again, just brushing and using toothpaste alone were not enough.

(01:31:34):

We did see that the prevalence of untreated decay did go down as home water fluoride levels went up. But even as those went up, if you didn't have access to care, you could still have untreated decay. It's just like any other disease process. You're diabetic, is it just what you eat? You've got to exercise, you've got to check your blood pressure. It's wraparound, it's multifaceted. So what can we do to start answering these questions? We're going to leverage an ongoing large-scale longitudinal study called the HEALthy Brain and Child Development Study. Here, we're looking at biological, social, and environmental factors, including fluoride, that influence growth and brain development. And this HBCD study is multi-site, longitudinal across 27 sites across the U.S. that's more than 7,000 participants that are pregnant. So we start at the very beginning in utero, and then they're followed up to about age 10.

(01:32:40):

What are the objectives? To characterize brain development using medical exams, and biological, behavioral and environmental contexts, including water fluoride and ingestible fluoride exposures starting this year. And to identify and understand the developmental impacts of risk and resilience factors, including fluoride. And we'll be able to capture cumulative fluoride exposure during pregnancy, infancy, childhood.

(01:33:11):

So just a quick overview of the study. What you can see is, from the prenatal visits on up through age 10, there'll be assessments, biospecimens, biosensors, MRIs, and EEGs that occur across the lifespan, starting in pregnancy, and fluoride exposures will be assessed throughout the full study period. They will be captured in the context of neurodevelopment and other health outcomes, so we can begin to answer some of those questions about thyroid and other. As we do the follow-up, there'll be continued assessments that are including nutritional diaries, what is their fluoride exposure based on what the water is that they bring in? This comes out of their taps, nail clippings, exfoliated teeth, that can tell us about cumulative exposure. We'll also look at oral health outcomes, but we can also look at the microbiome, and ask many other comprehensive questions.

(01:34:07):

We have the opportunity to reuse large datasets, like the ECHO program, or Environmental influences on Child Health. This includes 44 states across the nation, more than 60,000 children. These study data can help us assess fluoride exposure, both supplement use, and fluoridated water exposure. The health outcomes that can be assessed are cumulative fluoride exposure, thyroid health, gut and microbiome, and oral microbiome, as well as inflammation and others. And those biospecimens are available to help us answer those questions.

(01:34:42):

Fourth and final study is the ABCD Study or Adolescent Brain Cognitive Development Study. This is a largest, long-term study of brain development and child health in the United States. It's about 21 different research sites, and over 11,000 children have been invited to participate. So here, we'll learn

how childhood experiences interact with each other, and with a child's [inaudible 01:35:09] biology to affect brain development in the context of multiple outcomes, including fluoride exposure.

(01:35:19):

So, just again, it's not a magic bullet. Very quickly I'll share that we also have efforts ongoing related to diet and nutrition, and support investigator-initiated research, and inter-agency collaborations in longitudinal studies to look at fluoride dietary intake, including supplements. We are collaborating with the FDA right now to look at the impact of added sugars, and we have nutrition initiatives to look at dietary influences, and behavioral interventions.

(01:35:50):

Finally, we're also supporting mechanistic toxicology and multi-level intervention studies. We are studying how can we protect against potential toxic effects of high-level fluoride by modulating a fluoride-induced adaptive response pathway by leveraging antioxidants. Those types of things are ongoing. There are many projects on dental fluorosis where people and animals are getting very high levels of fluoride. So it gives us the opportunity to really ask about toxic effects, not only looking at dental tissues, but other extra oral tissues. And we're looking at comprehensive multi- level approaches, working with care providers, with patients and their families, and across communities.

Susan C. Winckler, RPh, Esq. (01:36:37):

And with that, we'll have to direct people to the slides on the website.

Dr. Webster-Cyriaque (01:36:41):

All right.

Susan C. Winckler, RPh, Esq. (01:36:41):

If that's all right?

Dr. Webster-Cyriaque (01:36:42):

That's good.

Susan C. Winckler, RPh, Esq. (01:36:43):

Okay. All right. Let's thank Dr. Webster-Cyriaque. I will keep track of the valuable equipment. And I should note, as we did in session one, I am doing very brief introductions that do not... I should say, you really should look at the bios of our distinguished speakers, because each of them is bringing a unique perspective to the stage.

(01:37:08):

So to bring our next perspective to the stage, I want to turn to Dr. Purnima Kumar, who's professor and chair of the Department of Periodontics in oral medicine at the University of Michigan School of Dentistry. Dr. Kumar, please proceed.

Dr. Purnima Kumar (01:37:23):

Thank you. Thank you for inviting me to talk about fluoride and the gut microbiome. There are two keywords here, fluoride and microbiome. And my colleague, Dr. Moran, is going to be speaking on the impact of fluoride, and so I thought I would take this opportunity to make sure that we really

understand the other thing that we're going to be talking about, which is the microbiome. So I hope to set the stage by really discussing what the microbiome is.

(01:37:52):

This plays a very important role in my practice as a surgeon, as well as in my life as a researcher who studies human health and disease, and I have no conflicts to disclose. And so basically, what is the microbiome? It is a collective community of microorganisms that reside in a specific microenvironment. It's not just the organisms, it is their genes, their interactions, and the products they produce.

(01:38:20):

We have all kinds of microbiome. We have soil microbiome, water microbiome, termite microbiome, human microbiome, all of those things. And within the human microbiome, we have different microbiomes in different parts of the body. Here you see the skin, the stomach, the colon, vagina, all of those different things. So there are all kinds of microbiomes.

(01:38:40):

What the microbiome is not is just a collection, a random assortment of microorganisms or microbes. And unfortunately, even our government websites represent the microbiome as just an amorphous grouping of organisms. The microbiome is essentially a superorganism. Work... I'm sorry, I have to go back on this, which I don't know how... Oh, yes. Work from Gary Borisy's lab, as well as our own lab has set the stage for understanding how these communities interact with each other, how they live with each other. And what we are learning is that we are dealing with a highly organized biological system that operates in a different set of rules than do a random collection of organisms.

(01:39:31):

We're also dealing with a structurally and metabolically cooperative communities that have very specific, very deep rules of engagement, both within themselves, and with the host that they share. The microbiome, everybody, when they say microbiome, we think of bacteria. Our work here has shown that this... Yes, there are bacteria, and they're the major part of the microbiome, but the microbiome also consists of other kingdoms, the back fungi, viruses, protozoa. And these kingdoms, different kingdoms, different domains, interact with each other in very defined, very organized forms. And this is how they contribute to health, or how they set the stage for having disease.

(01:40:21):

I bring this up because there are some important lessons that we learned from antibiotic sensitivity testing. Those of you who have had been tested for antibiotic sensitivity, especially... Or if you're a dentist and you're sitting in the room and you've done antibiotic sensitivity testing on your patient, you scrape off a bit of a biofilm from either the vagina, or the mouth, or any part of the body, put it in a little tube of broth, transfer it to the lab, where the biofilm is broken down into individual organisms, which are then plated on a plate like this. And little disks containing antibiotics are placed on this disk, and you get to see whether this antibiotic works against these organisms or not.

(01:41:05):

The lab then sends back a list of antibiotics that you are susceptible to, your doctor prescribes it, and nothing happens. The reason is because what we are looking at is a biofilm. When you take a biofilm and break it down to its component bacteria, they get to a cellular state where they're far more vulnerable, where they're far more... They respond in different ways. And there's years of research that has shown us that not only does antibiotic sensitivity, this conventional type of antibiotic sensitivity not work, but it has contributed to antibiotic resistance on a very large scale. And therefore, we need to study the

microbiome as an organized, cooperating, multi-species, multi-kingdom domain rather than a collection of species.

(01:41:57):

We can borrow a lot from ecosystem biology. We've learned a lot about the coral reefs, or about the Amazonian rainforests. These are ecosystems that contain multiple species, multiple biomes, multiple systems. And when we use the principles of ecosystem biology to study the microbiome, we learned something very important. The microbiome physiology, the way this microbiome works is habitat-specific. We published this data in 2018 on a group of 200 women where we compare their vaginal, oral, rectal, and skin microbiomes, and you can see how they branch off in different directions. Each of these microbiomes is very, very specific. Not just in the type of species that live there, but also in how they function, and how they interact with each other. The other picture here actually says the same thing, where we are looking at... Look at this red group of organisms. There's so much more in the skin, very little in the oral cavity, much more in the skin, hardly in the vagina, and hardly in the colon. So different group of organisms exist in different ratios and proportions across different biomes.

(01:43:11):

What we also learned very important is that just because these biomes are different, and their physiologies are different, the same product can have two different impacts on two different places. For example, let's take the example of short-chain fatty acids. We all know that short-chain fatty acids are what keep us happy, what keep us skinny, and make our skin glow. But that's when short-chain fatty acids are produced in the gut. When short-chain fatty acids are produced in the gums, you get gum disease, and you get to see me. So short-chain fatty acids in the gut promote health, the same in the mouth, promote disease. And therefore, the impact of one biome cannot be extrapolated to the impact of another biome in another habitat.

(01:43:55):

We've also learned the same lesson from probiotics. Probiotics work great for the gut health. In the oral cavity, probiotics don't work. And there's a very evolutionary principle that underlies the reason why probiotics in the mouth don't work. That is because the oral microbiome is established very early in life. This is something we published in the General Microbiome way back in 2015, and what we're seeing here is this, this is the microbiome of babies one day to one month old before teeth erupted. You can see that there's a core group of organisms here. This is the microbiome of babies 6 to 9 months old. You can see a second group of organisms are starting to colonize, these organisms need teeth as a colonizing surface. What we see here is that 85% of the bacteria that were colonizing your mouth before you had teeth continue into adulthood. 45% of the bacteria that colonized after your teeth came out, your deciduous teeth, your baby teeth, still continuing to adulthood even though those teeth fell off, and you have replaced with a new set of teeth. Therefore, your adult microbiome is established before you blow out your first birthday candle. And it is that familiarity. The mouth is a different space than the rest of the body. This is the gateway to the human body and stability is key. Otherwise, every time I drink a bottle of water, the bacteria that live in that glass of water are going to try and colonize my mouth. It is this sense of familiarity. It is this fundamental evolutionary principle that keeps us healthy.

(01:45:27):

So where does this connect to fluoride? Well, what fluoride does is that these pioneer species, the ones that you get before your first birthday, fluoride makes very sure, ensures. And there's years of study, and I'm not quoting those studies here because that would fill an entire thing, but fluoride basically interferes with enzymes involved in glycolysis, which basically prevents bacterial energy production. It inhibits the growth of caries-causing bacteria such as streptococcus mutans. Not just streptococcus

mutans, also bacteria from other kingdoms. It affects the structure and composition of dental biophones, making it different for pathogen colonization. And unlike antibiotics, fluoride does not indiscriminately kill your pioneer species. It doesn't kill the good with the bad. It is selective and it reduces the synergy between all those different kingdoms that I talked about.

