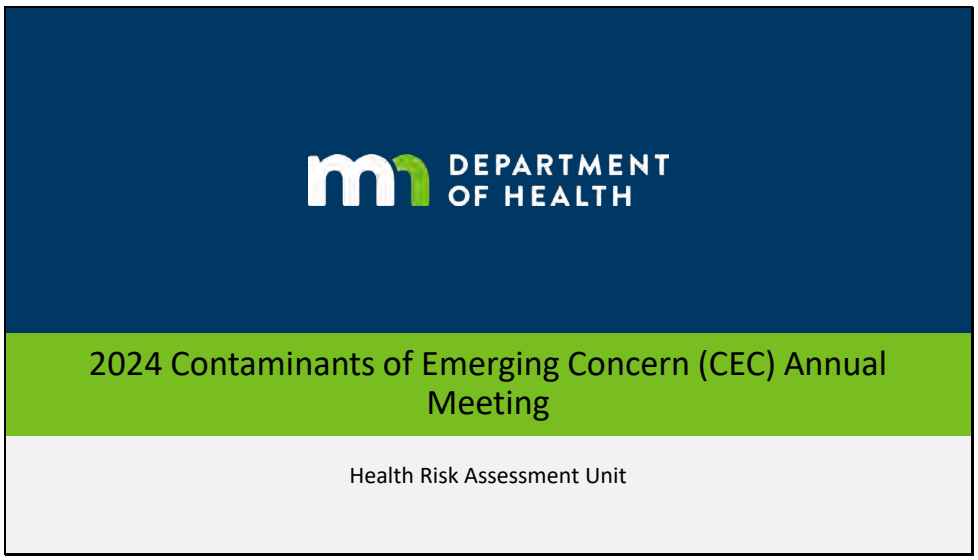
2024 Contaminants of Emerging Concern (CEC) Annual Meeting Summary

Slide 1: 2024 Contaminants of Emerging Concern (CEC) Annual Meeting



Slide Text and Image Description

Minnesota Department of Health logo.

Health Risk Assessment Unit.

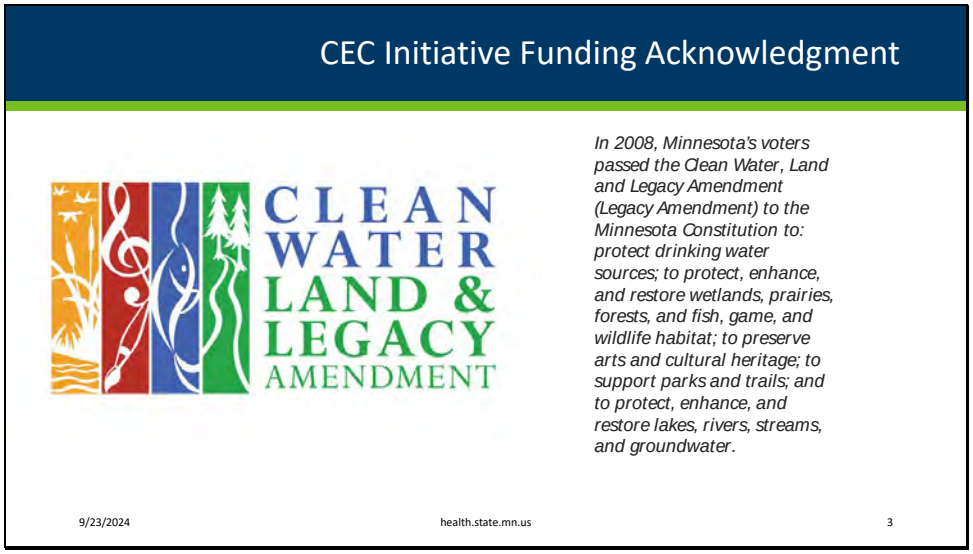
Slide 2: Tribal-State Relations Acknowledgement Statement

Slide Text and Image Description

The state of Minnesota is home to 11 federally recognized Indian tribes with elected Tribal government officials. The State of Minnesota acknowledges and supports the unique status of the Minnesota Tribal nations and their absolute right to existence, self-governance, and self-determination. The United States and the State of Minnesota have a unique relationship with federally recognized Indian tribes, formed by the Constitution of the United States, treaties, statutes, case law, and agreements. The State of Minnesota and the Minnesota Tribal governments significantly benefit from working together, learning from one another, and partnering where possible.

The Minnesota Department of Health (MDH) recognizes, values, and celebrates the vibrant and unique relationship between the 11 Tribal nations and the State of Minnesota. MDH believes that the partnerships formed, through a government-to-government relationship, with the 11 Tribal nations will effectively address health disparities and lead to better health outcomes for all of Minnesota.

Slide 3: CEC Initiative Funding Acknowledgement

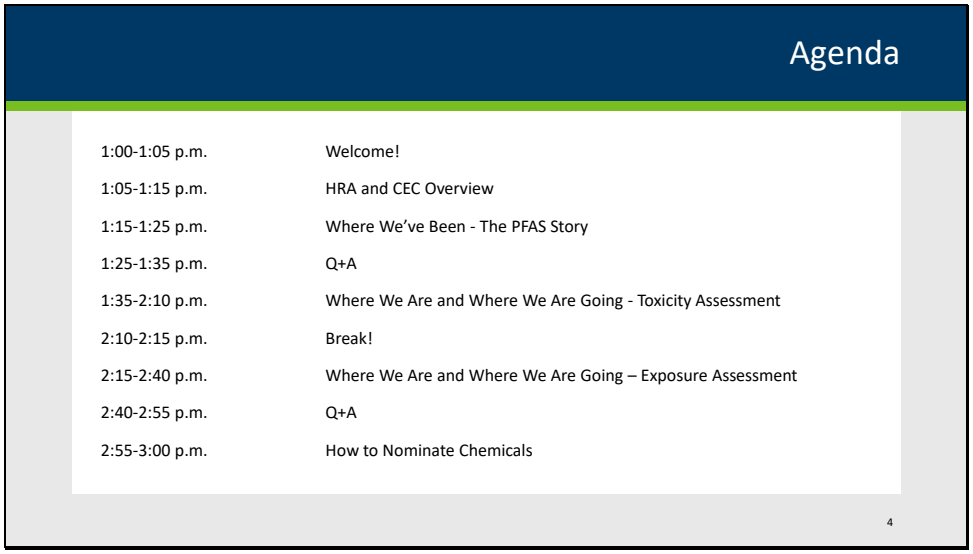


Slide Text and Image Description

Clean Water Land and Legacy amendment logo.

In 2008, Minnesota's voters passed the Clean Water, Land and Legacy Amendment (Legacy Amendment) to the Minnesota Constitution to: protect drinking water sources; to protect, enhance, and restore wetlands, prairies, forests, and fish, game, and wildlife habitat; to preserve arts and cultural heritage; to support parks and trails; and to protect, enhance, and restore lakes, rivers, streams, and groundwater.

Slide 4: Agenda



Slide Text and Image Description

1:00-1:05 p.m. Welcome!

1:05-1:15 p.m. HRA and CEC Overview

1:15-1:25 p.m. Where We've Been - The PFAS Story

1:25-1:35 p.m. Q+A

1:35-2:10 p.m. Where We Are and Where We Are Going - Toxicity Assessment

2:10-2:15 p.m. Break!

2:15-2:40 p.m. Where We Are and Where We Are Going – Exposure Assessment

2:40-2:55 p.m. Q+A

2:55-3:00 p.m. How to Nominate Chemicals

Slide 5: Health Risk Assessment (HRA) and Contaminants of Emerging Concern (CEC) Overview

Slide Text and Image Description

Minnesota Department of Health logo.

Image: A stream surrounded by greenery on either side.

Health Risk Assessment (HRA) and Contaminants of Emerging Concern (CEC) Overview

Kristine Klos, PhD; HRA Supervisor.

Summary

I want to welcome everybody today.
This is a great opportunity for us to share our work and get feedback and input from all of you. Today we're sharing our Contaminants of Emerging Concern Initiative and we're going to be telling you all about what we did the in the last year.

Slide 6: Minnesota Department of Health-Health Risk Assessment Unit

Slide Text and Image Description

Image: a hand holding a drinking glass that is filling up with water from a kitchen faucet

Text: Mission: Protecting, maintaining, and improving the health of all Minnesotans.

Summary

We are from the Minnesota Department of Health and the mission here is to protect, maintain and improve the health of all Minnesotans and our unit, the Health Risk Assessment Unit, does that by developing water guidance.

Slide 7: HRA Develops Health-Based Guidance

Slide Text and Image Description

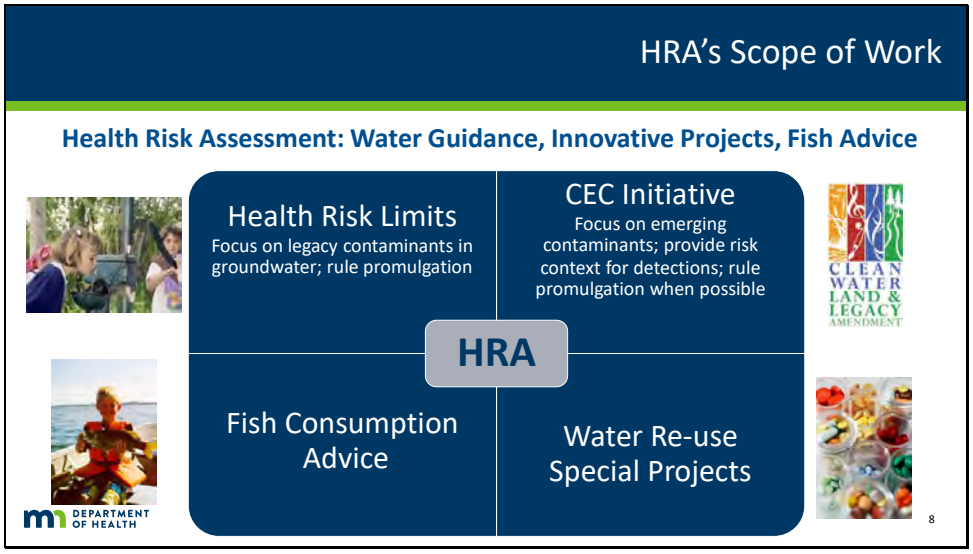
Image of a girl drinking a glass of water through a straw, giving a thumbs-up sign.

Health based guidance: Concentration of a contaminant(s) in water that is likely to pose little or no health risk to people who drink the water, including sensitive and highly exposed populations.

Summary

What is health-based guidance? Health-based guidance is the concentration of contaminants in water that is likely to pose little or no health risk to people who drink the water, including sensitive and highly exposed populations. We represent these concentrations in micrograms per liter. You will see this on our Water Guidance Table on our website.

Slide 8: HRA's Scope of Work



Slide Text and Image Description

Health Risk Assessment: Water Guidance, Innovative Projects, Fish Advice

Four images: Clean Water Land and legacy amendment, picture of different colored pills in medicine cups, boy carrying a fish, girl drinking water from a water fountain.

The Health Risk Assessment unit consists of four areas:

- Health Risk Limits: focus on legacy contaminants in groundwater; rule promulgation
- CEC Initiative: focus on emerging contaminants; provide risk context for detections; rule promulgation when possible.
- Fish consumption advice
- Water re-use special projects

Summary

When we look at what the Health Risk Assessment Unit does, at our core we make water guidance, but we also have innovative projects and develop fish consumption advice.

To address contaminants in water, we began our program with health risk limits or we what we like to call our HRL program. This group in our unit focuses on legacy contaminants and groundwater. If they're found in Minnesota's waters, we can put them through rulemaking. These are often contaminants that

are natural in the environment, like manganese or boron. They're also pesticides, and they're also just contaminants that we know are around.

With the Clean Water, Land and Legacy Amendment that Minnesotans voted for in 2008, the Clean Water Fund was created. We receive a portion of this money, and this money runs our CEC Initiative. We thank all Minnesotans for voting on that back in 2008 –we are here because of you.

The CEC Initiative focuses on emerging contaminants, and that's what we're going to talk to you about today. We provide risk context for detections and if we can, we put those into rule too. Sometimes, there's not enough toxicity information for us to put the health-based guidance of a CEC into rule.

We also have staff members working on water reuse. This is going to become more important as climate change progresses.

Lastly, we now have the Fish Consumption Guidance Program in our unit.

Slide 9: Health Risk Assessment Unit-Team

Slide Text and Image Description

Images: headshots of Health Risk Assessment team members

CEC Research Scientists: Alex Bogdan, Sara Fossen Johnson, Lindsay Wilson, Christopher Greene, Benjamin Blair

Health Risk Limits Research Scientists: Katie Fallace, Christopher Schaupp, Nancy Rice

Fish Consumption Guidance Scientist: Angela Preimesberger

Planner: Azra Thakur

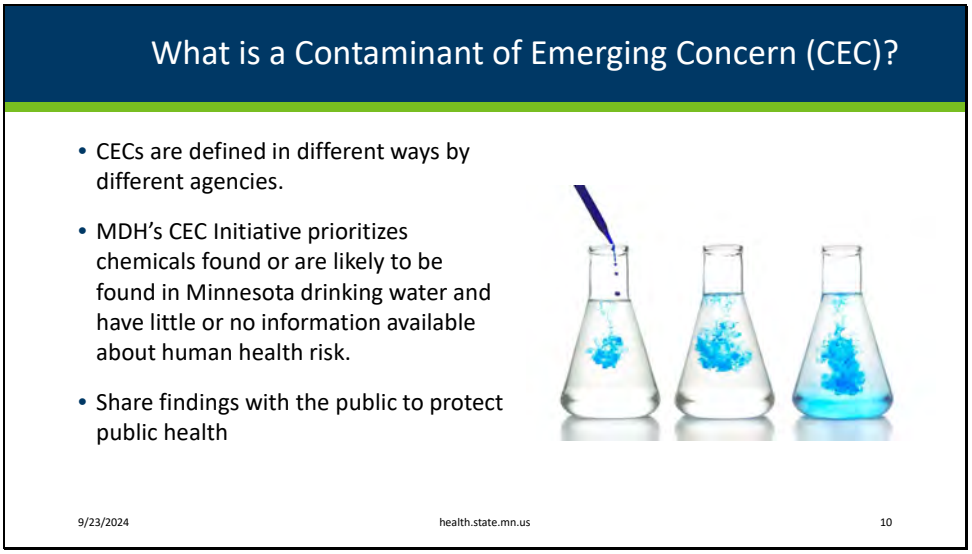
Unit Supervisor: Kristine Klos

Summary

Here is our team. We are a group of research scientists. You will notice that some pictures have a green circle around them. These are the Contaminants of Emerging Concern team, and you will hear from this group of people today. Other pictures have a blue circle around them. These are people from the HRL team , and they are helping out today.

Today you're going to hear from Alex Bogdan, Sarah Fossen Johnson, Lindsay Wilson, Chris Green, and Benjamin Blair. Helping out today is Katie Fallace, Chris Schaupp and Nancy Rice. We also have our fish consumption guidance staff, Angela Preimesberger and our planner extraordinaire, Azra Thakur.

Slide 10: What is a Contaminant of Emerging Concern (CEC)?



Slide Text and Image Description

Image: three beakers with a blue liquid dispersing in each beaker.