(01:46:20):

Does fluoride impact the gut microbiome? When you look at physiologic doses, it shows that there is a limited or a positive impact on gut microbiome. There are three human studies all using the fluorosis model. Two of them come from China, and I'm going to let Dr. Moran speak about those and get to my next slide because I'm running out of time.

(01:46:44):

So to conclude, fluoride helps your pioneer species be better mouth guards. Pun intended. Habitat specificity dictates that the gut and oral microbiomes respond differently. We have circumstantial evidence, but we definitely have evidence. And fluoride in low levels has a limited impact on the gut microbiome and the only reported evidence we have so far on subjects with extreme fluoride exposure that is skeletal or extreme dental fluorosis. Thank you.

Susan C. Winckler, RPh, Esq. (01:47:17):

Thank you so much. Thank you so much. And so with that background in the microbiome, then... I'm bringing you the power. Indeed. So with the discussion of better understanding our mouth guard if I listened correctly, then Dr. Gary Moran, who is a professor in microbiology at Trinity College in Dublin, Ireland will speak to the fluoride component and impact there.

Dr. Gary Moran (01:47:49):

Great, thank you very much. Thank you very much to Dr. Kumar for that wonderful introduction to the microbiome and thanks to the FDA for the invitation to come and get involved in this fantastic platform for discussion. That's the wrong way.

Susan C. Winckler, RPh, Esq. (01:48:06):

Big button.

Dr. Gary Moran (01:48:07):

Oh, big one. Okay. Very obviously the big button. So I'm going to continue the discussion about fluoride and its impact on the oral and gut microbiomes in humans. I don't have any disclosures to make, financial disclosures to make around fluoride. I do like to mention though that I was a member of the Irish expert body on fluorides and health, a body that was set up to advise the Irish Minister for Health on safety concerns surrounding fluorides and the use of fluorides in community water fluoridation.

(01:48:36):

So we've already had a wonderful introduction to the human microbiome, so I don't need to go over this in too much detail. I would like to draw your attention to some of the initial studies. So the Human Microbiome Project, the initial project to characterize this microbiome was an NIH funded study. And as you can see, it characterized the diversity of bacteria, viruses and fungi that are present in and on the human body.

(01:48:58):

What I'd like to draw your attention to is the date on this. So this is a review which was published soon after this study was completed in 2012. And the point I'd like to make is that this is a relatively new science. So it's only in the last 15 years that we've actually characterized the human oral microbiome and the human gut microbiome, and we're only beginning to understand its role in regulating human health and human physiology. So there's still a lot of things that we don't understand.

(01:49:24):

So a few things that we do know, we know that there are a hell of a lot of these organisms. They probably outnumber our cells in the body by maybe up to 10 to one according to some studies, and they do have very important roles in regulating our physiology. For example, the gut microbiome has a role in extracting energy from food, producing essential vitamins. For example, vitamin K is produced by bacteria in the colon. The regulation and development of our immune system, the gut microbiome has a very important role in that. Regulating our metabolism and also protecting us from invading pathogenic microorganisms. So all of these things are very important and the development of a healthy microbiome is important for these processes.

(01:50:05):

We know that disruption of the microbiome at infancy, so for example, use of antibiotics in infancy, which can have a devastating effect on the microbiome, can affect a lot of processes later in life. So for example, there's evidence that disruption of the infant microbiome increases your chances of having allergic disease later in life, increase in obesity and also some evidence that there might be defects in neural development on cognition later in life.

(01:50:33):

So what about fluoride and its impact? We've heard a lot about fluoride, its protective role. Normally doses of about 50 micrograms for kg per day is considered optimal for maintaining good oral health. However, we do know that increased dosages can have effects such as dental fluorosis and even higher levels then can also cause skeletal fluorosis as well.

(01:50:55):

So what about the impact on the human microbiome? What impact does it have? Well, this is just an outline of the human body I suppose, and it shows the two main areas where the microbiome may come into contact with fluoride, namely the oral cavity and also the human GI tract, particularly the gut where most of the microbiome is located.

(01:51:14):

So the oral cavity comes into contact with fluoride first and as we know, fluoride enters the oral cavity through food, water and possibly through ingestible fluorides. And again, the optimal concentration for maintaining oral health, around 50 micrograms per kg per day, is often what's quoted. So the oral microbiome will contact this first. We know fluoride will have its protective effect by strengthening tooth enamel, but a secondary effect that it has at the oral cavity may be to inhibit the growth of bacteria that cause dental caries. And Dr. Kumar referred to this that there is a selective process here where it seems to target the bacteria that cause tooth decay, and that may be because fluoride is more soluble in acidic environments. When it forms hydrogen fluoride, it becomes more soluble and it can attack those bacteria. So those bacteria that cause caries create acidic environments AND acidic biofilm and in that environment, fluoride increases in solubility, AND it may actually target those cariogenic bacteria.

(01:52:11):

So once it leaves the oral cavity. Then descends into the human gut then, we know that absorption begins to happen. So absorption starts in the stomach. Again, the acidic environment increases the solubility. We get the formation of hydrogen fluoride, it moves into the bloodstream and that process continues in the small intestine as well. And certainly, over 50% of the ingested fluoride has been absorbed by the time it gets to the large intestine, which essentially means that the main part of the microbiome and the large bowel isn't exposed to the same types of concentrations that the oral microbiome would be. Probably less than 50% of what is ingested. And we note in feces, probably about 10% of ingested fluoride emerges in feces and the rest is absorbed into the bloodstream.

(01:52:58):

So what are the potential impacts then on the microbiome? Most studies have been carried out in animals, largely rodent studies, rats and mice. It's worth noting that there are differences in fluoride absorption and metabolism between mice and rats. You generally need higher concentrations of fluoride in mice and rats to reach the same sort of physiological effects that you would have in humans just due to differences in metabolism. Even taking that into account, most of the animal studies use extremely high concentrations.

(01:53:27):

So for example, this study here by Zong et al. (2022), they use concentrations of 25 to 100 mgs per liter of fluoride. At those high concentrations, 75 to 100 mgs per liter, you start to get intense damage of the intestinal barrier. Under those conditions, you get severe disruption of the gut microbiome. But these are extremely high concentrations that humans certainly wouldn't be exposed to.

(01:53:49):

Probably a more nuanced approach was taken in this other study on the right, Yasuda et al. where they exposed mice to four mix per liter of fluoride, something I would consider will be more in line with what humans would be exposed to. In this particular study, they found that an improvement in the oral microbiome in terms of a reduction in acid-producing species and a very limited impact on the gut microbiome, which the authors put down to the fact that most of the fluoride has probably been absorbed before it has reached the large intestine.

(01:54:19):

Humans then, very few studies have examined the impact of fluoride on the human microbiome. There's one study which mentions ingestible fluorides that I'll mention in a little while. No studies have properly examined community water fluoridation and most studies examine individuals with fluorosis that we consider have been exposed to very high concentrations of fluoride.

(01:54:41):

So this is example of some studies that Dr. Kumar mentioned, and quite a lot of these studies are carried out in regions of the world where there's endemic high fluoride concentrations either in groundwater or in these two studies, in Guizhou Province in China, individuals who live in that part of the world, they depend on heat and fuel for cooking on coal, which has high levels of fluoride in it. So they're burning this coal in the home, producing smoke and they're inhaling fluoride-containing smoke. There's quite a high level of both dental fluorosis and skeletal fluorosis in these populations, and studies have looked at the impact on the microbiome.

(01:55:17):

It must be said like a lot of these studies, they're very small. The top study as you can see, where they look at individuals at dental fluorosis, only looks at nine individuals. The lower study looking at individuals with skeletal fluorosis only has 32 participants. And what we can see from these studies,

dental fluorosis is associated with relatively minor changes in the gut microbiome. However, in individuals with skeletal fluorosis, which we would assume individuals have been exposed to much higher concentrations of fluoride, we do see much more severe changes in the gut microbiome.

(01:55:48):

However, we have to look at this and say how realistic is this compared to an ingestible fluoride? We're looking at polluted smoke, which may contain fluoride, may contain other pollutants as well, which may also damage the microbiome. So it's very difficult to draw any conclusions from these studies.

(01:56:04):

Studies have also been carried out in vitro. So for example, we could take fecal matter, we can ferment it in the lab and ferment just like this and expose it to fluoride. This is an example of one of these studies where they looked at 1, 2, 10 15 mgs per liter fluoride. The low concentrations, the authors concluded that these low concentrations may have a positive impact on the gut microbiome by eliminating pathogens or negative microorganisms. High concentrations then, 10 mgs per liter or higher did have detrimental effects on the microbiome, but they would be considered concentrations which probably wouldn't be reached in the gut in individuals taking regular dosages of ingestible fluorides or fluoridated water.

(01:56:45):

Studies that humans also involve the oral microbiome, again, also looking at individuals with fluorosis again, in these parts of the world. Again, they've shown that dental fluorosis may be associated with changes in the microbiome, but only individuals with severe sclerosis do they see significant changes in the oral microbiome.

(01:57:05):

I mentioned ingestible fluorides. There is one study from 2019 where they looked at the composition of the microbiome in adults and they looked back at the childhood history of those individuals, and individuals who have been exposed to ingestible fluorides either through salt or tablets in childhood, they did note that there were some changes in oral microbiome composition in those individuals. Relatively minor and the impact on health would be difficult to ascertain what they would be.

(01:57:31):

Okay. To finish up then, there's still a lot of work to do, but I think from the data I've presented, fluoride consumption at levels which we consider good for maintaining good oral health probably have limited impact on the oral and gut microbiomes. Increased exposure, very high levels which would induce severe dental fluorosis or skeletal fluorosis may have an impact or probably will have an impact on microbiome composition.

(01:57:55):

We certainly need more studies. There's an over-reliance in animal models. I'm glad to hear that the NIH is starting longitudinal studies to look at the impact of fluoride from infancy throughout life. These are the types of studies I think we need in order to fully understand the impact of fluoride on the developing microbiome. So finally, thank you and I'll just leave you with a picture of Trinity College Dublin here where I'm based. So thank you very much.

Susan C. Winckler, RPh, Esq. (01:58:19):

Thank you so much, Dr. Moran. I will take the power. All right. So now we're going to turn from the discussion on microbiome and turn to four presentations on the potential neurocognitive safety

concerns and potential risks associated with use of the orally ingestible unapproved prescription drug products containing fluoride.