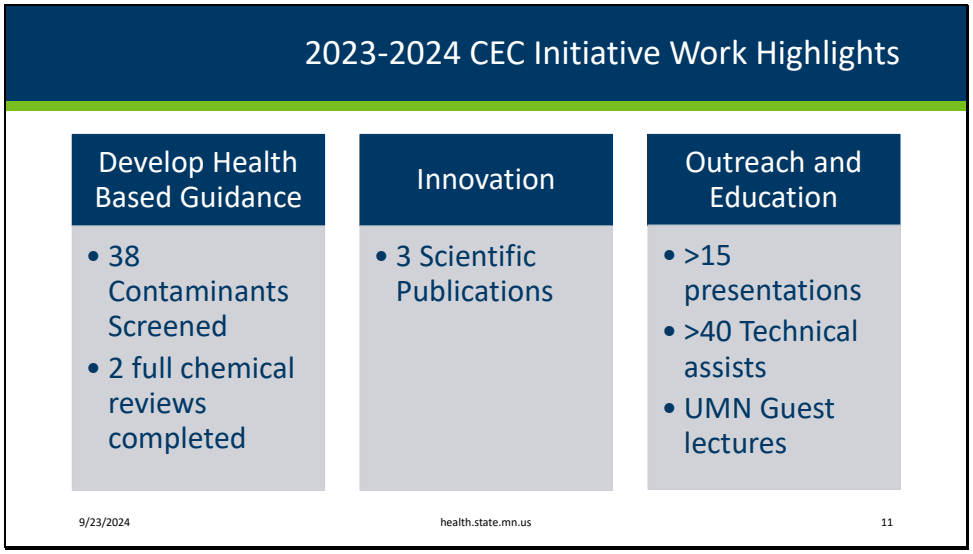
Text:

- CECs are defined in different ways by different agencies.
- MDH's CEC Initiative prioritizes chemicals found or are likely to be found in Minnesota drinking water and have little or no information available about human health risk.
- Share findings with the public to protect public health

Summary

So just a bit of background for those of you that are new to contaminants of emerging concern, what are they? Well, they're defined differently by different agencies in different ways.
We define it as chemicals that are found or likely to be found in Minnesota drinking water and have little or no information available about human health risk. And then what we try and do is share our findings with the public to protect public health.

Slide 11: 2023-2024 CEC Initiative Work Highlights



Slide Text and Image Description

Develop Health Based Guidance:

- 38 contaminants screened
- 2 full chemical reviews completed

Innovation

- 3 scientific publications

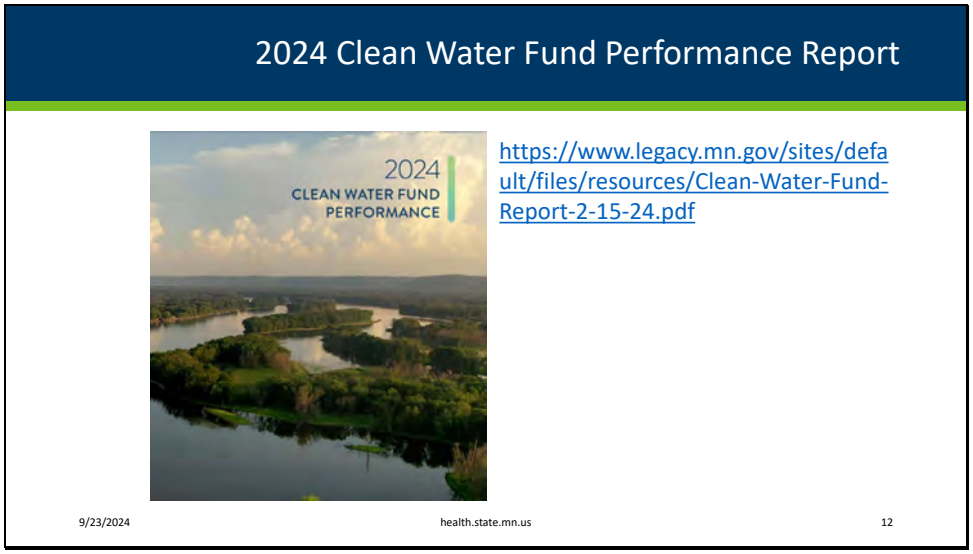
Outreach and Education

- More than 15 presentations
- More than 40 technical assists
- UMN guest lectures

Summary

This is a quick snapshot of our highlights from the last fiscal year. We screened 38 CECs and we completed two full chemical reviews. We like to be innovative—we published three scientific publications. We're also busy with outreach and education. Our staff gave over 15 presentations in the last year. We had over 40 technical assists with other agencies. We also have a close relationship with the University of Minnesota School of Public Health. We give guest lectures there on an annual basis.

Slide 12: 2024 Clean Water Fund Performance Report



Slide Text and Image Description

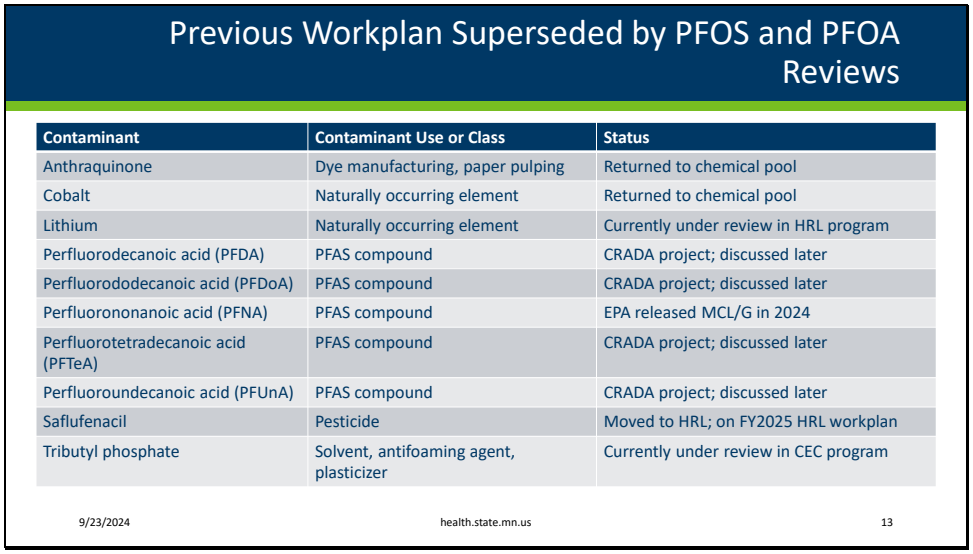
Image: 2024 Clean Water Fund Performance Report screenshot

Link: 2024 Clean Water Fund Performance Report (https://www.legacy.mn.gov/sites/default/files/resources/Clean-Water-Fund-Report-2-15-24.pdf)

Summary

You can read more about what we do in the 2024 Clean Water Fund Performance report.

Slide 13: Previous Workplan Superseded by PFOS and PFOA Reviews



Slide Text and Image Description

Contaminant	Contaminant Use or Class	Status
Anthraquinone	Dye manufacturing, paper pulping	Returned to chemical pool
Cobalt	Naturally occurring element	Returned to chemical pool
Lithium	Naturally occurring element	Currently under review in HRL program
Perfluorodecanoic acid (PFDA)	PFAS compound	CRADA project; discussed later
Perfluorododecanoic acid (PFDoA)	PFAS compound	CRADA project; discussed later
Perfluorononanoic acid (PFNA)	PFAS compound	EPA released MCL/G in 2024
Perfluorotetradecanoic acid (PFTeA)	PFAS compound	CRADA project; discussed later
Perfluoroundecanoic acid (PFUnA)	PFAS compound	CRADA project; discussed later
Saflufenacil	Pesticide	Moved to HRL; on FY2025 HRL workplan

Contaminant	Contaminant Use or Class	Status
Tributyl phosphate	Solvent, antifoaming agent, plasticizer	Currently under review in CEC program

Summary

This is a snapshot of our previous work plan. As you know, the best plans often go astray and that happened with us. r Most of our plan was superseded by the PFOS and PFOA reviews. We have created guidance for these chemicals many times before, however, there was new human data that we needed to look at and we needed to update our guidance, again with this new information. Our whole staff was involved with these chemical reviews. And again, they took the whole year last year.

Slide 14: Where We've Been: The PFAS Story

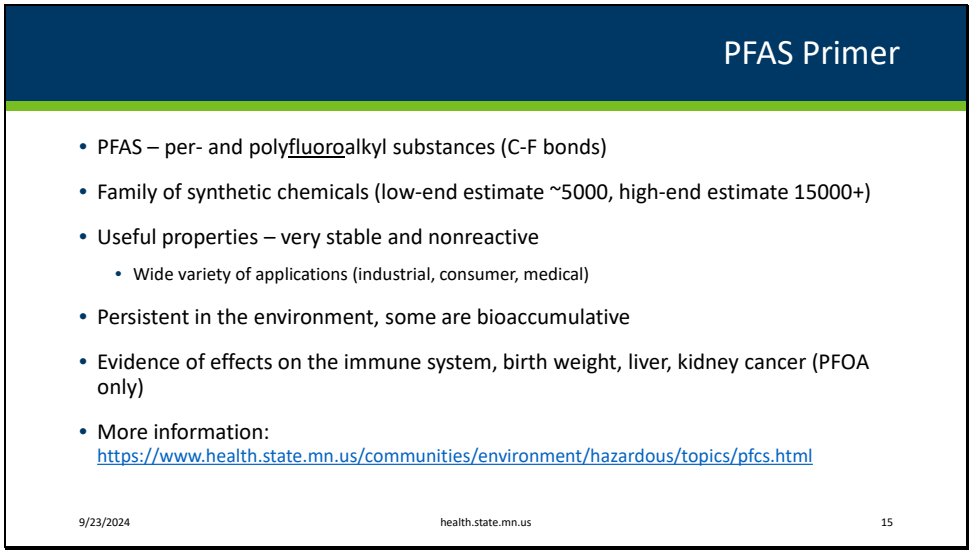
Slide Text and Image Description

Alex Bogdan, PhD; Toxicologist and Risk Assessor

Summary

I'm going to spend a few minutes talking about just where we've been as a program very briefly with PFAS and then what we've done over the last year and completed regarding PFAS.

Slide 15: PFAS Primer



Slide Text and Image Description

- PFAS – per- and polyfluoroalkyl substances (C-F bonds)
- Family of synthetic chemicals (low-end estimate ~5000, high-end estimate 15000+)
    - Useful properties – very stable and nonreactive
- Wide variety of applications (industrial, consumer, medical)
- Persistent in the environment, some are bioaccumulative
- Evidence of effects on the immune system, birth weight, liver, kidney cancer (PFOA only)
- More information: https://www.health.state.mn.us/communities/environment/hazardous/topics/pfcs.html

Summary

I'm sure many of us are very familiar with PFAS, but for those of us who aren't, here's a very quick primer on what they are. There’s a lot more information available at the link that's on the bottom of the screen.

PFAS stands for per- and poly-fluoroalkyl substances. And the underlined fluoro there kind of tells you what's special about them. It's a fluorine atom in there or actually multiple fluorine atoms.
I's the carbon fluorine bond that gives it some special properties. PFAS are a family of synthetic chemicals. Depending on the definition that you use, because there are many definitions depending on

who you ask, that on the low end there's an estimate of about 5000 PFAS in existence and, on the high end, it can exceed 15,000.

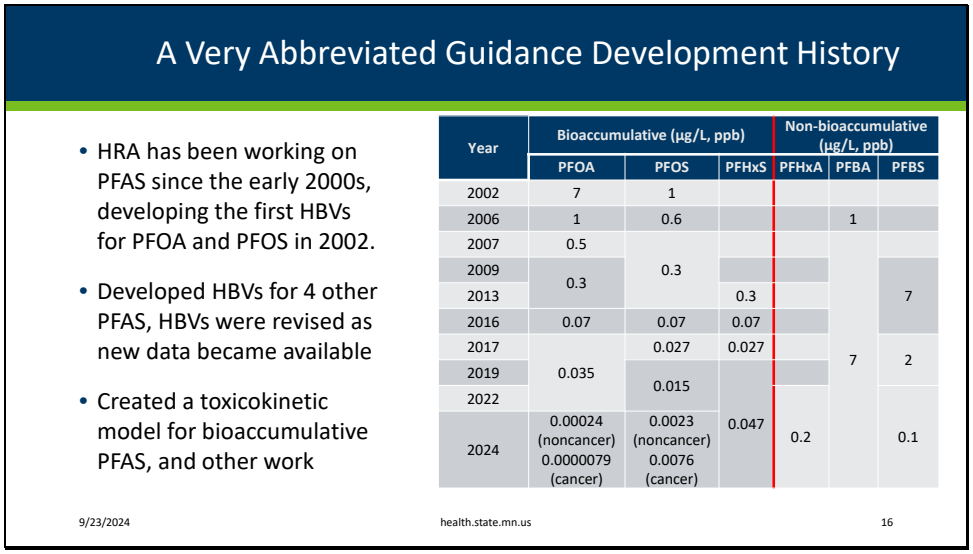
These chemicals that have very useful properties. Which means that they have many, many applications in industry and consumer products and medical applications and those properties are that they are very stable and very non-reactive. You can use them in things like non-stick coatings, grease resistant coatings. They are water resistant or oil resistant, so you can use them in a lot of different things and we have used them in a lot of different things.

But because they are so stable and non-reactive, that means that they can also be very persistent in the environment. Where there has been environmental contamination, they can persist there for decades and presumably centuries. Beyond that, we know that some of them are bioaccumulative. They can have half lives in the human body of years or decades.

We also now know that that there are health risks associated with these chemicals. We're seeing across chemicals in this family effects on the immune system. Low birth weight effects on the liver, and specifically with PFOA associations with development of kidney cancer after a lifetime of exposure.

If you want more information on PFAS, I encourage you to check out that link on the bottom of the page there.

Slide 16: A Very Abbreviated Guidance Development History



Slide Text and Image Description

- HRA has been working on PFAS since the early 2000s, developing the first HBVs for PFOA and PFOS in 2002.
- Developed HBVs for 4 other PFAS, HBVs were revised as new data became available
- Created a toxicokinetic model for bioaccumulative PFAS, and other work

Year	Bioaccumulative (µg/L, ppb)			Non-bioaccumulative (µg/L, ppb)		
	PFOA	PFOS	PFHxS	PFHxA	PFBA	PFBS
2002	7	1	--	--	--	--
2006	1	0.6	--	--	1	--
2007	0.5	0.3	--	--	7	--
2009	0.3	0.3	--	--	7	7
2013	0.3	0.3	0.3	--	7	7
2016	0.07	0.07	0.07	--	7	7
2017	0.035	0.027	0.027	--	7	2
2019	0.035	0.015	0.047	--	7	2
2022	0.035	0.015	0.047	0.2	7	0.1
2024	0.00024 (noncancer) 0.0000079 (cancer)	0.0023 (noncancer) 0.0076 (cancer)	0.047	0.2	7	0.1

Summary

This slide sums up about 20 years of work of guidance development within HRA.
So this is extremely abbreviated and HRA has done work well beyond only guidance development for PFAS. This is a snapshot of a very small slice of a very large pie of PFAS work, but HRA has been working on PFAS since the early 2000s, which is when contamination in the East metro was first discovered after manufacture by 3M.

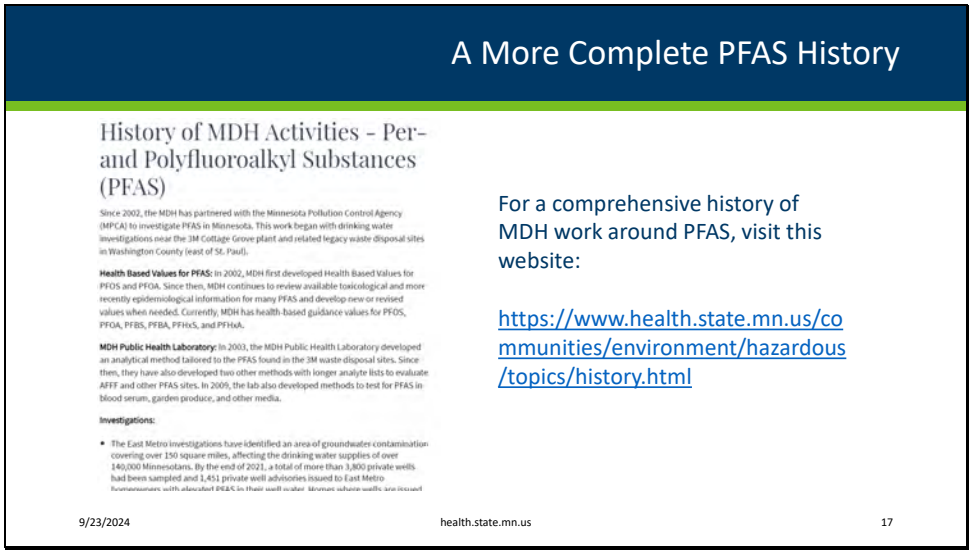
The first HBV, or health based values, one of the types of guidance values that we develop were for PFOA and PFAS, which are kind of the prototypical PFAS first developed in 2002.
And subsequently we developed HBV for four other PFAS listed in the table and over the years you can see that we have revised these HBVs over and over as new data have become available and more study was done on these chemicals.

As they gained more and more attention and were discovered in more and more places outside of Minnesota, they gained more research attention and more data became available and they became more and more studied. We reevaluated them as more information became available.

One thing that really became apparent around 2016-2017 was the need for a toxicokinetic model for bioaccumulative PFAS. The three on the left side of the screen: PFOA, PFOS, and PFHXS.
So toxicokinetic is just a fancy word for how a chemical moves around the body. It really became apparent that our normal water guidance derivation equations weren't sufficient for all of the exposure scenarios. We knew by that point that these chemicals could cross the placenta and the fetus could be exposed during pregnancy, and we knew that these chemicals could be present in breast milk, and an infant that was breastfeeding could be exposed. So we needed a model to mathematically track and predict those types of exposures.

This is one of those innovative projects that Kris was talking about. We recognize the need for a way to track that kind of exposure that our approach at the time couldn't do. So we developed that sort of thing and there's other work as I mentioned that isn't captured on this slide that we did.

Slide 17: A More Complete PFAS History



Slide Text and Image Description

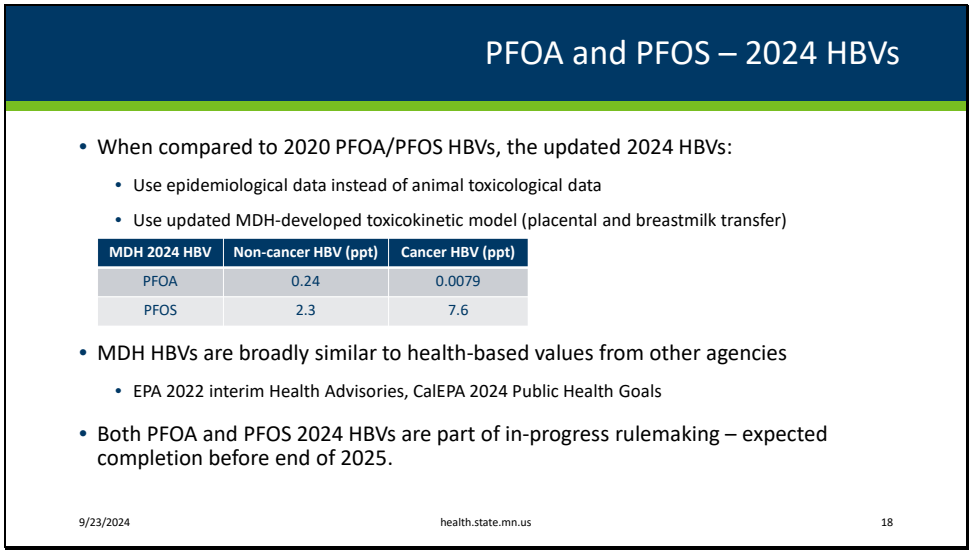
Image: Screenshot of the History of MDH Activities—Per and Polyfluoroalkyl Substances (PFAS) website

For a comprehensive history of MDH work around PFAS, visit this website:
https://www.health.state.mn.us/communities/environment/hazardous/topics/history.html

Summary

If you want a more complete PFAS history not only of our group but of the many, many other groups that have been involved over the last two decades, please take a look at the full timeline on the MDH website. It really is very enlightening.

Slide 18: PFOA and PFOS-2024 HBVs



Slide Text and Image Description

- When compared to 2020 PFOA/PFOS HBVs, the updated 2024 HBVs:
    - Use epidemiological data instead of animal toxicological data
    - Use updated MDH-developed toxicokinetic model (placental and breastmilk transfer)

MDH 2024 HBV	Non-cancer HBV (ppt)	Cancer HBV (ppt)
PFOA	0.24	0.0079
PFOS	2.3	7.6

- MDH HBVs are broadly similar to health-based values from other agencies
    - EPA 2022 interim Health Advisories, CalEPA 2024 Public Health Goals
- Both PFOA and PFOS 2024 HBVs are part of in-progress rulemaking – expected completion before end of 2025.

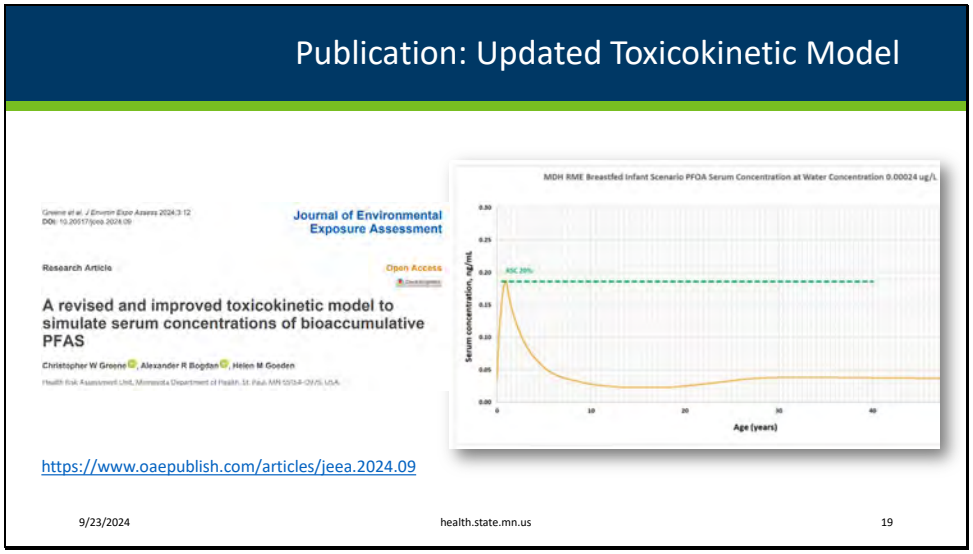
Summary

Kris mentioned the 2024 PFOS and PFOA HBVs. These really were an incredible amount of work for the entire unit. It wasn't just the CEC team, the HRL staff were involved as well, in double checking all the work that the CEC staff did. We have a multi-level review process in our chemical reviews.
Kris mentioned the incorporation of epidemiological data that used human based observational data for the first time instead of the animal toxicological data that had been the basis of all the previous reviews. That's an incredibly important thing because it gives us a lot more confidence in these HBVs.

Even though the types of health effects that we're seeing in the epidemiology studies are seen in the animal studies. The fact that it was also observed in humans does give us more confidence.

We also updated the toxicokinetic model that I just talked about. It had been about seven to eight years since the first version was developed, which means that there had been a lot of research done in the meantime on a lot of the parameters that were used to develop that model. It was time to update that. That took a bit of time and effort as well to update that model. So again, we developed new HBVs. I'll note that these HBVs are broadly similar to health-based values that came out from other agencies, including the EPA 2022 Interim Health Advisories and the CalEPA 2024 public health goals.
And both of these HBVs are part of in progress rule making that are expected to be completed before the end of 2025 as part of the last legislative session. We were directed to put the PFAS HBV through rulemaking.

Slide 19: Publication: Updated Toxicokinetic Model



Slide Text and Image Description

Image: screenshot of "A revised and improved toxiocokinetic model to simulate serum concentrations of bioaccumulative PFAS" publication from the *Journal of Environmental Exposure Assessment.*

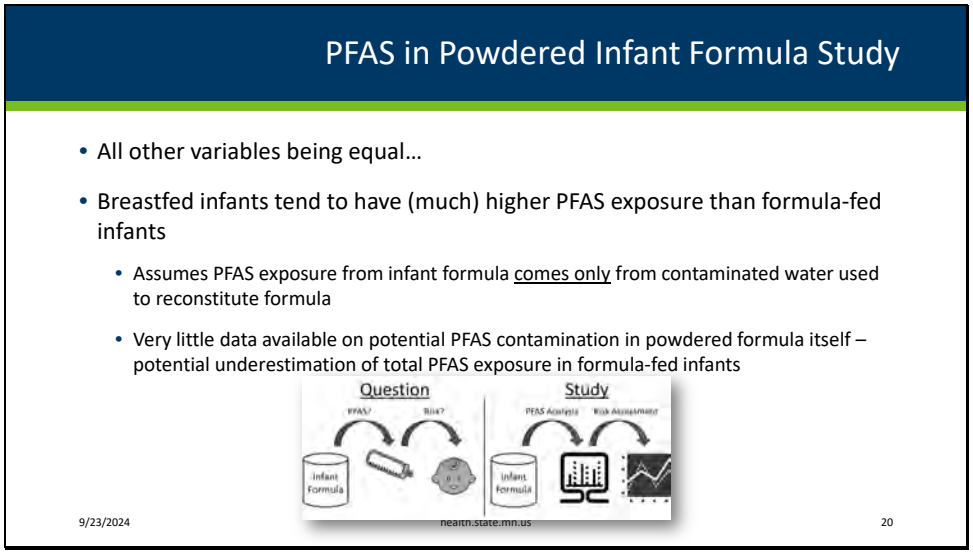
Link: https://www.oaepublish.com/articles/jeea.2024.09

Figure: MDH RME Breastfed Infant Scenario PFOA Serum Concentration at Water Concentration 0.00024 μg/L of serum concentration (ng/mL) over age (years). RSC is 20% from 0 years to 40 years in a dashed green list. Serum Concentration is represented on the graph by a yellow line, peaks early at 1 year of life (0.20 μg/mL) before dropping to 0.02 μg/mL at 10 years old, before rising to 0.40 μg/mL at 30 years old.

Summary

Kris mentioned some publications. We did go ahead and publish the updated toxicokinetic model. This is Open Access so it's freely available for anyone to read and the model itself is freely available to anyone who requests it. We want this to be out there. We want people to use it. We fully believe that this should be available and open for anyone to use.

Slide 20: PFAS in Powdered Infant Formula Study



Slide Text and Image Description

Images:

- Question: Infant formula, bottle, baby with PFAS? Risk? in text
- Study: infant formula, computer, graph alongside PFAS analysis and risk assessment text

Text:

- All other variables being equal…
- Breastfed infants tend to have (much) higher PFAS exposure than formula-fed infants
    - Assumes PFAS exposure from infant formula comes only from contaminated water used to reconstitute formula
    - Very little data available on potential PFAS contamination in powdered formula itself – potential underestimation of total PFAS exposure in formula-fed infants

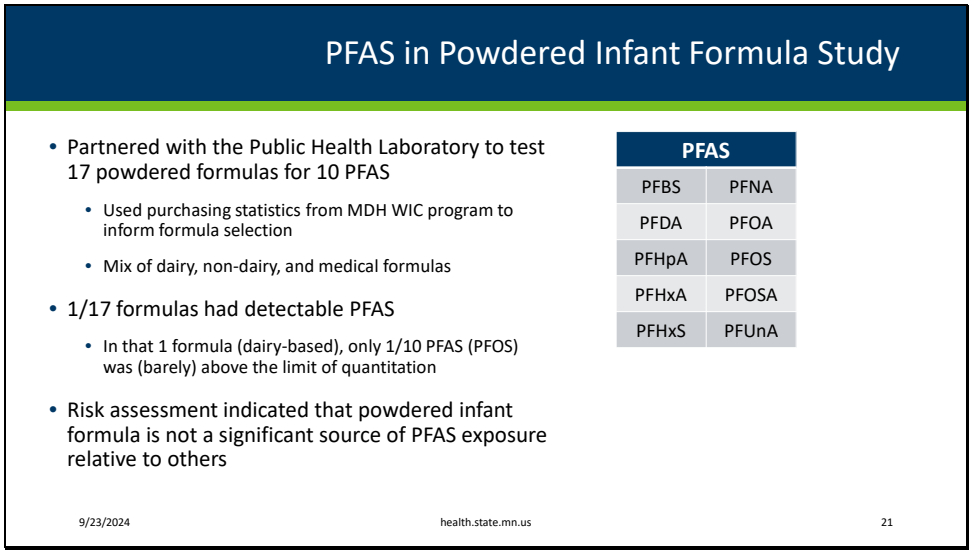
Summary

Another project that we undertook this year is taking a look at PFAS in powdered infant formula. Breastfed infants were kind of the reason that we developed the toxicokinetic model because there were these alternative exposure pathways that meant that they were getting exposures to PFAS that we couldn't account for and they were very high. And it turns out that all other variables being equal, breastfed infants tend to have much higher PFAS exposures than formula fed infants because the

breastmilk will have a higher PFAS concentration than the drinking water that you're using to reconstitute the powdered formula. That assumes that the PFAS exposure from the infant formula is only coming from the contaminated water. That the formula itself does not have any PFAS in it. And that's an assumption that we had to make because there was very little data available on if there's any PFAS contamination in powdered infant formula.

And we didn't like having to make that assumption because it means that there's a potential underestimation of total PFAS exposure to formula fed infants. But it's one we had to make because we didn't have any data to tell us otherwise. So, there was a data gap there that we wanted to fill. We made a proposal and we got an approval to do a pilot study to answer that question and analyze some powdered infant formula, looking for PFAS contamination.