(01:58:40):

Our next speaker is joining us virtually and so I believe from our production team... Great. Great to see you, Dr. Cole. We are going to hear from Dr. Griffin Cole who is past president of oral and medicine and toxicology and serves... Sorry. Past president of the International Academy of Oral Medicine and Toxicology and serves as conference chairman and fundamentals course director. Dr. Cole, please proceed.

Dr. Cole (01:59:05):

Thank you. It's a pleasure to be here. You'll control my slides, correct? Thank you. So first and foremost, there are no studies to show the effectiveness or safety of fluoride supplements. And as we're discussing supplements, obviously we can mention water fluoridation because we're talking about systemic ingestion.

(01:59:28):

So science has shown and the CDC admits and has for decades that fluoride's beneficial effects are topical, not systemic. With topical application, we can kind of control the swallowing of it, but with supplements we have no choice. We swallow every bit of it. So now we're concerned about the negative systemic effects, particularly neurocognitive effects in children.

(01:59:49):

Next slide. So the effects are only topical, as you can see. I need to make that screen bigger. It's real small for me. Let me see if I can do that. Can you make that screen... All I see is a little tiny square up there and that's my only access to the slide. So is there a way you... Ah, thank you. Perfect.

(02:00:13):

Okay. So in 1999 by Burt and he was talking about fluoride supplements in the Journal of Public Health Dentistry, he found these things. The efficacy is weak, there's a coarser risk of fluorosis and fluoride has very little pre-eruptive effect in caries prevention. Next. Likewise in 2000, John Featherstone and JADA found that fluoride in drinking water and in fluoride-containing products reduces caries only through topical mechanisms.

(02:00:41):

Next. 2001, as was mentioned earlier, the CDC said this quote on their website. "Fluoride's predominant effect is post-eruptive and topical." This is exactly opposite of what water fluoridation and supplementation is for. And as was mentioned earlier as well, the oral health director at the time, Casey Hannan in 2018 under oath recognized that there was no benefit from systemic fluoride in the first six months of life. And when he was asked was there any benefit for toddlers, he said no.

(02:01:12):

Next. This was also mentioned earlier, the Cochrane Oral Health Group. The Cochrane collaboration is about 37,000 researchers, very reputable. When they give a report out, it's well done under a good scientific method. And in 2011, they said supplements fail to reduce decay in primary teeth.

(02:01:32):

Next. NHANES was mentioned as well, but what wasn't mentioned was that in 2019 by NEURATH and the Journal of Dental Research, they show that over 70% of US children have fluorosis. So a huge

amount of US children now have this damage. Next. Most importantly, fluoride is ubiquitous. It's in all most processed foods and beverages and even some medicines including some antibiotics.

(02:01:58):

Next. So supplements are not approved as we all know, and they should be removed from the market. They were introduced in the 1950s on two false assumptions. Number one, that it's a nutrient. This was mentioned earlier as well. It's not a nutrient. It's a mineral and it's very disingenuous to compare it to things like riboflavin or vitamin C or folic acid. Those are nutrients that are needed for bodily functions. We will suffer if we have a deficiency of them. Nobody will suffer from a deficiency of fluoride. The other false assumption was that it's effective when swallowed. This is not true. I've already shown you some things and you've heard some things earlier as well.

(02:02:36):

Next. Just to go a little further on the Cochrane collaboration here, here's what they found. No safety studies and no conclusion about the effectiveness in preventing decay in children under six. I think Dr. Tidmarsh mentioned that as well. Next. So this is the important thing. We have mounting research now showing the things that I've highlighted for you here on blue like low birth weight for Hispanic newborns, lower testosterone and sex steroid hormones, symptoms of sleep disorders in adolescents, increase in pediatric bone fractures, kidney and liver impairment in adolescents. But arguably and most importantly, decreased IQ and more neurobehavioral disorders. This was explained in detail in the 2024 NTP systematic review.

(02:03:23):

Next please. Next. Not to mention there are over 80 studies now worldwide showing neurocognitive effects including lower IQ. These few that I've mentioned here are some of the higher quality ones that were included in the NTP report, which would be the Bashash 2017 and '18, Green 2019 till 2020, Goodman 2022. And of course, the meta-analysis by Taylor that came out early this year. They looked at 74 studies and found a significant inverse relationship between fluoride exposure and children's IQ scores. Now I included at the bottom here this study in 2023 by Dr. Kumar because he's a panelist today where he actually found very similar results early on in his research.

(02:04:12):

Next slide please. So I just want to throw this one slide in because it's probably going to come up at some point, and this is about NASEM here. And so this is the National Academies of Science, Engineering and Medicine and many fluoride advocates will say that they found the NTP report unreliable. That they didn't think it was a good report and that's actually not true. They did have one criticism, but let me tell you what they actually said about this NTP report. Number one, they did not challenge the scientific basis of NTP's presumed hazard conclusion.

(02:04:48):

Next. They actually suggested ways for NTP's evidence to be used more strongly to support their conclusion. And next, here's a quote from their report. " The committee found the meta-analysis to be a valuable addition to the monograph. The meta-analysis applied standard, broadly accepted methods and the data shown and the related evaluations are especially informative." Next. The only criticism that they had was that the NTP included claims of evidence of exposures below 1.5 milligrams per liter were inconsistent and unclear. So the problem was that they hadn't done rigorous dose response analysis, so shouldn't really offer any conclusions about what dose may or may not be low enough to avoid neurotoxic harm.

(02:05:34):

Next slide please. So I want to show you just two graphs that I think do a nice job of showing IQ deficits in these studies here that were done by the NTP. This first one is really good. It's done by Chris Neurath, who's the Science Director of the American Environmental Health Studies Project. In '23, he did this and what he's looking at is on the X-axis, that horizontal bottom line, the mean exposure in milligrams per liter. And on the Y-axis, the IQ loss at mean exposure. The only thing I've added to this slide is that little light blue line that you can see coming up from the X-axis at 1.5 milligrams per liter of fluoride. Because this is the number that everybody agrees, whether you're a fluoride advocate or an anti-fluoridationist or an expert at the EPA, we all agree that at 1.5 milligrams per liter, we're going to see some neurocognitive effects and lowered IQ. Notice to the left of that light blue line, those dots are representing some of the high quality studies deemed by the NTP and you can see numerous dots there that are below 1.5 milligrams per liter. This is a dose-response curve, a linear curve that was done by Chris Neurath.

(02:06:49):

Next slide. This is from early discovery of Dr. Kumar who's going to speak today. So I don't want to steal his thunder, but this is a non-linear graph here. So this is in his initial research here. And if you'll notice here, the only difference is that on the Y-axis he did standardized IQ. So on the previous graph where you had zeros, sort of the baseline point of about 100 IQ points, here on this graph you can actually see he's got IQ points there. So we're around 100 would be the average and normal IQ. So everything below that would be drops in IQ. The things I've added to the slide or that light blue line at 1.5 milligrams per liter that goes up and the red arrow showing from the baseline of the IQ down to the lowest point of that main dose-response curve, a drop of 16 IQ points. Now I should say that this was not included in his manuscript, this was not published, but this was what he found early on in his discovery.

(02:07:54):

Next slide. So it's time. It's time for the FDA to actually enforce their unapproved classification of supplements. They are definitely unnecessary, unapproved and unproven. And thank you for your time.

Susan C. Winckler, RPh, Esq. (02:08:11):

Thank you Dr. Cole, and we will see you back for the reactor panel and panel discussion as we make our way through the presentations today. So thank you for joining us virtually. We're going to return to the in-room session and hear from Dr. Jayanth Kumar, who is former State Dental Director at the California Department of Public Health. So Dr. Kumar, please proceed.

Valerie (02:08:32):

Thank you FDA for inviting me. Thank you Dr. Cole for showing that graph. It was not published because what Dr. Professor Liu wanted to demonstrate was when you place a knot at 1.5 where there were no data, that curve behaves poorly. But what did Dr. Lu say? The good news is that no matter which way we analyze the data, I'm quoting here, we do not see a significant fluctuation in levels of IQ when fluoride dosage is in low normal range, which clearly support our hypothesis. It is safe to drink fluoridated water when fluoride dosage is in low normal range. So that's what Professor Lu said.

(02:09:22):

So today I'm going to summarize consensus findings because I don't believe experts' opinions, especially as expressed by individuals, should be relied on because they are ranked lowest in the hierarchy of evidence. Therefore, we should base our decisions on impartial consensus reports. So I'm going to summarize the consensus reports, especially on fluoride and IQ, validity of spot urinary fluoride, study design quality and interpretability.

(02:09:56):

And the first is the National Academy's consensus report and that found that the NTP draft monograph fell short of providing clear and convincing argument that supported its assessment of presumed neurodevelopmental hazard. Other reputable groups from New Zealand, Canada and Germany have also reached the same conclusion. The report also stated that the evidence generated primarily from high fluoride areas cannot be used to draw conclusions about fluoride levels typically used in community water fluoridation.

(02:10:31):

So this comment should also apply to fluoride supplement. So there is a scientific consensus that spot urine samples during pregnancy or childhood are not accurate and reliable biomarker of long-term fluoride exposure, especially to the fetus. So Dr. Ragan who has authored several of these reports recently wrote, "Fluoride IQ studies relying on individual urine measures are worthless."

(02:11:02):

So I use this when WHO radio frequency field on, there's a highly controversial topic, cell phone and cancer. There is consensus that cross-sectional studies and ecological studies should not be used to establish a cause and effect relationship. So there are guidance in all these endemic communities, especially in India. I've seen them. There are campaigns available and they say to avoid drinking high fluoride water. So one should not rely on the history of residents to assess temporality in cross-sectional studies.

(02:11:42):

It is entirely possible that high IQ families had access to low fluoride water, which influenced their low urinary fluoride excretion rather than the other way. This is a classic case of reverse causality. The cohort studies included in the NTP systematic reviews are secondary data analysis projects. In other words, data were gathered first and the research questions were asked later. So these types of studies cannot test the causal relationship between fluoride and IQ.

(02:12:12):

So we published a meta-analysis. We asked the question does fluoride exposure recommended for care ease prevention, decrease children's cognition and IQ scores? This is most relevant for our discussion. And these meta-analysis show that fluoride exposure at the concentration used in community water fluoridation is not associated with lower IQ. As you see in this, there is no association in non-endemic areas, meaning there are no skeletal and severe dental fluorosis cases. Whereas we see it in endemic areas and we say these two should not be combined because there are more studies from endemic areas compared to non-endemic areas.

(02:12:56):

So we submitted a letter to JAMA Pediatrics which published where we highlighted that if you stratify the data that NTP used and looked at only non-endemic areas, there is no association. So what about dose-response analysis? This is what the NASEM Consensus Report said. "Given the substantial concerns regarding health implications of various fluoride exposures, comments or inference that are not based on rigorous analysis should be avoided." So they said don't do this dose response analysis and NTP went ahead and performed a dose, published and I'm focusing on dose response maternal below 1.5, urinary fluoride.