Slide 21: PFAS in Powdered Infant Formula Study



Slide Text and Image Description

- Partnered with the Public Health Laboratory to test 17 powdered formulas for 10 PFAS
    - Used purchasing statistics from MDH WIC program to inform formula selection
    - Mix of dairy, non-dairy, and medical formulas
- 1/17 formulas had detectable PFAS
    - In that 1 formula (dairy-based), only 1/10 PFAS (PFOS) was (barely) above the limit of quantitation
- Risk assessment indicated that powdered infant formula is not a significant source of PFAS exposure relative to others

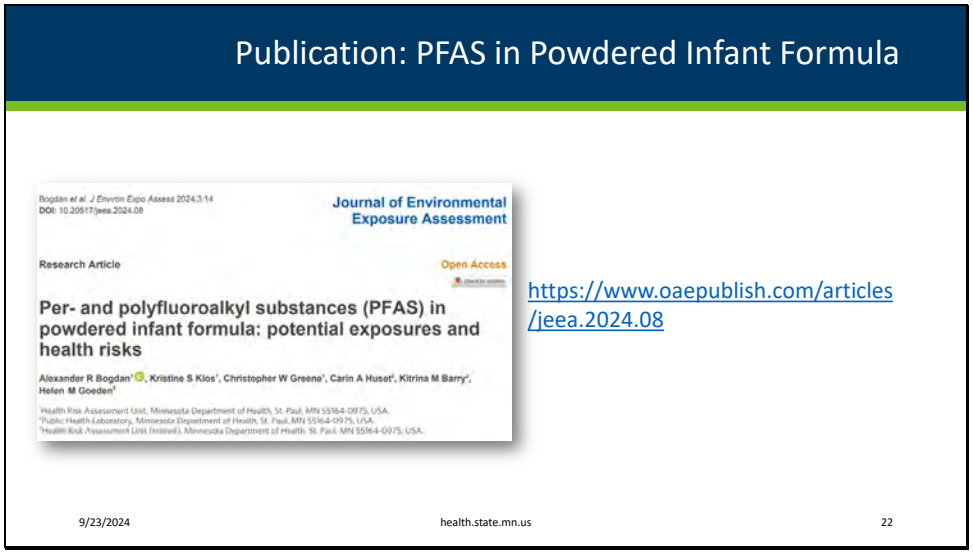
PFAS table: PFBS, PFNA, PFDA, PFOA, PFHpA, PFOS, PFHxA, PFOSA, PFHxS, PFUnA

Summary

We partnered with the Public Health Lab here at MDH, and we tested 17 powdered infant formulas for 10 different PFAS, which are listed on the right here. We talked with MDH's WIC program to help us. Using WIC purchasing statistics, we selected a variety of mixture of dairy, non-dairy and medical formulas for a total of 17 formulas representing some of the most popular formulas in Minnesota. Only one formula had a PFAS detection – a dairy-based formula – and that formula only had one type of PFAS detected – PFOS.

The PFOS detection was barely above the limit of quantitation of the assay, indicating the amount of PFOS in the powdered formula was very low. A subsequent risk assessment indicated that powdered infant formula is not a significant source of PFAS exposure relative to others. We went on to publish this study as well.

Slide 22: Publication: PFAS in Powdered Infant Formula



Slide Text and Image Description

Image: Screenshot of Per- and polyfluoroalkyl substances (PFAS) in powdered infant formula: potential exposures and health risks in *Journal of Environmental Exposure Assessment*

Link: https://www.oaepublish.com/articles/jeea.2024.08

Summary

Here's that article again, Open Access. Anyone should be able to read it without a subscription, and if you're interested I definitely recommend it.

Slide 23: Q+A

Slide Text and Image Description

Minnesota Department of Health Logo.

Image: Raised hands

Summary

Question: I'm curious if birth order matters for PFAS exposure to breastfed infants. Does the body burden of PFAS decrease in the mother with each pregnancy and infant that she breastfeeds?

Answer: It can, yes. There's a notable and measurable decrease in the mother's body burden with each birth and with breastfeeding. Given enough time between births, and it's a very long time, the mother's will start to go back up.

Question: Did MPCA's conclusion change after revising the study and looking more closely at formula? *[Editorial note: for clarification, this question was about MDH's revised toxicokinetic model]*

More specifically, my question was in regard to the serum concentration of PFAS dramatically decreased with the revised model. I was wondering if you could speak to this change.

Answer: There are several contributors to the differences seen in the updated model. Modifications to the model calculations themselves and updating parameters such as transfer factors for the specific chemicals.

Question: based on the report, the LOQs for the various PFAS were well above the PFOA/PFOS HBVs and MCLs and are above the pooled LOQs for 1633—any reason for the elevated limits in the study and how this impacts your conclusions?

Answer: The method used was a modification of the Public Health Lab's published breastmilk method. Powdered formula and breastmilk are both much more challenging matrices to analyze than water because of other substances in the solution like proteins and fats. These raise the LOQ. It's accounted for in our risk assessment and, given the single detection across 17 formulas, other sources of PFAS exposure – particularly in utero exposure, are still likely much higher than any exposure from powdered infant formula.

Question: I was wondering what concentration of PFAS in the water was used for the analysis for the preparation of the infant formula for the comparison?

Answer: The water used was ultrapure water. The concentration was below limit of detection.

Question: The limit of quantitation on all those are above our HRLs and MCLS for PFOA and PFOS. And wonder if there is some you mentioned later on on the table there. Some notes about some of those interference with what was PFBA and PFDA on there with the recoveries on those. Just wondering if there's if this was 1633, an internal lab method or if there's been attempts to go back and perhaps re look at this with some more sensitive instrumentation to get down below those drinking water standards?

Answer: We're basically measuring milk, rather than water. So there's all sorts of interfering compounds in there, if I'm understanding the question properly. It's basically a modification of the Public Health Lab's published breast milk method. So there's like proteins and fats and stuff in there that makes it much more challenging than just water.

Question: Do we know what the biological mechanisms of the formation of cancer from PFAS compounds that have values are? Do you know if there is an ADAF placed on the cancer values or are they based on adults?

Answer: No, that's not something we have a clear idea on yet, but it is something that a lot of people are very interested in and are looking at closely. As far as the ADAF, yes, there is for PFOA, and yes on the PFOS value there is as well.

Question: It appears that the serum concentrations of PFAS dramatically decreased with the revised model—could you speak to this change?

Answer: There were several contributors in the graphic that you posted there that shows the original model and the revised model with serum concentration lower in the revised model. The revision of the model falls into two sorts of general categories of modifications.

One were actual modifications to the way the model does its calculations, and then there were also modifications that were more like updating parameters that were specific to the chemicals that we were evaluating.

So the first one of those, the modifications to the calculation. That the model does is that we had improved the way that the model tracks the mass of chemical as it moves from mother to infant and we had been tracking it based on concentration, and we found that it was more accurate to track the mass of the chemical rather than the concentration. It really only makes a difference when the body weight of the simulated person and the model changes a lot from one day to the next and throughout most of your lifetime, your body weight does not change a huge amount from one day to the next.

However, there's one phase of life where that does happen and that is infancy, and we found that it's not a huge difference, but it was. It was a notable difference in the model results. When you track the mass, rather than the concentration, because a newborn infant does gain. It can potentially gain a substantial amount of weight even in just one day. That’s part of what contributed to the peak being lower.

Some of the other factors included the transfer rates. The ratio of infant to maternal serum concentration at birth, which effects the starting point of the simulated lifetime and also just some of the transfer factors like through breastmilk and other chemical specific parameters. So.
It was a variety of different changes to the model that caused the results to be different as that. graphic indicated. The best way to get more detail on that would be to click on the link to the study that was in the slide and the paper itself should explain it in more detail.

Slide 24: Where We Are and Where We're Going—Toxicity Assessment

Slide Text and Image Description

Minnesota Department of Health logo

Image: Hand holding a compass.

Summary

In this section I'm going to talk about what we're working on currently with PFAS and hopefully where we're going to go with it over the next year and then perhaps beyond.

Slide 25: HRA PFAS Current Work and Future Approaches

Slide Text and Image Description

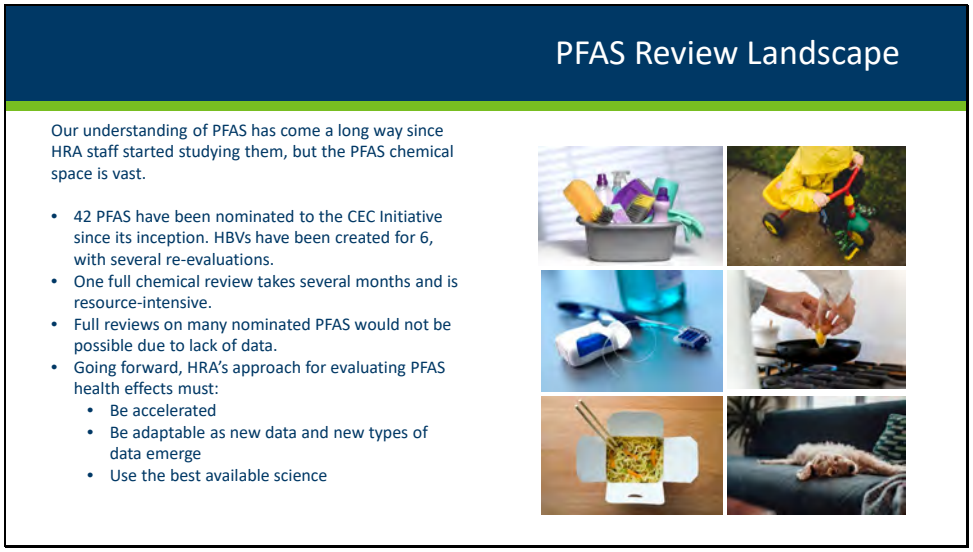
MN Department of Health Logo.

Image: glass of water.

Alex Bogdan, PhD; Toxicologist and Risk Assessor

Lindsay Wilson, PhD; Toxicologist and Risk Assessor

Slide 26: PFAS Review Landscape



Slide Text and Image Description

Images: cleaning products in a cleaning caddy, a child riding a tricycle, floss and a toothbrush, egg going into a frying pan, noodles in a takeout container, dog on a sofa.

Text:

Our understanding of PFAS has come a long way since HRA staff started studying them, but the PFAS chemical space is vast.

- 42 PFAS have been nominated to the CEC Initiative since its inception. HBVs have been created for 6, with several re-evaluations.
- One full chemical review takes several months and is resource-intensive.
- Full reviews on many nominated PFAS would not be possible due to lack of data.
- Going forward, HRA's approach for evaluating PFAS health effects must:
    - Be accelerated
    - Be adaptable as new data and new types of data emerge
    - Use the best available science

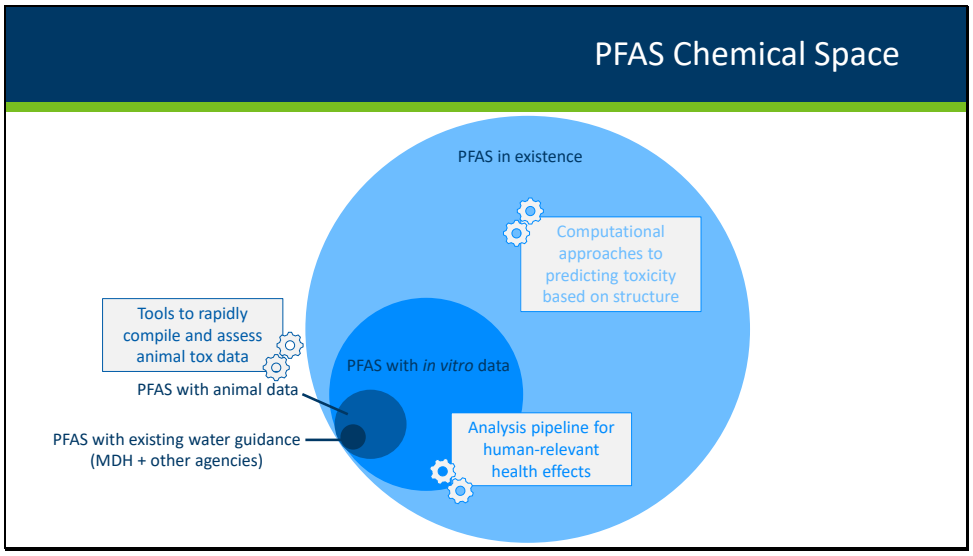
Summary

Like I mentioned, our understanding of PFAS have come a long way over the last 20 years, but the PFAS chemical space is vast—at least 5000 chemicals perhaps over 15,000. We have had 42 different PFAS nominated to the CEC Initiative since its inception, and what that means is anyone can nominate a chemical to the CEC initiative, which basically just means that they can put a chemical on our radar. There's a process to do that that we'll talk about at the end of the talk today, where we will take it through a screening process and possibly put it on a work plan for possible guidance development.

As mentioned, HBVs have been created for six and they've gone through several reevaluations. A full chemical review can take several months and is very resource intensive. Full reviews on many nominated PFAS just aren't possible due to lack of data. I would say for probably the vast majority of those 42, we would be unable to make an HBV or HRL.

What this means is that going forward, our approach for evaluating PFAS health effects needs to be faster because we can't take several months going one by one on PFAS. It has to be adaptable as new data and new types of data emerge. We need to continue to use the best available science.

Slide 27: PFAS Chemical Space



Slide Text and Image Description

Image description:

Concentric circles representing PFAS chemicals. The smallest circle represents PFAS with existing guidance values. The next larger circle represents PFAS with available animal data. The next larger circle represents PFAS with in vivo data. The largest circle represents PFAS requiring computational approaches.

Summary

When considering all the PFAS in existence in kind of this big circle (this is not going to be to scale). Think about all the PFAS that have existing water guidance—whether it's from MDH or other agencies—as kind of the small, very small circle right here.

Going to the next tier, these are PFAS that have animal data or human epidemiologic data. These are chemicals that potentially we could create HBVs for using our traditional methods. And there are there are a few out there now. Are there tools or can we develop tools to rapidly compile and assess that animal tox data and maybe speed up the process of our full reviews and make that happen a little bit faster? But that's still a very, very small fraction of PFAS in existence.

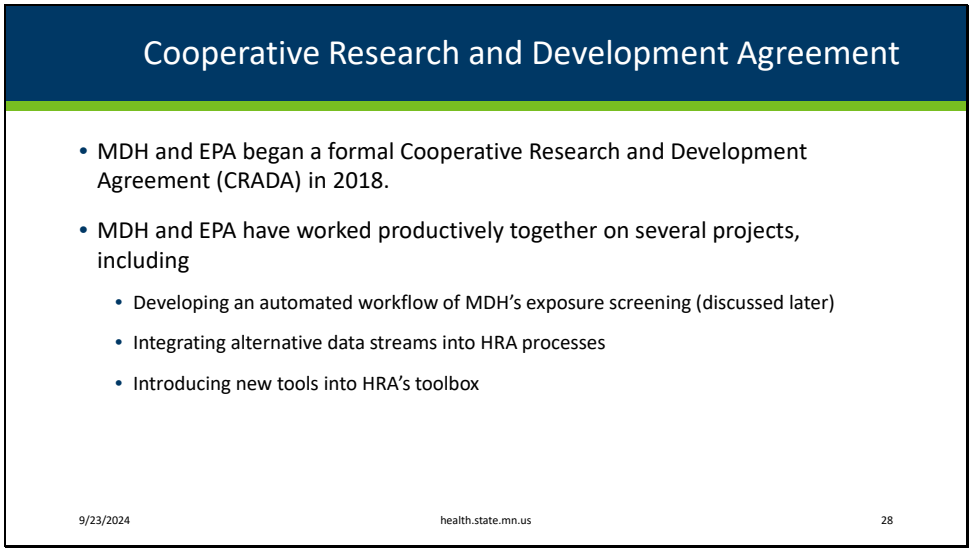
But even going one step further, you have PFAS that have in vitro data—think cells in a Petri dish. Now in vitro data can be generated much faster. Whereas an animal study may take 6-12 months or up to two years to actually perform the study and then another year to analyze all the data and it could cost $1,000,000 or $2,000,000 to actually perform.