(02:13:41):

There are four studies. N equals four. There are seven effect sizes. Total is 4,179 children. Most of them came from endemic areas. I would not have combined endemic and non-endemic areas in this analysis.

Secondly, if you look at the studies, an increase, no change, inconsistent and a decline. In the U study, the urinary fluoride level went from zero to 5.6. There was one IQ point difference. You look at this data, population norm is a hundred IQ and we are saying 106 IQ in endemic areas where the fluoride exposure was very high and they had IQ of 100.

(02:14:32):

So this is the maternal urinary fluoride exposure data. There are four studies. Taylor's analysis included three studies, and the coefficient was negative, but it was not statistically significant. If I add the Ibarluzea study and delete the element study salt, it becomes clinically not significant at all. Almost zero.

(02:14:59):

So about the element study, so first of all, the exposure is salt. Salt is also associated with unhealthy habits. So it is a potential confounder. The other thing is in this popular 45%, I checked this figure a couple of times, 45% of pregnant women reported ever smoking. That is really high. So the other studies came from Denmark, Canada and Spain. So there is concern about selective reporting in publication bias. So if you take away one coefficient, substitute with another, the results alter dramatically.

(02:15:43):

The second one is, for example, in the element study, this is NIH funded element birth cohort study. Overall, this investigation found no evidence of detectable adverse outcome on offspring neurobehavioral development associated with maternal fluoride exposure during pregnancy at ages one, two, and three. But this is not included in the systematic reviews because it's not published.

(02:16:12):

And this is the NTP neurotoxicity study conducted equivalent to two to four parts per million fluoride and it found no effect as well as no alteration of thyroid hormone levels, T3, T4 or TSH. No alteration of thyroid hormone at levels two to four parts per million. So no human exposure. No exposure related pathology, no evidence of neuronal depth.

(02:16:47):

So overall, fluoride exposure at the concentration used in community water fluoridation not associated with lower IQ scores. So if you ask me where should we do these studies, I say it should be done in endemic areas, we strongly encourage this. And no one actually recommends what type of studies. We boldly recommended interventional studies. We don't believe that cohort studies will definitively answer these questions because the challenges of conducting these studies are very high.

(02:17:25):

So I want to go back to this one slide and summarize. This morning, Dr. Osman said, "If you don't control for socioeconomic, it is dead meat." And type of analysis using unadjusted mean IQ scores is dead meat according to his own definition. Thank you.

Susan C. Winckler, RPh, Esq. (02:17:49):

Thank you, Dr. Kumar. So we'll move to the other podium and hear from Dr. Susan Fisher-Owens, who is Clinical Professor of pediatrics at the University of California San Francisco School of Medicine and Clinical Professor of Preventive and Restorative Dental Sciences at the UCSF School of Dentistry. Dr. Fisher-Owens, please proceed.

Dr. Susan Fisher-Owens (02:18:16):

Thank you very much. I'm delighted to be able to be here and share my perspective as a pediatrician. I am a breastfeeding to birth control pediatrician working in a county public hospital. These are the

patients I see every day. And so with that, I want to start by talking about the fact that I care about the whole patient. I care about my patients as they're getting ready for school and as they're going off into the world to get jobs. And also as they have risks, including need for being hospitalized, having antibiotics. All those different pieces.

(02:18:55):

I'm also an academic. So you've heard me as a pediatrician. I'm an academic. I teach at a top 10 medical school in this country. So I have the brightest minds that are constantly challenging me. I have to stay on top of the research. As a researcher, I need to understand the science and know what can and cannot be proven with different types of studies.

(02:19:19):

So when we talk about our charge today... Well, first I'll back up and say many of us have talked about risk. There is nothing without risk. I argue perhaps chocolate, but nothing else. You can have too much vitamins, you can have too much oxygen. Everything has risk. And so our job as scientists, as advisors, is to look at those risks and try to balance them for our patients, for our communities and work with them together. So we talk with the challenge today. The first we've mentioned is whether or not we're talking about ingestible fluoride. I will note, first of all, that we don't recommend ingestible fluoride in the first six months of life. That's not relevant.

(02:20:13):

The main benefit from fluoride ... Yes, it's topical, but even with ingestion, you're supposed to be swishing or swallowing in the mouth, and so that fluoride deposits into the plaque and remains there until that point where plaque is brushed off. With water, it has repeated exposures during the day, and so even though it is systemically taken, it's the water running over the teeth that provides benefit. We know, as was mentioned earlier, and I'll reiterate from McLaren's study in Calgary, that even with fluoridation at ... Sorry, with tooth brushing at 94%, 95% of the population, there still was an increase in cavities when one of the levels of fluoride, community water fluoridation, was removed.

(02:21:02):

The next topic we say is for being unapproved. The FDA declined initially to review fluoride products, and so it's legacied at that point, but the vast majority of products used in pediatrics are not FDA licensed for use in pediatrics. We estimate it's around 70% of the medications that I use, and I counted last Friday in clinic, and indeed the vast majority were not approved. Just because it wasn't approved doesn't mean it's not appropriate. These are recommended by the US Preventive Services Task Force. They're recommended by the AAP, the American Academy of Pediatrics, the American Academy of Family Physicians, Health Canada, the New Zealand World Health Organization, and hundreds others of reputable expert organizations.

(02:21:56):

We heard a great deal about the microbiome, so I'm going to skip this slide and talk about tests because I said, as a researcher, I look at tests. What makes a good test? Every test is right for the right question, and so we have to make sure that the question is fitting the test, but the results we get can't be viewed in a vacuum. We've discussed already the fact that confounders can influence how we understand pieces. The examples before given of high fluoride coal, if that's in ventilation, that's going to influence a test or nutrition. Background levels of fluoride in the water inherently or location. We know there also are factors that influence intelligence, that coal, arsenic, lead, tobacco ... Having those in an environment is going to, in fact, impact intelligence, so we need to have these and, of course, socioeconomics used as part of our adjusting as we look at results. Now, spot urine fluoride can be a great test for blood in the urine. It can be a great test. I used it last week for infection, but it's not a great

test for fluoride. Fluoride in urine varies on the day, on the diet, on the season, even the trimester of pregnancy. And when we think that, by the age 10, a youth has over 10,000 voids. Picking one is not going to be representative of their exposure.

(02:23:33):

Is IQ testing a good test? Not in little kids. Little kids it really varies. It varies by the time of day. It varies if they've had a nap or if they've had a snack. Kids vary when they're little. There's also a pretty big cultural bias with IQ testing that doesn't get affected. It doesn't really balance out until kids have gone through school for a period of time. Different IQ tests have been shown to get different results, and so we have to be careful about pooling results from different tests. And I give you this example here, looking at the same relative exposure of fluoride and an eight-point IQ difference in Canada versus Denmark. Clearly, there's more going on in that picture.

(02:24:25):

Going on, I'll give you one more example about location. This is unpublished data that came from the MIREC study, but in looking at six different cities, three of which were fluoridated, and three of which were not, that had testing done by different research assistants in each location, we found, or they found, excuse me, overall, if we look at the bottom point, that the mean IQ was the same, but yet there was wide variation between those sites. We have to say, is it really about that city? Or is it about the tester? Or is it about something else? We can't use that as a good test.

(02:25:15):

What we can look at is IQ tests done later in life. What I show you here is that there is no difference between fluoridated and non-fluoridated communities when tested with older children and multiple times through their life in adulthood in New Zealand, in Canada, in Spain, and in Australia, which are also communities more similar to us in the United States.

(02:25:45):

I'm doing fine with my time. In summary. When I think about balancing the risks and the benefits, I am ... There we go. First, I want to highlight the picture I have on the left. You've heard a lot today about fluorosis, and fluorosis is not one similar group. Fluorosis is many different entities throughout and that, in fact, for our examples, as we go across this, this goes from no fluorosis all the way to the most severe fluorosis. We all agree that this is not healthy to have severe fluorosis. We all agree that this is not good for the teeth to have severe fluorosis. But in fact, for mild and for moderate fluorosis, it both strengthens the teeth and actually cosmetically makes them appear whiter. Aesthetically, most people prefer a mild amount of fluorosis. When you hear, "Well, fluorosis ... There's more fluorosis in our country," that's not necessarily a bad thing. When we're looking ... Even the numbers that were presented today shows it's less than 1%.

(02:26:59):

On the other hand, I worry about this. This is a patient of mine on the right who was someone who had not had access to care. I hadn't seen him for a year and a half, and he came in and had a whopping dental abscess. This was a little one who needed to be admitted to the hospital, needed to have IV antibiotics to help control his diabetes and his blood sugars, and this is my concern.

(02:27:24):

In summary, studies that show negative effects of community fluoridation were done outside the US or not with reliable measures. Those within or similar to the US did not show difference in neurocognition. Spot urinary fluoride is not a good test. We need to think about the whole body and how to protect

children's health. Overall, fluoride should remain an option as one of the options for our families. Thank you.

Susan C. Winckler, RPh, Esq. (02:27:59):

Thank you, Dr. Fisher-Owens. And we will conclude our four presentations in the neurocognitive space with a presentation from Dr. Kyla Taylor, who is epidemiologist in the Division of Translational Toxicology at the National Institute of Environmental Health Sciences. Dr. Taylor, thank you for being here, and please proceed.

Dr. Kyla Taylor (02:28:19):

Do I press the screen?

Susan C. Winckler, RPh, Esq. (02:28:20):

The giant button, yes.

Dr. Kyla Taylor (02:28:22):

Wait. That one?

Susan C. Winckler, RPh, Esq. (02:28:23):

Yes, the green one.

Dr. Kyla Taylor (02:28:24):

All right, thank you. Thank you so much for having me. I'm excited to be talking about the work that we do at NIHS in the National Toxicology Program.

(02:28:34):

As a brief background, in 2006, the National Research Council reported evidence of neurotoxic effects of fluoride in humans and animals. In 2015, this topic was nominated to the NTP for evaluation. And in 2016, NT published its first monograph, which was of the experimental animal studies, and this found low to moderate evidence of adverse effects on learning and memory. Last August in 2024, we published our second NTP monograph. This included human, animal, and mechanistic studies. We screened over 14,000 studies and identified over 500 that were relevant. Two independent reviewers critically assessed study quality based on criteria that was determined a priori, and all the data has been documented and is available online. Based on the epidemiological evidence, we concluded with moderate confidence that there's an inverse association between fluoride exposure and children's IQ, and this moderate confidence does apply to all fluoride levels of exposure.