In vitro data can be generated in a matter of weeks to months and be put out faster and you can screen hundreds of chemicals versus a single chemical, or maybe half a dozen chemicals at a time in an animal study. The volume of data that you can generate is a lot faster and the field is moving in that direction. So you can expect this bubble is going to get a larger faster.

And what that means is that you're going to be dealing with a tremendous volume of data. Techniques need to be developed and an analysis pipeline needs to be built to screen all of this data for human relevant health effects because you can imagine cells in a petri dish are not humans and trying to extrapolate the types of data that you get from those experiments, to make them into human relevant conclusions is challenging. It takes different types of thinking.

But that's still not the totality of PFAS in existence, for which still don't have any data. So what do you do with that? For that you need in silico approaches and computer modelling. Things like computational approaches to predicting toxicity based on structure. And that's another thing that we're exploring. And very recently, we actually brought on a computational toxicologist. You'll hear from him a little bit later. We're very excited to have him on. He's not going to talk about PFAS specifically at this talk, but it is something we're starting to explore.

Slide 28: Cooperative Research and Development Agreement



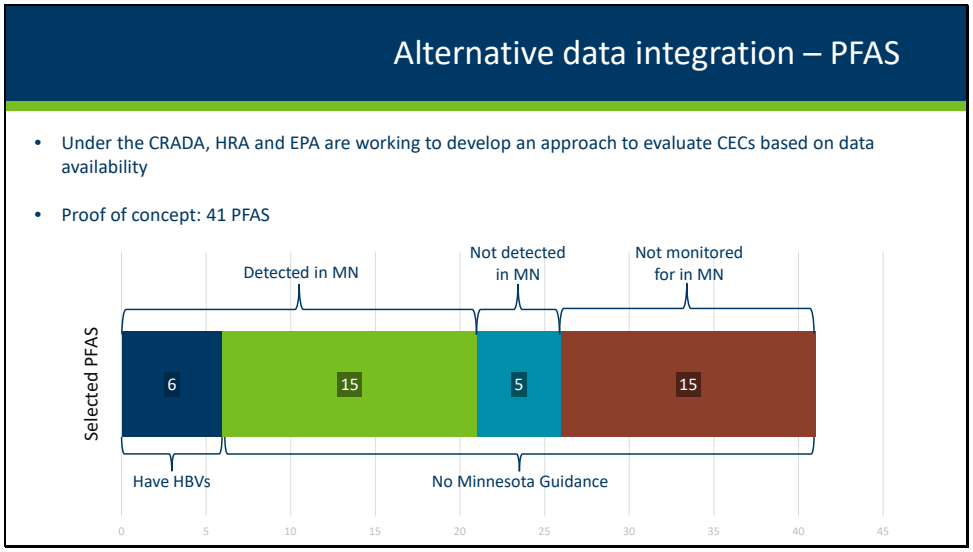
Slide Text and Image Description

- MDH and EPA began a formal Cooperative Research and Development Agreement (CRADA) in 2018.
- MDH and EPA have worked productively together on several projects, including
    - Developing an automated workflow of MDH's exposure screening (discussed later)
    - Integrating alternative data streams into HRA processes
    - Introducing new tools into HRA's toolbox

Summary

We are working with the USEPA and back in 2018, we began a formal cooperative research and development agreement (CRADA). We've worked productively on several research projects together, including developing an automated workflow on MDH's exposure screening, which you'll hear about later—integrating these alternative data streams into our processes and introducing new tools into our toolbox.

Slide 29: Alternative data integration—PFAS



Slide Text and Image Description

- Under the CRADA, HRA and EPA are working to develop an approach to evaluate CECs based on data availability
- Proof of concept: 41 PFAS

Figure: graph depicts the following information:

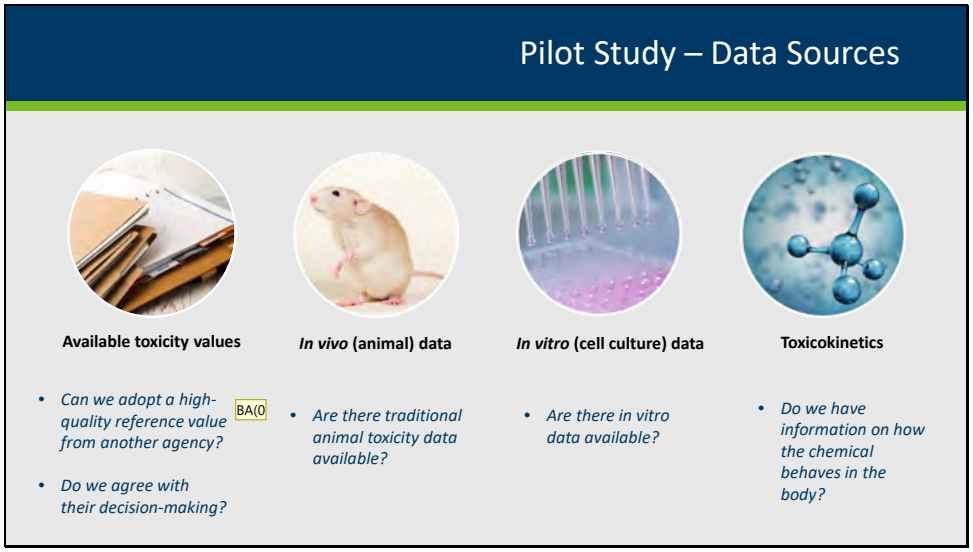
- 6 PFAS detected in Minnesota have HBVs
- 15 PFAS detected in Minnesota have no state guidance.
- 5 PFAS not detected in Minnesota have no state guidance
- 15 PFAS not monitored for in Minnesota have no Minnesota state guidance

Summary

We have a pilot project going that's focused on PFAS, but hopefully can be expanded into other chemical families and other CECs. We're working with 41 different PFAS and you can see them categorized down here. The six that have HBVS.

We have another 15 that don't have any Minnesota guidance but have been detected in Minnesota. Another five that haven't been detected in Minnesota. And then another 15 that we don't monitor for in Minnesota, but we know EPA has data for.

Slide 30: Pilot Study—Data Sources



Slide Text and Image Description

Images: file folders, mouse, pipettes, molecule

Available toxicity values

- Can we adopt a high-quality reference value from another agency?
- Do we agree with their decision-making?

In vivo (animal) data

- Are there traditional animal toxicity data available?

In vitro (cell culture) data

- Are there in vitro data available?

Toxicokinetics

- Do we have information on how the chemical behaves in the body?

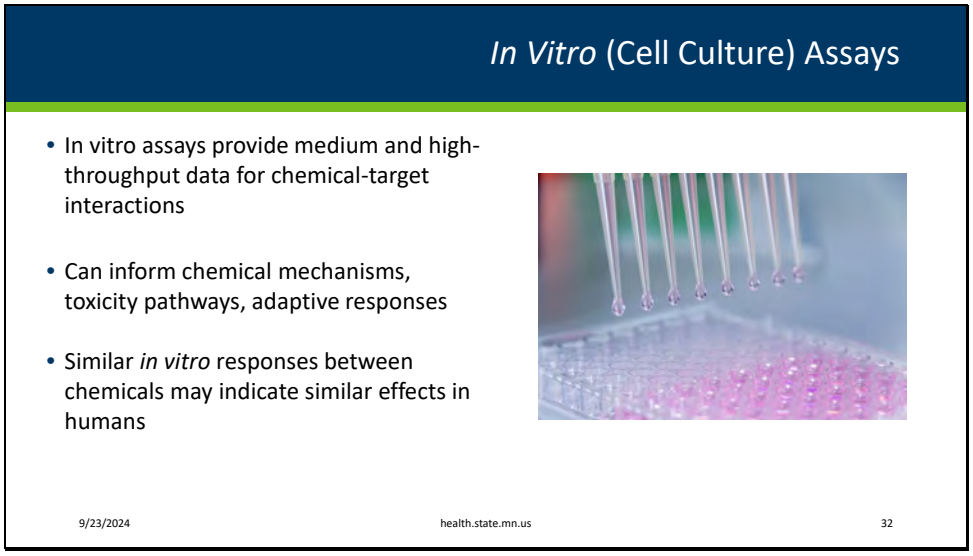
Summary

We're looking at different sorts of data. Are there any available toxicity values from either other states or just from the research literature? We're looking at available in vivo data, in vitro data. We're looking again at toxicokinetics, chemicals moving around the body; we know that's very important for PFAS,

whether it's bioaccumulative or whether it crosses the placenta or gets into breast milk or things like that.

All of this information is available out there. Can we get it in an automated way or can we sort it more efficiently? These are all very important questions for us. Next slide please.

Slide 31: *In Vitro* (Cell Culture) Assays



Slide Text and Image Description

Image: pipettes

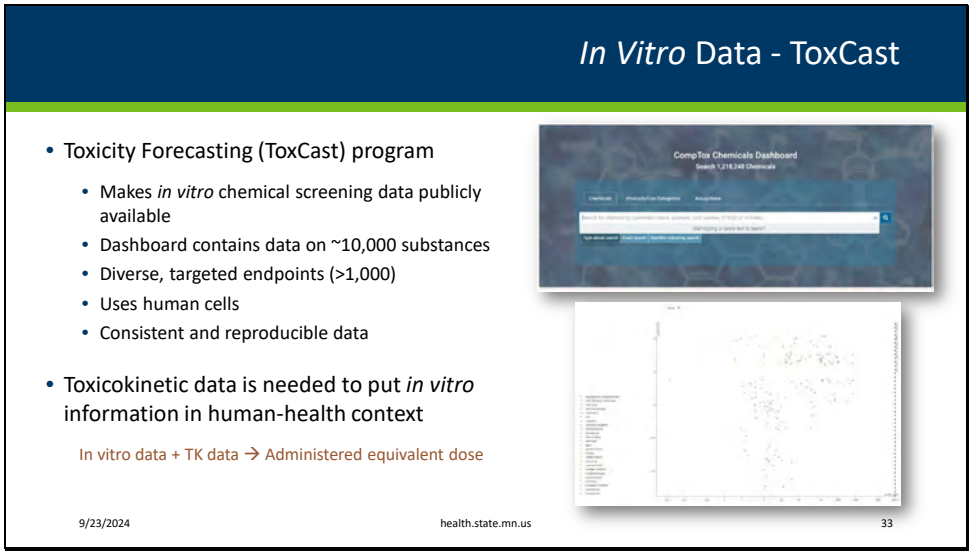
Text:

- In vitro assays provide medium and high-throughput data for chemical-target interactions
- Can inform chemical mechanisms, toxicity pathways, adaptive responses
- Similar *in vitro* responses between chemicals may indicate similar effects in humans

Summary

This is medium and high throughput, so this type of data can be generated very quickly, and EPA and others are doing a lot of that. This is very high-volume data generation which makes data analysis a very interesting challenge that we haven't necessarily had to deal with before. In vitro data is good at informing chemical mechanisms and types of pathways that a particular chemical can hit.

Slide 32: *In Vitro* Data—ToxCast



Slide Text and Image Description

Image: CompTox Chemical Dashboard screenshot; scatterplot

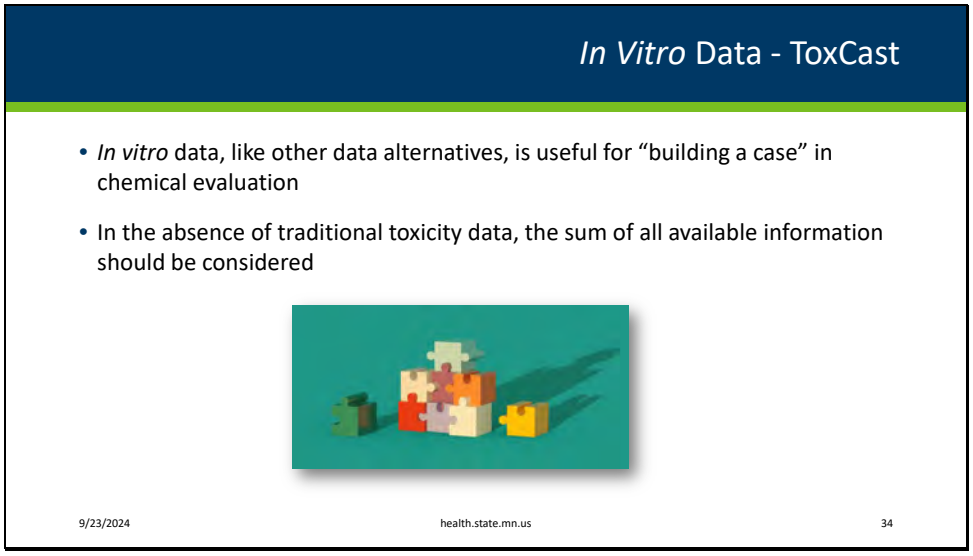
Text:

- Toxicity Forecasting (ToxCast) program
    - Makes *in vitro* chemical screening data publicly available
    - Dashboard contains data on ~10,000 substances
    - Diverse, targeted endpoints (>1,000)
    - Uses human cells
    - Consistent and reproducible data
- Toxicokinetic data is needed to put *in vitro* information in human-health context

Summary

We're doing a lot of work with EPA ToxCast program, which has data on over 10,000 substances. It looks at over 1000 different endpoints using human cells. It's a very standardized program, which is great for comparisons. And EPA has also been very generous with their time and expertise.

Slide 33: *In Vitro* Data—ToxCast



Slide Text and Image Description

Image: multicolored puzzle pieces

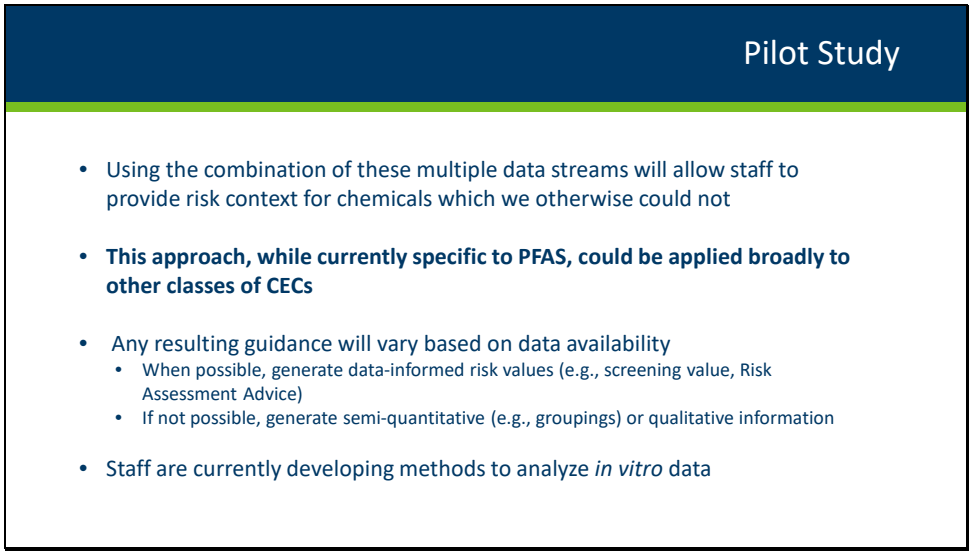
Text:

- *In vitro* data, like other data alternatives, is useful for "building a case" in chemical evaluation
- In the absence of traditional toxicity data, the sum of all available information should be considered

Summary

A lot of this work is going to be useful for what we're terming building a case in chemical evaluation. Because these really are puzzles pieces coming together to put the whole picture together. Because for these chemicals that do not have that traditional animal data, it really is the sum of all the information to really give us the full context to really tell people what we know and get all the information out there that we can, whether it's going to be quantitative, semi quantitative or qualitative.