(02:29:42):

Now, I'll be talking about a systematic review and meta-analysis that was published in January of this year in JAMA Pediatrics. This is the most comprehensive and transparent meta-analysis or systematic review of the children's IQ studies to date. We conducted a targeted analysis of 74 studies. 22 of these were determined to be high-quality studies.

(02:30:04):

We followed a peer-reviewed protocol, and this ensures that all data is used as opposed to relying on biased subsets of data. Two independent reviewers assessed the methodological quality, or were also called the risk of bias, for each study. And high-quality studies had to meet pre-specified criteria across

seven different risk of bias domains. Those included selection bias, confounding, exposure characterization, outcome assessment. For an example, a high-quality study would have to adjust for key confounders, such as age, sex, socioeconomic status, and co-exposures to other neurotoxicants like lead and arsenic.

(02:30:48):

Studies reported group and individual-level data, and fluoride exposure was measured primarily or estimated primarily in water and urine. And I'd like to point out that this meta-analysis is set apart from others due to the high level of transparency. All the data that we extracted and the risk of bias assessment is publicly available, and all of it is downloadable for researchers who can replicate and extend our work.

(02:31:18):

We conducted three different meta-analyses. The first two use group-level data, and this compares children living in high-fluoride-exposure areas to children living in low-fluoride-exposure areas. The third included studies that had individual-level urinary fluoride levels.

(02:31:37):

Now, I'll be showing you the results of these different analyses. The first is the mean effects of meta-analysis which used group-level data. Right now, what we're looking at is a forest plot of the standardized mean differences that were calculated for each study. These are the 47 low-quality studies that reported group-level data. On the right side of the figure are the standardized mean differences. And you may notice that almost all of these SMDs fall to the left of the solid black no-effect line, and that means we're looking at a consistent pattern of inverse associations across this evidence.

(02:32:15):

When we look at the 12 high-quality studies, you can see that that consistent pattern does continue. And when we look at the pooled SMDs of both the low and high-quality studies, they were both inverse and statistically significant. Next, we estimated pooled dose-response curves using linear and nonlinear models. The linear models were the best fit for the data. We did this separately for fluoride measured in water and fluoride measured in urine. And this is important, an important distinction, because urinary fluoride is a valid measure of total fluoride exposure. That's fluoride ingested from all sources, including drinking water. Regulatory agencies like the EPA routinely rely on urinary measurements as exposure estimates in their risk assessments.

(02:33:05):

When we looked at the high and low risk of bias studies together or the high and low quality studies together across all exposure levels, we saw a significant inverse dose-response in water and in urine. When we restricted this analysis to only the high-quality studies, you can see that those associations are very similar. And when we restricted the high-quality studies to those that had a high exposure group of less than 1.5 milligrams per liter, both the data for the water and urinary fluoride remained inverse. And only the urinary fluoride association was statistically significant.

(02:33:48):

Next, we estimated pooled regression slopes and these are also called beta coefficients, and this was using the 13 studies that included individual-level urinary data. Again, we have a forest plot. You can see the 11 high-quality studies and the two low-quality studies. Again, there's a consistent pattern of inverse associations. Both groups of studies low and high quality. The pooled estimates were inverse, and they were statistically significant.

(02:34:22):

Three of the studies that I just showed you took multiple urinary measurements throughout pregnancy, and this is the robust measure of prenatal fluoride exposure. And that's really important because the developing brain is most susceptible to neurotoxicants.

(02:34:42):

The highlighted studies here are the three high-quality prospective cohort studies. They all measured IQ around seven years. The first two in the Canadian and Mexican cohorts had maternal urinary fluoride levels that were comparable to what is seen in the United States. And in Denmark, they don't fluoridate their community drinking water, so those levels are actually much lower than what we see in the US.

(02:35:05):

We pooled these three regression slopes together, and we found an inverse association that was not statistically significant. A recent study by Grandjean et al ... The authors were actually able to pool all of the individual-level urinary data from each of the cohorts together. They found a similar inverse association that was statistically significant.

(02:35:28):

Before I get to that, I'd also like to note that we did conduct sensitivity analyses. We did include studies like Ibarlucea. Studies like that did not measure IQ directly, which is why they were not included. They measured other cognitive ... They used other cognitive tests. When we included those studies, the effect estimates did not change much. The inverse associations remained statistically significant.

(02:35:56):

Overall, we took multiple different approaches for assessing the data, and we consistently found statistically significant inverse associations between fluoride exposure and children's IQ. These associations held when they were restricted to the best available evidence, which are the high-quality studies. We found linear dose-response relationships across all the data and when fluoride exposure was limited to levels at less than 1.5 milligrams per liter. This was in both urine and water, and that's important because it means that we're not relying on any one exposure measure.

(02:36:35):

Additional prospective cohort studies at lower fluoride exposure levels would be very informative. And overall, the consistency ... What stood out to us was the consistency and robustness of the inverse association across this large body of literature. This was across different study populations in multiple different countries with different exposure levels and exposure sources, both group and individual- level data and, of course, fluoride measured in different ways such as urine and drinking water.

(02:37:09):

A dose-response and a high level of consistency in the direction of an association in hazard assessment that strengthens our confidence in the overall inverse association. I'd like to thank my co-authors at NIEHS and at ICF for all of their incredible work on this. And thank you so much for your time and attention.

Susan C. Winckler, RPh, Esq. (02:37:29):

Thank you, Dr. Taylor.

(02:37:33):

And with that, those of you who are keeping track, we now have one more section in this session, and then we'll turn to our panel discussion. But thank you so much, Dr. Taylor, for rounding out our neurocognitive component. I do need to pass the power to our next speaker, which is Dr. Christine Till.

Dr. Till is a professor in the faculty of health at York University in Toronto. We appreciate you joining us here today, and we'll turn the podium over to you.

Dr. Christine Till (02:38:04):

Thank you for the invitation. I have been asked to speak about fluoride and thyroid function, an area that I've done research on in addition to studies on fluoride in IQ.

(02:38:20):

I have no disclosures. Thyroid hormones, which are small iodine-containing molecules, play a key role in regulating many biological and physiological functions and are essential for brain development and function. Fluoride has been considered to be an endocrine disruptor that can interfere with thyroid function. And the potential for thyroid dysfunction is a possible mechanism underlying developmental fluoride neurotoxicity.

(02:38:55):

In the 1950s, fluoride was used to treat overactive thyroid. Specifically, sodium fluoride was used pharmacologically to treat iodine-induced hyperthyroidism, or too much thyroid, because it can effectively reduce plasma-bound iodine and relieve the clinical symptoms of hyperthyroidism.

(02:39:17):

High fluoride levels have also been associated with increased incidence of goiter, which is an enlargement of the thyroid gland. This eloquent study on zebrafish shows dose-dependent effects of fluoride, including reduced body weight and length, enlarged thyroid tissues, and elevated thyroid-stimulating hormone levels in a dose-dependent manner.

(02:39:46):

In humans, there have been several systematic reviews looking at the association between fluoride and thyroid function. I will focus on the one published in 2024 by Iamandii et al.

(02:39:59):

Shown here is a forest plot of child thyroid-stimulating hormone, or TSH, as a function of fluoride measured in water, urine, and serum. The blue squares represent the mean difference in TSH levels in a high-fluoride group compared to a low-fluoride group, and the red diamonds represent the weighted mean difference across the studies. What we see is a overall consistent pattern of association with higher levels of fluoride measured in water, urine, or serum associating with higher levels of TSH in children. And when the researchers focused only on the highest-quality studies, the pattern of association between fluoride and TSH remained consistent and significant. I should add that an elevated TSH on its own is not considered to be adverse, but it is a signal that there is a perturbation to the thyroid homeostasis. The researchers also conducted a dose-response meta-analysis. Regarding water fluoride levels, we see a rise in TSH levels at water fluoride concentrations of about two milligrams per liter and above. Whereas, when looking at the individual biomarkers, including urinary fluoride and serum fluoride, there is no threshold. We begin to see the rise in TSH even at low levels. Again, to reiterate what was said earlier, these biomarkers are assessing total fluoride intake as opposed to water fluoride concentration which may not take into account an individual's overall exposure.

(02:41:42):

In adults, there are fewer studies looking at thyroid hormone and fluoride exposure, but what we do see is a consistent pattern with higher fluoride exposure measured in water or in urine and higher TSH levels in the adult studies.

(02:41:58):

Fluoridated water has also been associated with clinical hypothyroidism in adults, and I'm raising this because fluoridated water is considered a low exposure. One study conducted in England by Peckham et al found an association between higher levels of fluoride in drinking water and higher prevalence of hypothyroidism. This was an ecological study, so potential unmeasured confounding may be a concern. Another study conducted out of Iran found an association between water consumption habits and increased risk of hypothyroidism. Now, our group conducted a study on a large sample of pregnant women living in Canada using the Maternal Infant Research on Environmental Chemicals cohort. We looked at the association between fluoride measured in drinking water as well as in urine and how that was associated with thyroid hormones. What we found was a positive association between maternal urinary fluoride and TSH levels, especially among women carrying females. Specifically, a one-milligram-per-liter increase in urinary fluoride was associated with a 35% increase in TSH.

(02:43:06):

Regarding free T4 and total T4, these levels showed a gradual decline at higher exposure levels, but the overall difference did not reach statistical significance. Was trended, though.

(02:43:20):

We did another study looking at fluoride exposure measured in water, urine, and estimated using self-reported questionnaire data to estimate fluoride intake with the outcome being primary hypothyroidism.

(02:43:38):

What we found was that pregnant women exposed to higher concentrations of fluoride in drinking water were at increased risk of hypothyroidism, specifically a 0.5 milligram-per-liter increase in water fluoride, which is roughly the difference between living in a fluoridated and non-fluoridated community, was associated with a 65% greater odds of meeting criteria for hypothyroidism.

(02:44:03):

During the trial, a question was asked as to whether we had controlled for duration of residence. We returned to our model, an excluded woman who had not lived in their home for at least a year, and we found that the association between drinking water and hypothyroidism increased and became a little bit stronger and remained significant. We also re-ran our model excluding women who were positive for thyroid hormone antibodies, which would signal an autoimmune thyroid disease, and again found that the association remained significant. It became stronger.

(02:44:38):

Now, hypothyroidism in pregnancy, particularly in the first trimester, is critical because the fetus is completely reliant on the maternal thyroid supply. And if there is deficiency in thyroid hormones during this period, this could contribute to adverse neurodevelopmental outcome.

(02:44:56):

We looked at child IQ scores as a function of whether the woman had hypothyroidism in pregnancy or not, and what we found was that boys born to women with hypothyroidism had significantly lower IQ scores compared to boys born to euthyroid or normal thyroid hormone levels in women.