Slide 34: Pilot Study



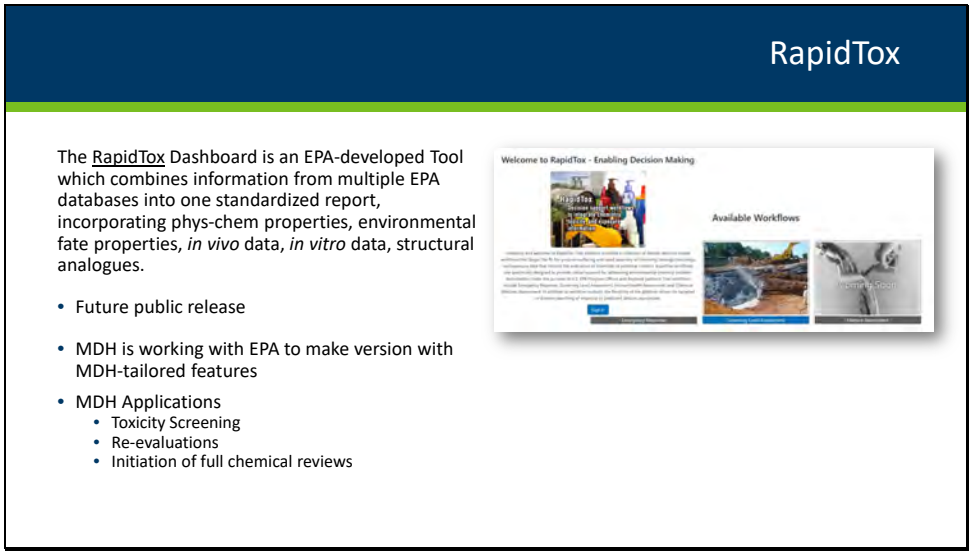
Slide Text and Image Description

- Using the combination of these multiple data streams will allow staff to provide risk context for chemicals which we otherwise could not
- **This approach, while currently specific to PFAS, could be applied broadly to other classes of CECs**
- Any resulting guidance will vary based on data availability
    - When possible, generate data-informed risk values (e.g., screening value, Risk Assessment Advice)
    - If not possible, generate semi-quantitative (e.g., groupings) or qualitative information
- Staff are currently developing methods to analyze *in vitro* data

Summary

Using the combination of these data streams we're going to provide the risk context for the chemicals that otherwise we wouldn't be able to say anything about. While we're currently working specifically with PFAS, this could be applied broadly to other classes of CECs and any resulting guidance is going to vary based on availability. We want to generate data-informed risk values, but if it's not possible, we want to generate what we can, whether it's semi quantitative or qualitative.

Slide 35: RapidTox



Slide Text and Image Description

Image: RapidTox Screenshot

Text:

The RapidTox Dashboard is an EPA-developed Tool which combines information from multiple EPA databases into one standardized report, incorporating phys-chem properties, environmental fate properties, *in vivo* data, *in vitro* data, structural analogues.

- Future public release
- MDH is working with EPA to make version with MDH-tailored features
- MDH Applications
    - Toxicity Screening
    - Re-evaluations
    - Initiation of full chemical reviews

Summary

I'll just end real quickly talking about RapidTox. Anyone in the risk assessment field may have heard about RapidTox, which is a forthcoming EPA tool. Very, very exciting stuff, where it will rapidly query existing databases to create standardized reports for the purposes of risk assessment, pulling

information based on physical properties, environmental fate. Different sorts of in vivo and vitro data. It'll do some QSAR type things - really, really cool stuff. It has a future public release plan.

EPA, again, has been extremely generous with their time and their expertise. They've actually connected us with their developers and they are making a version with some MDH tailored features for us. We have a couple of unique things that we do here in Minnesota. And we're planning to use RapidTox to help accelerate our toxicity screening reevaluations and initiating our full chemical reviews.

Slide 36: Integrating Computational Toxicology Into HRA Processes

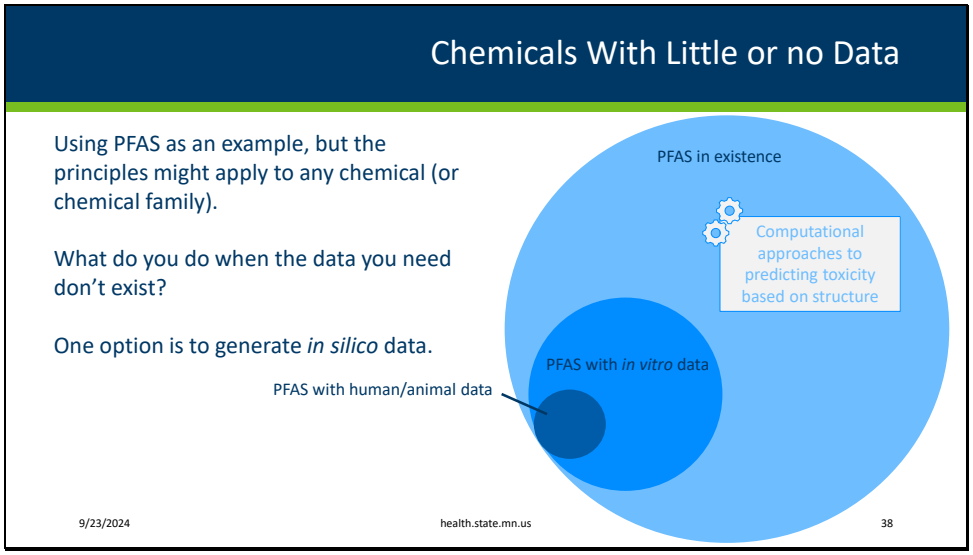
Slide Text and Image Description

Minnesota Department of Health Logo

Image: electronic network

Text: Alex Bogdan, PhD; Toxicologist and Risk Assessor

Slide 37: Chemicals With Little or no Data



Slide Text and Image Description

Image: A blue circle titled "PFAS in existence": Computational approaches to predicting toxicity based on structure, with a medium-sized circle titled "PFAS with *in vitro* data," with a smaller circle titled "PFAS with human/animal data."

Text:

Using PFAS as an example, but the principles might apply to any chemical (or chemical family).

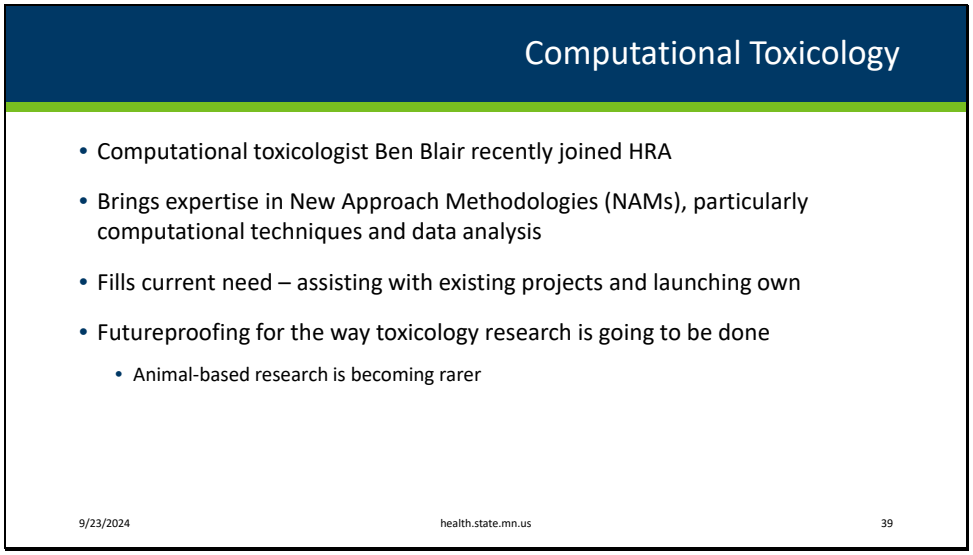
What do you do when the data you need don't exist?

One option is to generate *in silico* data.

Summary

We're talking about chemicals with little or no data. Going back to that figure, for all the PFAS in existence, the vast, vast majority just have no data at all on them. And kind of the quickest option to get data is to generate your own with in silico computer modeling.

Slide 38: Computational Toxicology



Slide Text and Image Description

- Computational toxicologist Ben Blair recently joined HRA
- Brings expertise in New Approach Methodologies (NAMs), particularly computational techniques and data analysis
- Fills current need – assisting with existing projects and launching own
- Futureproofing for the way toxicology research is going to be done
    - Animal-based research is becoming rarer

Summary

Recently, Ben Blair joined the unit. He's a computational toxicologist. We're very happy to have him. He brings expertise in new approach methodologies or NAMs, which is a hot term in the field, particularly in computational techniques and data analysis. He's assisting with some existing projects and launching his own projects. He's also future proofing for the way toxicology research is going to be done, because for all that I've talked about animal research and how important that is and how much we rely on that, it is becoming rarer. There has been marked push by EPA and other agencies in the US, and particularly in Europe, to move away from animal testing for a multitude of reason: The cost, the time, animal welfare reasons. He'll share a little bit of data showing that.

Slide 39: New Approach Methodologies (NAMs)

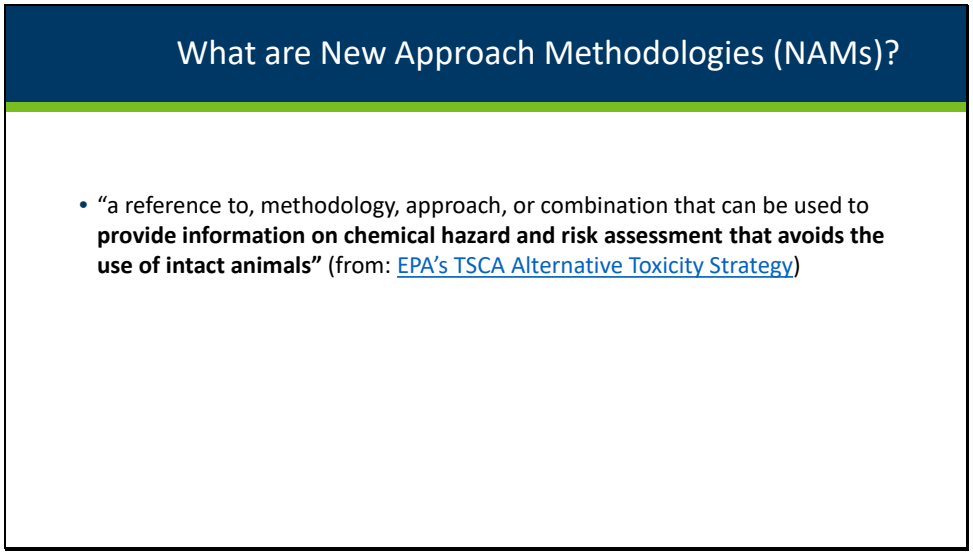
Slide Text and Image Description

Minnesota Department of Health Logo

Image: Electronic network

Text: Benjamin Blair, PhD; Computational Toxicologist

Slide 40: What are New Approach Methodologies (NAMs)?



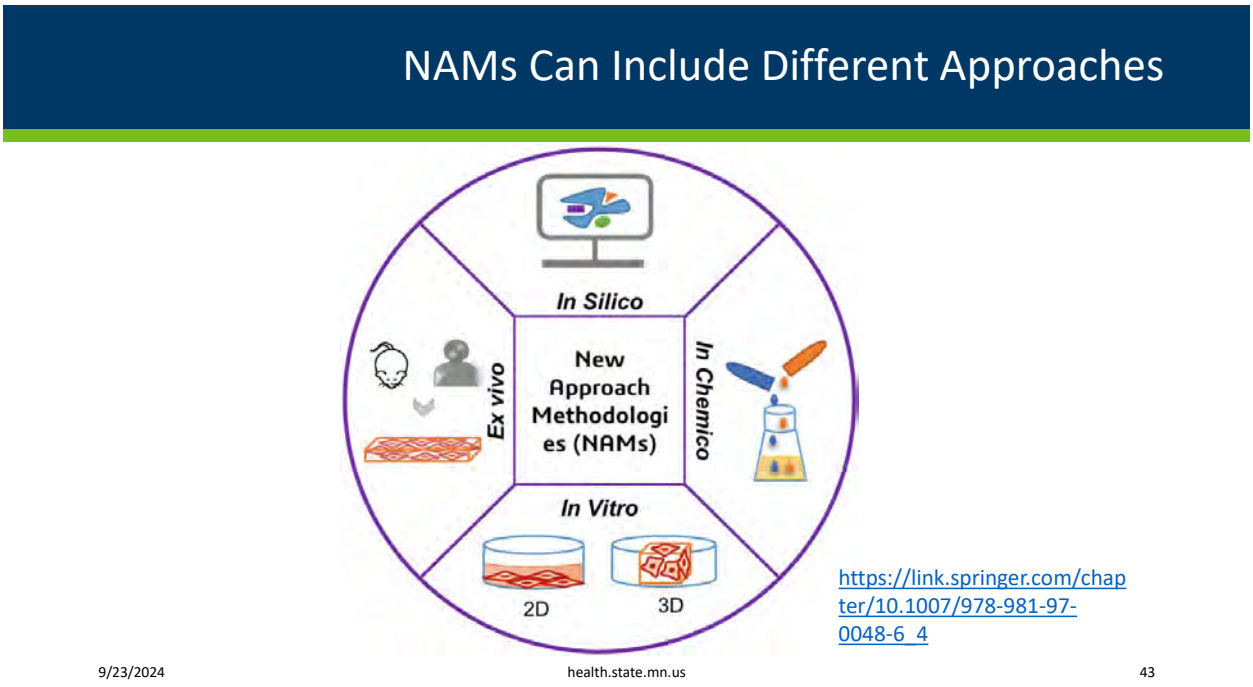
Slide Text and Image Description

"a reference to, methodology, approach, or combination that can be used to **provide information on chemical hazard and risk assessment that avoids the use of intact animals"** (from: EPA's TSCA Alternative Toxicity Strategy)

Summary

What are NAMs? It's a reference to a methodology approach or combination that can be used to provide information on chemical hazard and risk assessments that avoids the use of intact animals. This recently came from the EPA TSCA alternative toxicity strategy. Now we're not responsible for the acronym. It is just moving away from intact animals. If we're not using animals, as Alex has already mentioned several alternatives. But what else can we do?