(02:45:20):

Now, fluoride also has an interactive effect with iodine which is essential for thyroid hormone synthesis. In the case where there's iodine deficiency, this can exacerbate the thyroid disrupting effects of fluoride. And we have shown this in some of our studies looking at iodine-deficient individuals. And this is of concern because iodine intake in the US population, including pregnant women, is decreasing.

(02:45:46):

The study by Goodman et al looked at the association between urinary fluoride and child IQ, and we found that the effect of fluoride and IQ was stronger or more significant among boys who were born to mothers with low iodine intake in pregnancy compared to women who had adequate iodine levels during pregnancy.

(02:46:12):

Now, the mechanism by which fluoride interferes with thyroid function remains unclear, but there are some suggested mechanisms including inhibition of deiodinase activity, which is important for converting T4 to T3. Fluoride has also been shown to disrupt G proteins, which is important for mediating release of neurotransmitters. Fluoride has been shown to reduce thyroidal sodium iodine symporter expression and activity which is important for transporting iodine into the thyroid and may also impair and alter thyroid structure.

(02:46:47):

We now have evidence, experimental and epidemiological evidence, reporting associations between fluoride exposure and thyroid dysfunction, and this thyrotoxicity supports the plausibility of fluoride neurotoxicity. In conclusion, the potential for childhood sodium fluoride treatment to disrupt thyroid function must be taken seriously, particularly for children with suboptimal intakes of iodine.

(02:47:16):

Thank you.

Susan C. Winckler, RPh, Esq. (02:47:18):

Thank you, Dr. Till.

(02:47:23):

For our second and final presentation in the thyroid section of session two, our presenter is joining us virtually, and we will hear from Dr. Kathleen Thiessen, president and senior scientist at the Oak Ridge Center for Risk Analysis. Dr. Thiessen, we can see you in the room and see your slides. Please proceed.

Dr. Kathleen Thiessen (02:47:43):

Thank you. I hope that you can hear me.

Susan C. Winckler, RPh, Esq. (02:47:47):

Yes, we can.

Dr. Kathleen Thiessen (02:47:48):

Great. I want to thank you for the opportunity to speak at this meeting. This will be a very brief look at effects of ingested fluoride on thyroid function.

(02:47:59):

Next slide, please.

(02:48:03):

By way of context, just a reminder that whatever beneficial effect fluoride has on oral health is from topical exposure, not from ingestion. Most supplements are intended or at least expected to be ingested. However, the human body has no requirement for fluoride. From the CDC, fluoride's predominant effect is post-eruptive and topical. From a 1999 paper by Brian Burt, fluoride supplements

are a risk factor for dental fluorosis, and the risks of using supplements in infants and young children outweigh the benefits. From the Iowa study, which evaluated an individual fluoride intake from all sources, including supplements, the findings suggest that achieving a caries-free status may have relatively little to do with fluoride intake, and that's their emphasis.

(02:48:57):

The two most recent reviews of supplement use have found little or no benefit. These have been mentioned. Cochrane in 2011. Thomason et al in 2015. Overall systemic fluoride ingestion is not beneficial for oral health and comes with a number of health risks, including dental fluorosis, thyroid dysfunction, cognitive deficits, and others. Dental fluorosis as a marker of early fluoride intake is itself associated with reduced IQ, increased risk of bone fractures, and other effects. I want to also say that supplements can be contributing to fluoride exposure, I mean by design, in areas with no fluoridated water. And this means that, if you're looking only at the water fluoridation level, you've got exposure groups with overlapping exposures, and that complicates the studies. Next slide, please.

(02:49:56):

As many of you already know, and as Dr. Till has discussed, normal thyroid function controls or regulates a variety of physiological processes, including normal growth in development of infants and children, especially the normal development of the nervous system. Normal thyroid function is dependent on adequate iodine intake of the mother through during gestation and of an individual from birth throughout life. Maternal thyroid function is essential for the developing child, and iodine requirements are typically higher for pregnant women than for other adults.

(02:50:32):

The term thyroid hormones generally refers to T4, thyroxine, and T3, triiodothyronine. T4 is a major secretory product of the thyroid gland, while T3 is the active form which binds to the thyroid hormone receptors in various tissues. T3 is produced from the T4 by the deiodinases. These are primarily type one in the liver, kidney, and thyroid and type two in the non-hepatic tissues, including the brain and the pituitary. The level of thyroid-stimulating hormone, or TSH, is commonly considered to be indicative of the status of the thyroid function. This is produced in the pituitary as part of a feedback mechanism. Next slide, please.

(02:51:22):

The fluoride effects on thyroid function as observed in human studies have generally resulted in reduced thyroid function, including relief of hyperthyroidism in some patients, increased prevalence of goiter, altered concentrations of T4 and T3, and elevated concentrations of TSH. These effects have been observed at estimated fluoride intakes of approximately 0.05 to 0.1 milligrams per kilogram per day. This 0.05 is the same 50 micrograms per kilogram that Dr. Moran showed earlier. Effects occur at even lower fluoride intakes when iodine intake is not sufficient. Note that these estimates are group averages. They're not intakes for affected individuals specifically, but these ranges of the average intakes overlap with the estimated fluoride intakes in the US from drinking water or from fluoride tablets used according to the current recommendations. Next slide, please.

(02:52:28):

This graph is an example of a study of fluoride effects on thyroid function. In this case, prevalence of goiter with respect to fluoride concentration and drinking water. Note, especially, that when nutrition is inadequate, which is the top five points, there's a clear dose-response between fluoride exposure and goiter prevalence. This shows the importance of adequate nutrition, which would include things like iodine, but iodine is not the only one. Next slide, please. As one might expect from the complexity of normal thyroid function, there are several possible mechanisms by which fluoride can reduce thyroid

function. These include decreased production of thyroid hormones, effects on transport of iodine and of thyroid hormones, effects on peripheral conversion of T4 to T3 and on normal deiodination, and deiodinases are inhibited. These mechanisms are not mutually exclusive. More than one probably occurs. Some of these mechanisms might depend on particular genetic variance of enzymes within the population or on inadequacy of nutrition, especially iodine. Another example. Selenium is a requirement for normal deiodinase function, and that can be deficient in some cases.

(02:53:52):

In general, fluoride has long been known as a potent inhibitor of enzymes, and the variety of possible mechanisms means that the effects of fluoride intake on thyroid function can look different in different individuals. It can be complicated to evaluate different studies and understand what's going on physiologically, but if you take the trouble to look carefully, the studies are generally consistent, as we described in the 2006 NRC report, which concluded that fluoride is an endocrine disruptor in that it alters normal endocrine functional response. Next slide, please. The main implication of these findings is an increased prevalence of both symptomatic or clinical hypothyroidism and asymptomatic or subclinical hypothyroidism in the population. Subclinical hypothyroidism is not benign. It's associated with increased risks of cardiac disease, high cholesterol, higher likelihood of depression, diminished response to standard psychiatric treatment, cognitive dysfunction, for pregnant women, decreased IQ of the offspring. Next slide please.

(02:55:08):

In terms of the significance for public health, fluoride exposure range is necessary for many adverse effects of fluoride, including thyroid effects are reached routinely by people in the United States. The tablets prescribed according to ADA recommendations correspond to approximately 0.02 to 0.03 milligrams per kilogram per day in children apart from any other exposures. And it's rare in this country to have no other exposures, no other sources of fluoride intake.

(02:55:39):

Thyroid effects are seen when average group exposures are 0.01 milligrams per kilogram per day in the presence of iodine deficiency. So intakes from tablets already exceed the levels of intake associated with thyroid effects in the presence of iodine deficiency. And as you've heard, iodine deficiency is common in the US, especially among pregnant women. Again, the developing child is entirely dependent on the mother for thyroid function during much of gestation.

(02:56:14):

Additional risk factors for fluoride effects include chronic kidney disease, which results in reduced excretion of fluoride and calcium deficiency. The calcium deficiency produces a general increase in fluoride absorption and retention and in potential toxicity. More than 50%, apparently as high as 70% of US children have dental fluorosis. And this matter is even at the milder forms of dental fluorosis. This indicates over-exposure to ingested fluoride during early childhood.

(02:56:56):

At least 10% of the US population, including pregnant women, is estimated to have hyperthyroidism, clinical or subclinical, including 1% of children. The individuals considered most at risk for caries are not helped by fluoride exposure. These individuals are the most vulnerable to adverse effects from ingested fluoride due primarily to nutritional deficiencies and fluoride exposure does not make up for socioeconomic differences or for differences in access to care. Thank you for this opportunity.

Session 2 Reactor Panel:
Bruce Lanphear, MD, MPH, Simon Fraser University
Charlotte W. Lewis, MD, MPH, University of Washington School of Medicine

Susan C. Winckler, RPh, Esq. (02:57:29):

Thank you so much, Dr. Thiessen. And for all of those presentations I am... Well, one of the great things about moderating meetings like this is I get this immersion into a new topic. And I'm for sure taking mouth guards away. And was completely intrigued by the idea that how much we are learning about the microbiome to the exploration and different ways of thinking about the neurocognitive effects and how it is that we might explore that not only the effects but the exposure and then the emerging information about thyroid as well.

(02:58:08):

So for those who are in virtually and then those in the room, we know that we have our array of speakers and two new faces joining us. So let me introduce our reactor panelists. Here in the room is Dr. Bruce Lanphear, who is a preventive medicine physician and professor at Simon Fraser University in Vancouver. And then joining us online is Dr. Charlotte Lewis, who's a professor of pediatrics at the University of Washington School of Medicine.

(02:58:37):

We use the reactor panel construct to make sure that we have an engaging Q&A session, which clearly worked in session one. But I'll challenge us to in this second session to say I want to turn first to our reactor panelists and we asked you to listen and then apply your perspective and expertise. I'll turn first to Dr. Lanphear and then Dr. Lewis, if you want to ask any questions of presenters or simply share what you were thinking as you heard this array of presentations. And for those in the room, hit push to talk and get close to that microphone. There you go.

Dr. Scott Tomar (02:59:24):

Yes. Thank you. Thank you for inviting me to be here. I just wanted to start it out maybe with a brief overview and that is to raise this question for all of you. How many of you are convinced that low level lead poisoning is a problem for children? Let me just see a raise of hands. God, damn. Your life in the past. Is that all? Isn't everybody agree that lead poisoning is a problem?

(02:59:49):

Well, the reason I ask that is that the same type of studies that were used to ask those questions, which has been adopted by the EPA, by the CDC, by the American Academy of Pediatrics, by the World Health Organization, were the same type of study designs that you saw presented here today. There is one difference. With the lead studies, we relied on blood lead. With the fluoride studies we either used water fluoride, fluoride intake or urinary fluoride.

(03:00:23):

Now I've been studying how toxic chemicals from lead and arsenic and pesticides impact children for about 30 years. Urinary fluoride like urinary arsenic, like urinary organophosphate pesticides is the optimal way to measure these toxic chemicals in large epidemiologic studies. We may find it in the future that other things are better, but for today that's what we know. So if you have somebody that hasn't been studying this who minimizes that, I'd you to consider why they're asking that question that way.

(03:01:03):

What's the difference when we measure something like fluoride or pesticides or arsenic in urine? It is, as Susan pointed out, more variable. And that is important to know. What that means is we're less likely to show a true association, in this case IQ deficits, because of that. And yet even with that greater variability in the measure say than compared to blood lead levels, the vast amount of the evidence shows consistent inverse relationships with IQ. As fluoride goes up, whether it's in water or urine, IQ goes down.

(03:01:48):

I want to just bring up one final point. People have made the mistake of saying that the levels that we're exposed to where we see IQ deficits is much higher than what children are exposed to or pregnant women in optimally fluoridated communities. It's absolutely not true. So let me just stop there. Those are my points I'd like to bring in to make sure that we have those as base facts when we have the discussion.

Susan C. Winckler, RPh, Esq. (03:02:20):

Thanks, Dr. Lanphear. And I'll turn it to Dr. Lewis and then it is this discussion here. I think if you all turn your mics on at the same time, that won't work so well. But if you want to pop up your tent cards or in other way you see, I'll acknowledge the queue. And to doctors Cole and Dr. Thiessen, we can also see you. So you just need to give me the high sign or go ahead. But Dr. Lewis, you have the floor.

Sally Greenberg, JD (03:02:45):

Thank you. It's a pleasure to be here. America has been a powerhouse in medical research. And over my career I've seen some amazing things come from the research that's conducted in this country, starting with basic science and then translating to lives actually being saved. And a similar thing has happened with our understanding of fluoride, which began in the first part of the 20th century. And then through our understanding of naturally present fluoride, we were able to take advantage of that and apply that phenomena to what we know can prevent cavities in children.

(03:03:29):

And ever since community water fluoridation was introduced, there's been people that have tried to make it out to be risky or unhealthy or dangerous or mass medication. And we know those things based on very strong epidemiologic evidence from around the world is not true. I want to particularly focus in on something that was said by some speakers today when they said there's no benefit to swallowing fluoride. First though I want to make sure you understand that when we drink fluoridated water, we are allowing ourselves both a topical and a systemic source of fluoride. And both of these are important with the systemic sources of fluoride, more important for young children, which are the patients that I care for.

(03:04:20):

And this is what people have said, that there's no benefit to swallowing fluoride, but why does it make sense to say then that the only thing that happens when you swallow fluoride is that you get fluorosis? Well, we know that fluorosis is a result of systemic exposure and we also know that systemic exposure like occurs in the first eight years of life as our permanent teeth are developing, yes, does lead to fluorosis. And indeed, we've known for decades that teeth with fluorosis are more resistant to decay. So to say that there's no impact to swallowing fluoride is just completely false. And really reflects that people have taken essentially a biased approach to their understanding of the science.

(03:05:16):

And that's not how science should work. We should be embarking on this research and I'm glad to hear that our government is planning on this. But when we conduct research, we need to put our biases aside and keep an open and objective mind. That's the whole point of doing science.

(03:05:41):

So children who we know from epidemiologic research that people that are exposed to fluoridated water while their teeth are still developing, even if they leave the area when they're eight years old, let's say, and continue to drink lower than optimal fluoride and receive lower than optimal fluoride in the water, that they still have the benefits from that exposure early in their lives. And so to say that swallowing fluoride does nothing is really quite false.

(03:06:14):

I also want to speak briefly to the thyroid issues. Hypothyroidism in pregnancy is a fairly common thing. The most common etiology of that is chronic Hashimoto's. And indeed we do know that hypothyroidism in pregnancy, which in this country is typically recognized and treated, could have a potential impact on neurodevelopment. What we don't know though is that fluoride is a factor in the development.

(03:06:45):

And what we've seen today is people cherry-picking studies and making conclusions without presenting us with the complete data that we need to know to draw conclusions. And that's not what research in this country should be about. What research and science in this country should be about is having an unbiased objective approach to the research that we do and how we apply that to our populations. Thank you.

Susan C. Winckler, RPh, Esq. (03:07:10):

So let's think about that. And actually, I want to turn first to you, Dr. Webster-Cyriaque, because were speaking about the research that's underway and that will be pursued. How are there... And actually, I'll ask Dr. Taylor to address this as well, to just think about, so when we do that research, I know we always want to be seeking... Just to give us some elements of doing that well so that we can have more of this illumination of what's present versus what we might assume before we turn that light on.

Dr. Webster-Cyriaque (03:07:48):

Right. So the research needs to, in my opinion, reflect the demographic of the US. It needs to be representative. These need to be large, well-controlled studies. Okay. These studies need to be done at the levels present in the US, right? So what are the total exposures? Where do I live? Based on where I live my exposures may be different. Based on what I eat my exposures may be different. So they need to be very comprehensive.

(03:08:20):

And we need to tag team. For example, to ask questions about thyroid disease or endocrine issues we can do studies across the lifespan with NIDDK. And we've talked about with aging and also cohort studies in children with NICHD. So we can really look over time in a comprehensive way at all the different health outcomes in the context of all of the different contributors.

(03:08:53):

I think that we have to be careful about drawing these lines. So for example, the no benefit. There's also some benefit to bone health, but it's all about the amounts and the levels. We have to understand we have to ask the question in an unbiased way and understand the difference it makes here in the US, right? We know that there's some potential for improved bone health, but at very high levels you can

get skeletal fractures. But we've got to do the research to figure out where that is. So until we ask the question in the appropriate cohort and with the appropriate size, with the appropriate level of control, we're not going to be there.

Susan C. Winckler, RPh, Esq. (03:09:39):

Okay. And Dr. Taylor, I know you had spoken, I was struck in your description of the meta-analysis and the transparency and the data, some other components. Just what might you add to that? And then I do have you in the queue, Dr. Fisher-Owens.

Dr. Kyla Taylor (03:09:52):

Yeah. Our study followed best practices in systematic review, which is to include all studies, both high and low quality and to follow pre-established risk of bias criteria that are peer-reviewed in a protocol. And that's what we did and we presented all of that data following the predefined subgroup analysis that we said we would.

(03:10:16):

There are several studies that have comparable levels of exposure to the United States. And we know that from United States-based cohort studies based in California, based in New Hampshire, some other states that report very similar maternal urinary level fluorides to what is seen in the Canadian and in the element, the Mexican cohort studies.

(03:10:40):

And right now that is the most comparable data that is available. I don't think there is a large difference in the people who are living in Canada and Mexico. These studies controlled for socioeconomic status, they controlled for all of the things that we identified a priority were key confounding variables. And so that's very important. That's our best evidence in the highest quality evidence.

Susan C. Winckler, RPh, Esq. (03:11:06):

In what's been done, and then seeking, in continuing in this to have that sense going in, I think there was also a question, saying, "What is the research question that we want to answer and how are we constructing that?" So I've got Dr. Fisher-Owens and then Dr. Kumar and Doctor... Yep. That's great. Dr. Fisher-Owens.

Dr. Susan Fisher-Owens (03:11:29):

And just to go back, there was a comment made that where people drink water is the same around the world. We know that in China they drink roughly two to three times as much water per day as we do in the US and that their levels are at baseline three if not four or five times higher endemically from the soil than here. So there are great differences in terms of exposure even from "just drinking water."

(03:11:56):

I'd also add, we talked about the fact that urinary spot fluoride is a spot in time. Something like nail clippings at least gets a more contemporaneous idea of the total fluoride and not just from that one moment in time. And then last, absolutely we care about lead. Lead and in fact lead is something that should be controlled for when we're looking at IQ studies because we know that it is a true neurotoxin.

(03:12:27):

In my training, the level at which we worried about lead has decreased and I'm grateful for that because I don't want to risk that for my patients. But when I look at the studies that helped approve lead being

limited, which were appropriate and which were based on blood, which is a much better value, they allowed more difference in IQ than what the studies were looking at for fluoride when we're looking at places with comparable intake to ours. And so for that reason, it's not a perfect analogy.

Susan C. Winckler, RPh, Esq. (03:13:03):

But to the idea of learning more helpful, Kumar, Taylor, Webster-Cyriaque, and I'm just going to tell... Oh, there we go. Okay, Dr. Cole, I got you in the queue now after Kumar, Taylor, Webster-Cyriaque. Dr. Kumar.

Valerie (03:13:20):

Thank you. So this is one reason why we should rely on consensus report, urinary fluoride. We have a report, WHO, and that is based on daily urinary excretion data. That is 24 hour. And that is about surveillance. In other words, at the population level, if you monitor from year one to year two, you can tell at the population level whether fluoride exposure is going up or down at the population. It is not about individual level. And that is the consensus report.

(03:14:01):

If arsenic and other studies have used it, we have to go back and look at those studies. Actually and everyone looks at this one seminal paper by Lockind. Okay, in that one there is a whole section on single urinary sample. At the most three. If you look at some of the risk and bias tools like TASCA, if it is a single sample of biomarker, they say, "It is unacceptable." So I don't know where people get... And if two individuals given the same amount of fluoride, one is a vegetarian, other is on a meat-based diet, the fluoride content in urine will be entirely different.

(03:14:50):

And here we are talking about taking spot sample. Most of the time it is not adjusted for urinary dilution and calling it as total exposure. So we should go back to the WHO report and ask them. And everyone quotes Ragan. He wrote a nice opinion. He said for epidemiological studies, spot urinary sample is a worthless biomarker at the individual level. There's a big difference individual versus population.

Susan C. Winckler, RPh, Esq. (03:15:30):

Okay. Well, then I think we noted in the first panel that sweeping statements are probably challenging in our discussions, but very helpful clarifications on a few of the points. I do want to do Taylor, Webster-Cyriaque, Cole and then Till. And we are tightening our comments at this point.

Dr. Kyla Taylor (03:15:54):

Okay, to the spot urine samples. For an individual that may be true that we may be getting variability. Across a population and across a body of evidence that we had in our systematic review, as an example, what happens when you have imprecision based on spot urinary samples is that that introduces random noise to the data. And that typically biases those results to the null. Meaning that if you have exposure misclassification and you still see an association, that association may actually be stronger than what is observed.

(03:16:29):

Also for differential misclassification to occur, which I think is the concern, is that this spot urinary samples are somehow creating these inverse associations. The spot urinary samples would have to systematically and selectively misclassify children with both low fluoride exposure and with lower IQ. That is just highly unlikely given the diversity of the studies that we're looking at. Also, urinary fluoride

measurements are able to distinguish between populations who live in fluoridated areas and populations that live in non-fluoridated areas. I think Dr. Till has her study demonstrated that as well as many other observational cohort studies that measured urinary fluoride in fluoridated and non-fluoridated areas.