Slide 41: NAMs Can Include Different Approaches



Slide Text and Image Description

Image: New Approach Methodologies (NAMS) surrounded by four segments: *In Silico, In Chemico, In Vitro* 2D and 3D, and *ex vivo*

Text: https://link.springer.com/chapter/10.1007/978-981-97-0048-6_4

Summary

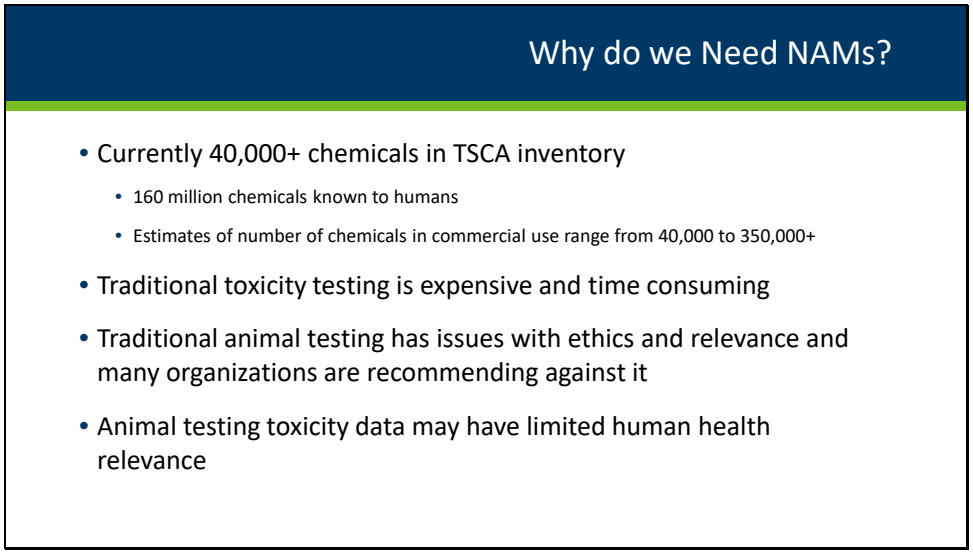
NAMS include all these different approaches from several disciplines and integrating them all together into toxicology as a whole. The in-silico approaches are the computer modeling approaches. These can include some of the methods like read across. Read across is one of the more accepted in silico approaches for understanding toxicology. It takes a structure, compares it to another structure, and you know an analog and tries to determine if there is enough similarity to attempt to draw conclusions. It can be done algorithmically as well. There are other approaches like QSAR that you may have heard quantitative structure, activity of relationship modelling. Now these models have evolved remarkably over the last decade. Because they've been able to also integrate machine learning in AI. I started using Qsar almost 15 years ago. A lot of the computational techniques weren't readily available or not as robust as they are today. Integrating these machine learning and artificial intelligence techniques is really an exciting time to be working in the in-silico models.

There are other critically important techniques like in vitro to in vivo extrapolation and of course some of the Holy Grail type approaches of looking at organs on a chip or humans on a chip. If we can try and

develop that entire approach, there are chemical approaches. The chemical reactions Alex touched a bit on in vitro, the in vitro approaches in the Petri dish are becoming really, you know, these high throughput approaches. It's often a big data problem.

It's certainly exciting work and ex vivo approaches. Taking tissue out of a limited living organism to study that tissue, these are all generally included in the new approach methodology.

Slide 42: Why do we Need NAMs?



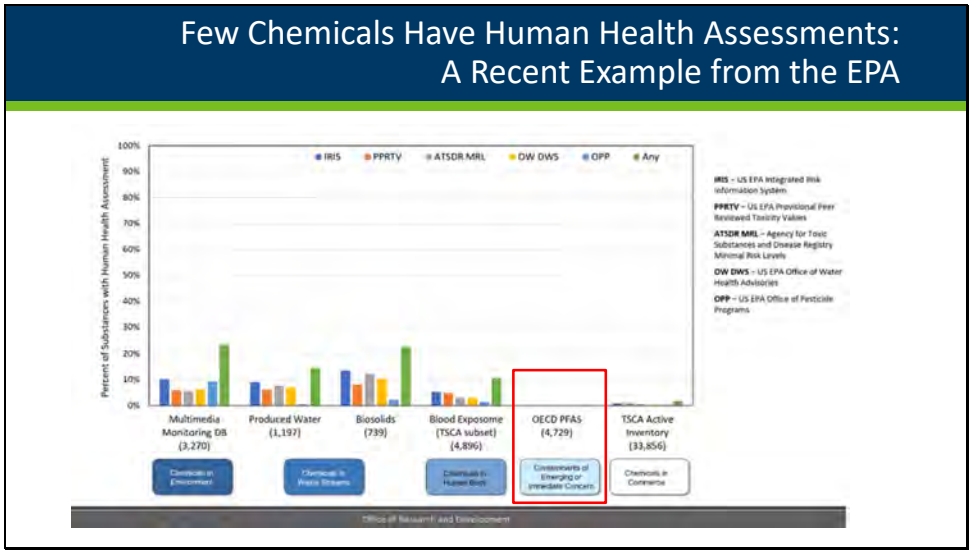
Slide Text and Image Description

- Currently 40,000+ chemicals in TSCA inventory
    - 160 million chemicals known to humans
    - Estimates of number of chemicals in commercial use range from 40,000 to 350,000+
- Traditional toxicity testing is expensive and time consuming
- Traditional animal testing has issues with ethics and relevance and many organizations are recommending against it
- Animal testing toxicity data may have limited human health relevance

Summary

We're touching on the need to move away from intact animals. For example, there's currently 40,000 plus chemicals in the TSCA inventory. If you look at the chemical extract services, 160 million chemicals known to humans. If you try and figure out how many chemicals are in commercial use, it's a wide range. Some estimates are 30-40 thousand, and some have more than 350,000. It's fascinating to think that we don't necessarily even have the best understanding of what's in commercial use currently. Traditional toxicity testing is expensive and time consuming. Alex mentioned that a little bit earlier. Traditional animal testing has issues with ethics and relevance in many organizations are recommending in ADD. Animal testing toxicity data may have limited human health relevance overall, so you put this all together, it starts to make the case of why we need to understand NAMs.

Slide 43: Few Chemicals Have Human Health Assessments: A Recent Example from the EPA



Slide Text and Image Description

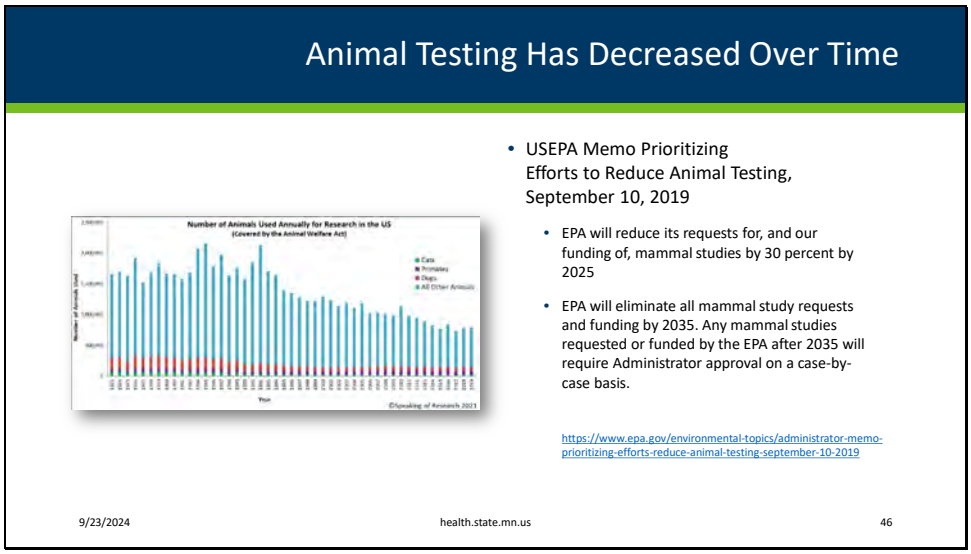
Image: Bar graph showing percent of substances with Human Health Assessment over Type of chemical/contaminant. Types of chemical contaminant are grouped according to the following: chemicals in environment (Multimedia monitoring DB), Chemicals in Waste Streams (Produced Water, Biosolids), Chemicals in Human Body (Blood Exposome TSCA subset), OECD PFAS (Contaminants of emerging or immediate concern), and Chemicals in Commerce (TSCA Active Inventory). OECD PFAS have no percent of substances with human health assessment.

Summary

I was able to borrow this from the EPA, some fresh data coming out. They just presented this a month ago—really highlighting that few chemicals have human health assessments. We highlighted the OECD PFAS where you look at the percent of chemicals or the percent of PFAS that have human health assessments and it's barely a blip on the scale. OECD is the Organization for Economic Cooperation and Development.

You can look at TSCA active inventory and you look at all of the TSCA active inventory compounds or chemicals and less than 5% have human health assessments from TSCA. Just showing it that we have very limited data to work with overall.

Slide 44: Animal Testing Has Decreased Over Time



Slide Text and Image Description

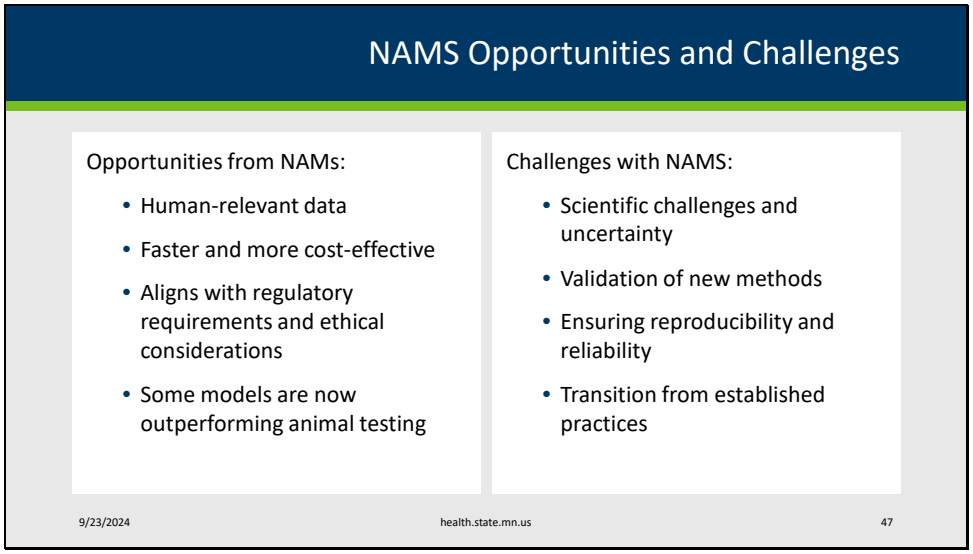
Image: bar graph showing number of animals used annually for research in the US that shows the number of animals used has decreased annually from 1973 to 2019.

Summary

Animal testing has been decreasing over time. most of the patterns show that really over the last 20 years animal testing has actually decreased over time in the United States. To further compound the issue with animal testing the US EPA, they published a memo prioritizing efforts to reduce animal testing in September of 2019. The EPA stated that it will reduce its request for and funding of mammal studies by 30% by 2025. 2025 is four months away—right around the corner. The EPA will eliminate all mammal study requests and funding by 2035. All animal studies requested or funded by the EPA after 2035 will require administrator approval on a case by case basis.

Now this was a little controversial. There's some groups that did not necessarily agree with this approach. The EPA is published in this memo is their goal and 2035 is not that far away either. These are some notable changes that really has led to animal testing decreasing over time and many expect this trend to continue. In particular, due to some of these mandates that have been issued.

Slide 45: NAMS Opportunities and Challenges



Slide Text and Image Description

Opportunities from NAMS	Challenges with NAMS:
Human-relevant data	Scientific challenges and uncertainty
Faster and more cost-effective	Validation of new methods
Aligns with regulatory requirements and ethical considerations	Ensuring reproducibility and reliability
Some models are now outperforming animal testing	Transition from established practices

Summary

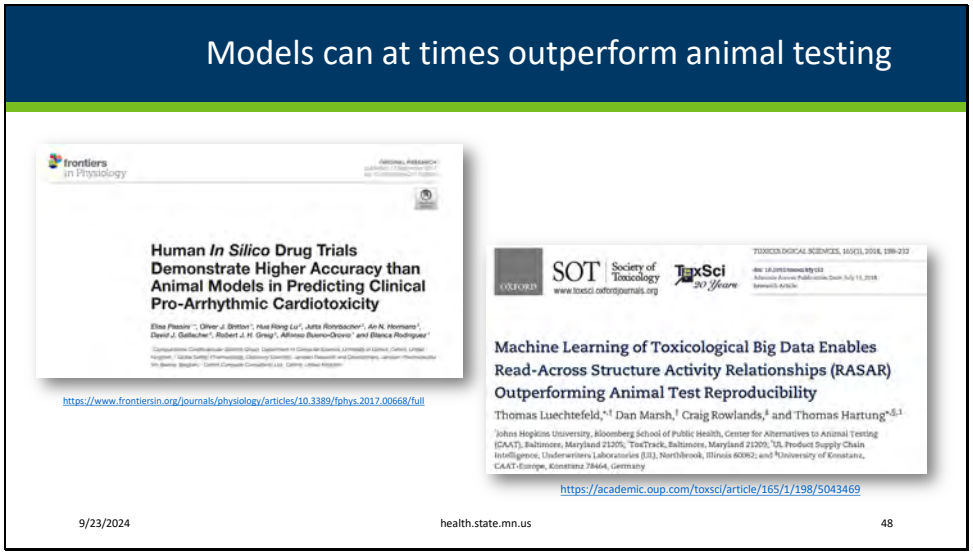
When we think about NAM's opportunity specific to our group in MDH, there's of course opportunities and challenges that go with this. The opportunities from NAMS is that we can work to generate truly human relevant data—data that is as effective of human health as possible. It can be faster and more cost effective. As Alex mentioned, it takes several million dollars or more to do an animal study with the amount of time where in silico models are good, good models can often be processed rather rapidly. It can align with regulatory requirements and ethical considerations. Some models are now outperforming animal testing.

There are also some challenges surrounding NAMs overall. In particular, scientific challenges and the uncertainty that can go with NAMS. We are scientists first and foremost, and so we intend to be truly transparent with any of the NAMs approaches. We're using the techniques, the methods, the models, the results, and transparency is crucial, and also being truly transparent with any uncertainty that we encounter other challenges. Validation of just these new methods. So as we explore these new

methods, as they're constantly being developed. Every day there's something really cool coming out surrounding NAMs approaches. They need validation. They need ensuring the reproducibility and the reliability overall, and so specific to MDH that something we will focus on, and this is a transition from established practices.

We have this void of data due to decreases in animal testing and so to fill that void, this will be a transition from those established practices and that certainly is a challenge and comes with its own set of challenges and so we will make sure we do this right.