Susan C. Winckler, RPh, Esq. (03:17:15):

Webster-Cyriaque, Till, Cole, Lanphear.

Dr. Webster-Cyriaque (03:17:18):

Okay. Quickly. To the samples, there are opportunities to utilize nail clippings and even exfoliated teeth, so you actually can have the cumulative level without the variance. And so maybe that's something we should think about moving towards.

Dr. Kyla Taylor (03:17:34):

Yes, definitely.

Dr. Webster-Cyriaque (03:17:36):

Yeah. The other thing is, to an earlier point, we are not optimally fluoridated here in the US, right? Our mean levels across the US are about 0.52, three-fold lower than the 1.5 level. Understood that it's not just the water, right? Not just the water. Clearly there are other sources, but we really need to ask the question in the context of all the potential sources that are additive, recognizing that we're starting off much lower than some of the other places that have been included in these earlier studies.

Susan C. Winckler, RPh, Esq. (03:18:12):

Dr. Cole.

Dr. Cole (03:18:14):

Yes, thank you. I just want to make two very quick points. Dr. Fisher-Owens had said earlier that fluoride strengthens the enamel and that's actually not true. Hydroxyapatite is much stronger than fluoroapatite. Fluoride actually, yes, it makes the tooth maybe less susceptible to demineralizing, but it's definitely more brittle, especially as we go up in levels of fluorosis. I just want to make that point as a person who practiced dentistry for 30 years and I saw it firsthand.

(03:18:44):

The second thing I'll do is I have a question for Dr. Lewis. In your 2014 paper you actually talked about supplements and said that the disadvantages of them are substantial. And you talked about how the effects were mostly topical and not systemic. And one thing you actually said, and this is quote from it, it says, "On the basis of some research evidence, fluoride drops are associated with more dental fluorosis and because they are swallowed, their routine use is inconsistent with the primarily topical mechanism of fluoride's action in preventing caries." Could you comment on that?

Sally Greenberg, JD (03:19:23):

Of course I can. And I also would be very interested in other dentists' perspective on the dose-response relationship in terms of the hardness of the enamel exposed to fluoride, because I know there's many experts in attendance to this meeting who could speak to that point. Yes. Let me say then 2014, and I still believe this, I still believe that supplements contribute to fluorosis moreso than swallowing

community water fluoridation. And I think another very important factor that contributes to fluorosis currently has to do with swallowed toothpaste.

(03:20:01):

Nevertheless, toothpaste functions, for the majority of the population as a topical source, but in children we know that they swallow a significant amount of that. And so swallowed toothpaste is also going to be a systemic source. I personally think there's a lot of disadvantages to supplements. They don't have anything necessarily to do with promoting resistance to dental decay. They have to do with the cost, with the fact that there requires a prescription, that it requires daily administration, things like that.

(03:20:34):

I would like to see us eventually move to the model that a lot of other people in the world have done, and that is to promote fluoride toothpaste. Nevertheless, and I agree for the vast majority of our lifespan, topical sources of fluoride are important. But I also know, and in the last 10 years have done substantial research and writing and consultation about fluoride and its benefits. And we know that fluoride beginning as early in life as possible is more beneficial than when it's started later.

(03:21:09):

And so based on that, we know that swallowing fluoride, whether that's in the form of water that provides both topical and systemic sources as well as supplements. Did those both promote resistance to dental decay? Do they also cause more dental fluorosis than we would like? Yes. Is most dental fluorescence in this country mild? Yes. Is it considered to be a mild thing that in some people's minds is more aesthetically pleasing? Yes. But let's get to the point that yeah, there are disadvantages to fluoride supplements. That's what we're supposed to be talking about today. But that doesn't mean that fluoride itself and swallowing it is not a valuable thing.

Susan C. Winckler, RPh, Esq. (03:21:57):

Thanks, Dr. Lewis. And for the question, Dr. Cole, I've got Dr. Till, Lanphear. And then I'm going to go to two voices that we haven't already heard before we take our break. All right. Yeah, go ahead, Dr. Moran. And then I'm going to do doctors Till, Lanphear and close out with Dr. Kumar.

Dr. Gary Moran (03:22:14):

Just to correct the science on the role of fluoride and its effect on enamel. It doesn't affect the mechanical strength of enamel, it makes it resistant to acid erosion. So just to get the pathogenesis of caries corrected is acid erosion. It's acid which dissolves the enamel. The replacement of a group on the enamel with the fluoride iron makes it acid resistant. It's nothing to do with mechanical strength.

Susan C. Winckler, RPh, Esq. (03:22:36):

Okay, thanks, Dr. Moran. Dr. Till, Lanphear, Kumar. Dr. Till.

Dr. Christine Till (03:22:41):

So my point was made by Dr. Taylor, but I want to reiterate that a spot sample may not be as accurate as a 24-hour urine sample, but this argument misses the fundamental principle of exposure misclassification, that when we are using a spot sample, which is moderately correlated with water fluoride concentration, so at about 0.5, that's a pretty good correlation between urinary fluoride and water fluoride. But if there is exposure misclassification, that reduces the size of the effect. So with anything, if we had a better exposure metric, we could actually find a stronger effect.

(03:23:15):

We are now measuring fluoride in toenails. And I can say that it is also quite complicated looking at fluoride in toenails. We're also measuring it in deciduous teeth so that data are forthcoming. But back to the dental fluorosis, I also want to remind the audience that we are seeing increased prevalence of dental fluorosis, which reflects an overexposure in early life. And we should be concerned about where those fluoride sources are coming from, what impact that might have on the developing brain. Because the sensitive period for dental fluorosis is the first few years of life. So that suggests that children are over ingesting fluoride. And in this critical window and brain development is undergoing significant brain maturation.

Susan C. Winckler, RPh, Esq. (03:24:03):

Dr. Lanphear and then Dr. Kumar.

Dr. Scott Tomar (03:24:06):

Thank you. A few follow-up points. First we did both in the MIREC study in Canada and a new study in Bangladesh, see IQ deficits at levels around or below the mean levels you showed Jennifer in the national survey. New studies absolutely will be useful and there's a lot ongoing. I think one of the challenges is that we need to make decisions now. And the reason I would suggest in just a minute why we need to do it now I'll get to in just a minute.

Susan C. Winckler, RPh, Esq. (03:24:38):

You have 15 seconds.

Dr. Scott Tomar (03:24:39):

Oh My god. All right. So it was said that there are no alternatives. We do have fluoride toothpaste. We have failed to explore other risk factors for tooth decay. We just published another study showing low-level lead poisoning is a risk factor for tooth decay. It's not the first one we did. We know that vitamin D deficiency puts children at risk. We've been so fixated on fluoride, supplement and otherwise, that we failed to protect children from tooth decay.

(03:25:13):

Finally, I have been involved with one of the most contentious areas of pediatrics, low level lead poisoning. I've been kicked off science committees, but we had the ability to look at it and say, "This was industry doing it to us. It was industry that was poisoning our children." Every one of us here needs to be absolutely clear, if we continue to put fluoride in supplements in the water, it is on us. It is not on some industry. We need to be absolutely clear when we use population level strategies that we have absolutely good evidence from randomized controlled trials that it's beneficial. And we-

Susan C. Winckler, RPh, Esq. (03:26:00):

For the supplements that we're talking about today?

Dr. Scott Tomar (03:26:02):

For supplements. Absolutely. And if-

Susan C. Winckler, RPh, Esq. (03:26:05):

Is it right, we're not on-

Dr. Scott Tomar (03:26:05):

As we've said-

Susan C. Winckler, RPh, Esq. (03:26:06):

... community water Florida.

Dr. Scott Tomar (03:26:06):

... we don't have evidence showing supplements reduced tooth decay. The only one that has been done randomized controlled trials, no benefit. So back to the point that Dr. Tidmarsh talked about this morning. If we don't have good evidence, we've got all this accumulating evidence of harm, how can we continue-

Susan C. Winckler, RPh, Esq. (03:26:31):

Which is one of the paths for an unapproved prescription drug to become approved just for that component.

Dr. Scott Tomar (03:26:37):

Thank you.

Susan C. Winckler, RPh, Esq. (03:26:37):

I've got to close it out, Dr. Kumar. Valerie, I give you the final piece if you want to say anything, but you do not have to. Dr. Kumar.

Valerie (03:26:47):

I just want to address a couple of things that is said. Yes. One of them is that fluorides don't reduce cavities. If you look at the data at the sense of the microbiome, fluoride does two things. One, it makes the enamel more resistant to acid erosion. It also reduces the type of bacteria and the bacterial interactions that lead to tooth decay. So fundamentally at the mechanistic level, fluoride is acting to reduce tooth decay.

(03:27:20):

Tooth decay is multifactorial. It has been said many times today. It happens A, because someone's eating too much sugar too frequently, which creates environments. One way of protecting is to make sure that the bacteria don't respond to those sugar triggers and fluoride allows that to do that in terms of the microbiome. The second thing I want to talk about for a second is fluorosis. And I've heard a lot about how it almost seems a terrible thing.

(03:27:47):

Most of the pictures we see on the internet of fluorosis are taken after we dry the mouth out. If you dried my teeth out to take those pictures, they would look much whiter than they actually are. So when I look at a person with fluorosis, it's hard for me for them, if they have mild fluorosis, it's very hard for me to say that they have fluorosis unless I'm taking a clinical picture in my practice, which is a completely different thing.

(03:28:13):

And the other thing is it takes really a professional to be able to diagnose fluorosis because many bleaching agents and the frequent use of these little whiteners, tooth whiteners and bleachers at a much younger age can mimic fluorosis. So we really need to think about when we si and we are calling something fluorosis, how sure are we that we are actually accurate in what we're saying.

Susan C. Winckler, RPh, Esq. (03:28:40):

Which maybe captures a lot of what has been said in all of this discussion. And I apologize, Dr. Lewis, I promised I'd keep us on time and I failed. So I know you have to get to clinic. So we are rounding out. That the pursuit of the information we should pursue and continue to have dialogue and disagreement. But then also to say, "How is it that we can gather more information to make the best decisions?" As the regulator, FDA will be considering an array of information.

(03:29:16):

And each of you contributed to that array of information that's available. So thank you for investing your time. Thank you for the research that you do and that you will continue to do. We know that the discussion is not over, but I do have to say this session is over because the number of people in this room who need to run and hit the restroom has reached a peak that I can assess. So that, thank you all for joining us. We will return at the top of the hour for the public comment period. Thank you.