Slide 46: Models can at times outperform animal testing



Slide Text and Image Description

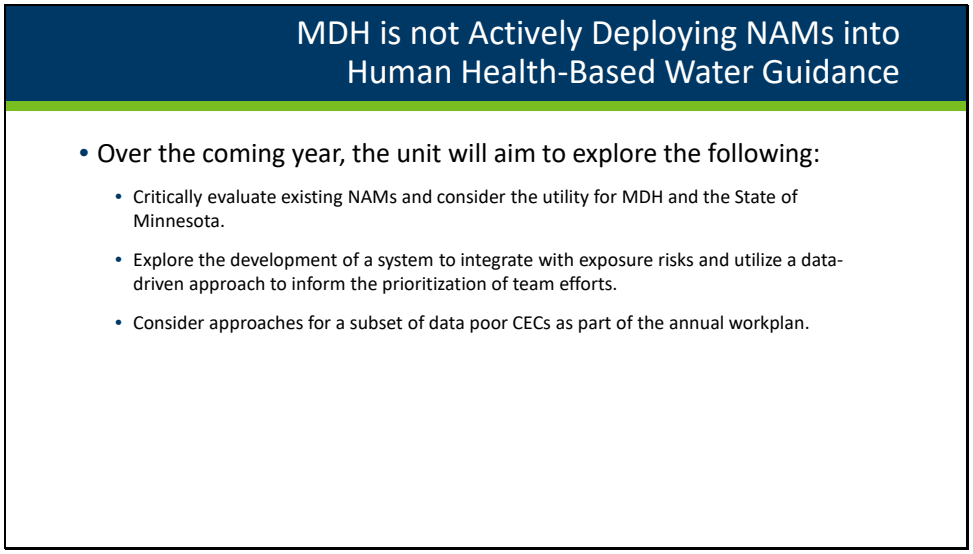
Images: Screenshot of "Human *In Silico* Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity" publication in *Frontiers in Psychology* (https://www.frontiersin.org/journals/physiology/articles/10.3389/fphys.2017.00668/full) and screenshot of "Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) Outperforming Animal Test Reproducibility" publication in *Toxicological Sciences* (https://academic.oup.com/toxsci/article/165/1/198/5043469)

Summary

For those of us that that have worked in this field and follow this, the last 10 years has just been amazing. Starting in 2016-2018, during that period, you started to see these amazing models being integrated into toxicology and in silico approaches. it's just some truly outstanding science. Two examples that always stick out in my opinion: this first study, this human in drug trials, demonstrate higher accuracy than animal models in predicting cardio toxicology. You're seeing where some models have greater accuracy than animal models overall.

Another example that sticks out to me that I recall is the machine learning of toxicological big data. It enables read across structure, activity, relationships, so this is read across plus QSAR and it is out for me outperforming animal tests reproducibility as a whole. Truly remarkable advances in integrating things like machine learning into read across structure activity, relationships to create some, some really impressive work overall.

Slide 47: MDH is not Actively Deploying NAMS into Human Health-Based Water Guidance



Slide Text and Image Description

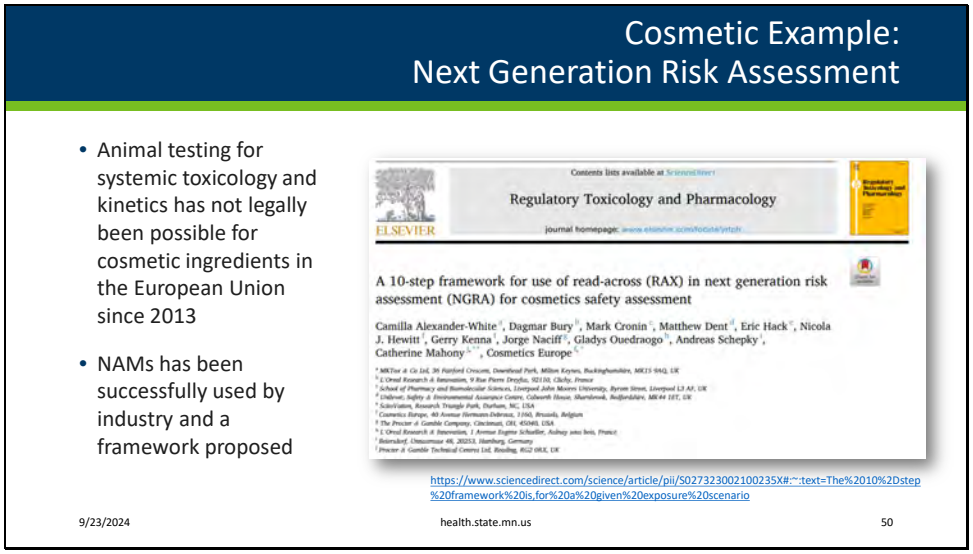
- Over the coming year, the unit will aim to explore the following:
    - Critically evaluate existing NAMs and consider the utility for MDH and the State of Minnesota.
    - Explore the development of a system to integrate with exposure risks and utilize a data-driven approach to inform the prioritization of team efforts.
    - Consider approaches for a subset of data poor CECs as part of the annual workplan.

Summary

We're not actively deploying NAMS into human health-based water guidance. We're going to look at critically evaluating the existing NAMs: a survey of all the existing tools, especially those used by government agencies. What benefit can they bring us, if any?

We want to explore the development of a system, integrate with risk exposure, and really utilize a data-driven approach to inform the prioritization of team efforts. Thinking about how we can take the automated approaches to risk assessment that Chris Green will be speaking on later and combine it potentially with NAMs to see what we're being exposed to in Minnesota. That that's really a large goal.

Slide 48: Cosmetic Example: Next Generation Risk Assessment



Slide Text and Image Description

Image: Screenshot of "A 10-step framework for use of read-across (RAX) in next generation risk assessment (NGRA) for cosmetics safety assessment" publication in *Regulatory Toxicology and Pharmacology.* *https://www.sciencedirect.com/science/article/pii/S027323002100235X#:~:text=The%2010%2Dstep%20framework%20is,for%20a%20given%20exposure%20scenario*

Text:

- Animal testing for systemic toxicology and kinetics has not legally been possible for cosmetic ingredients in the European Union since 2013
- NAMs has been successfully used by industry and a framework proposed

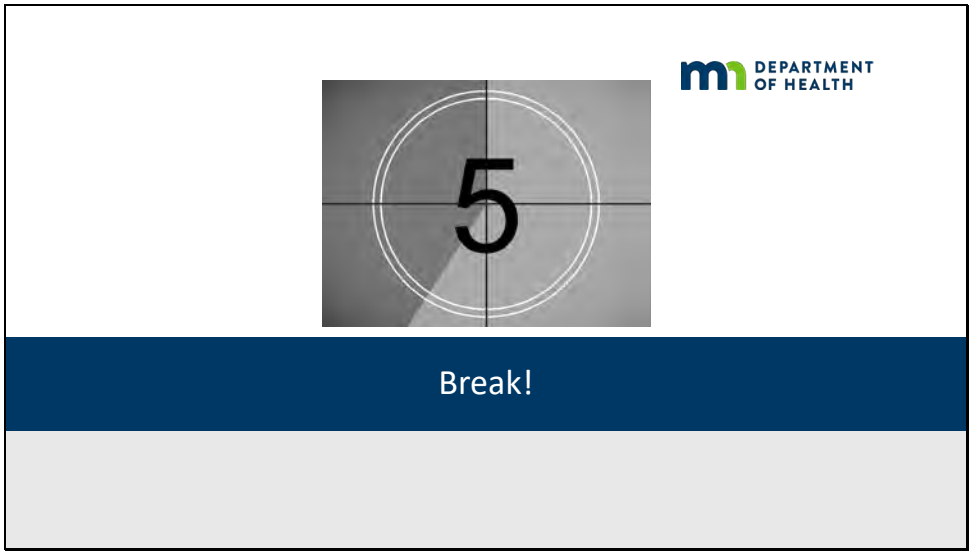
Summary

It's called next generation risk assessment coming out of the European Union and looking to them for some successes of how these things can be implemented. In the European Union, the animal testing for systemic toxicology has not been legally possible since 2013, and they've been successfully using NAMs across several industries now.

This came out of the cosmetic industry. I thought this was some really fabulous work of creating not just a single method, but a framework of how to integrate NAMs and read across into this next generation risk assessment. Industry and government came together and had agreed upon framework of how do you use the scientific method to test those hypothesis, to see what the data caps are to then develop

something like a point of departure and then look for some kind of margin of margin of safety. And is it sufficient? And so looking for those successes is really a beneficial approach for all of us as we try to understand how to integrate these things and it points towards the needs, the need for just a larger framework surrounding NAMs as a whole.

Slide 49: Break!



Slide Text and Image Description

Minnesota Department of Health logo

Image: Five-minute break.

Slide 50: Where We Are & Where We're Going—Exposure Assessment

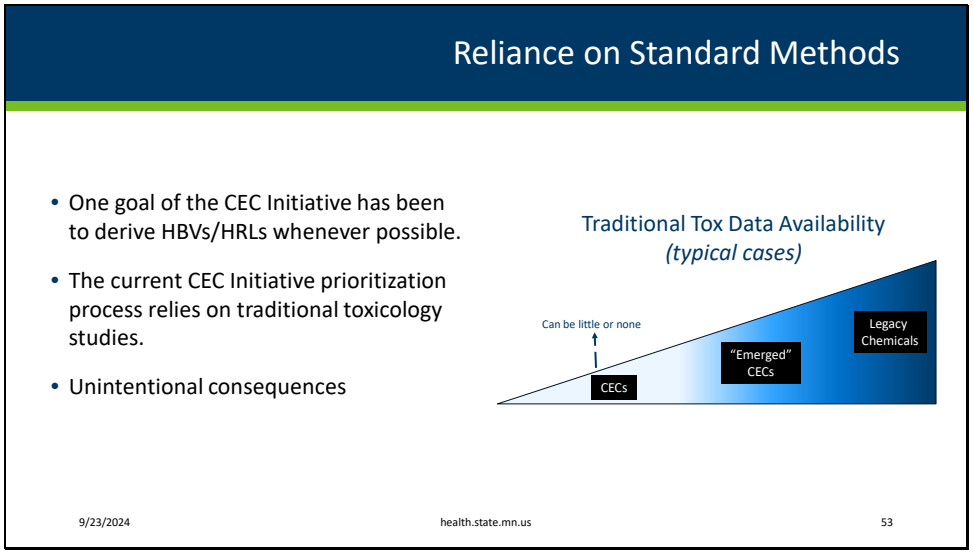
Slide Text and Image Description

Minnesota Department of Health logo

Sarah Fossen Johnson, PhD; Toxicologist and Risk Assessor

Chris Green, MS; Exposure scientist

Slide 51: Reliance on Standard Methods



Slide Text and Image Description

Image: Traditional Tox Data Availability (*typical cases*) figure shows CECs (can be little or none), "Emerged" CECs, and Legacy Chemicals

Text:

- One goal of the CEC Initiative has been to derive HBVs/HRLs whenever possible.
- The current CEC Initiative prioritization process relies on traditional toxicology studies.
- Unintentional consequences

Summary

I'm going to talk a little bit about some of the nuts and bolts of what we do in the CEC initiative to take a nomination all the way to the point where we are doing a full chemical review on it. you've heard my colleagues speak to you about the impact, the type, quality, and quantity of data can have for chemical reviews. It's true that data limitations can also affect our screening, scoring and ranking process as well. Often the outcome is biased towards selecting chemicals for review that have more traditional toxicological data available, such as animal studies. This is logical and totally unavoidable, right? You can't score what you don't have, so you must choose to score something as part of a prioritization process.

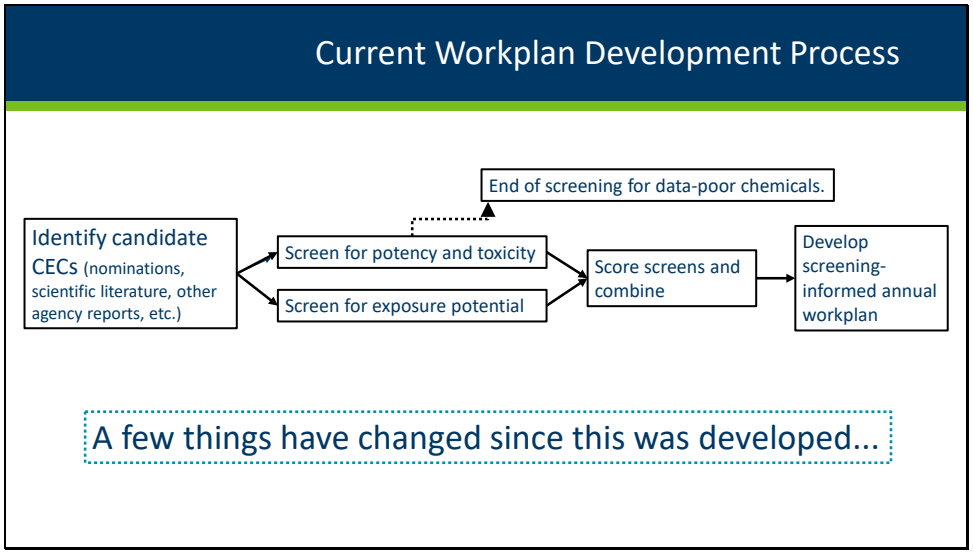
I'm going to share some of the ideas that we have for some upgrades to our prioritization process. It'll be high level because this is a project we've just begun, and we don't at this time have any draft processes or anything yet to share. But first I wanted to briefly set the table with a little bit of

background information, and I know we've talked about this in terms of PFAS so far, but this is more specific to the CEC program and how we fit into risk assessment at MDH.

Our risk assessment methods are based on US EPA standard methods. Of course, we have very intentional differences in our methods that enhance our ability to specifically look at particular life stages such as pregnancy, infancy and childhood to make sure that we are covering these sensitive populations. Our methods, though, like the EPA's methods, rely quite a bit on traditional toxicology data that's generated mainly through laboratory animal studies—this is in order to develop HBVs and HRLs, the preferred outcome of any chemical review.

The CEC initiative has been aiming to develop health-based values (HBVs) or health risk limits (HRLs) as frequently as possible. To develop these types of health-based guidance, we must use our standard promulgated methods which again generally rely on animal research. The prioritization process that is currently in use relies heavily on traditional toxicological studies for scoring. Unfortunately, one of the outcomes or one of the possible outcomes of our current toxicological framework is that some chemicals can get screened out regardless of the exposure potential. I don't want to make it sound like if we had something that was super high exposure potential, we wouldn't take a look at it and try to develop some kind of health context. I'm just saying that traditionally when you go through the screening process, certain chemicals end up on the not feasible list due to the lack of data or the type of data that's available.

Slide 52: Current Workplan Development Process



Slide Text and Image Description

Graphic:

1. Identify candidate CECs (nominations, scientific literature, other agency reports, etc.)
    - Screen for potency and toxicity
        - End of screening for data poor chemicals.
    - Screen for exposure potential
2. Score screens and combine
3. Develop screening-informed annual workplan

A few things have changed since this was developed…

Summary

This is a really high-level flow chart of our current prioritization process and I want to say again this process is fantastic. It's like the Cadillac of all prioritization processes. It's just so well thought out and has served us so well for so long. And it could continue to serve us for quite a while without any modifications. However, when it was developed, some of the options we are talking about today were either unavailable or were largely untested.

And so I want to stress that we really, really like external nominations so please nominate chemicals to

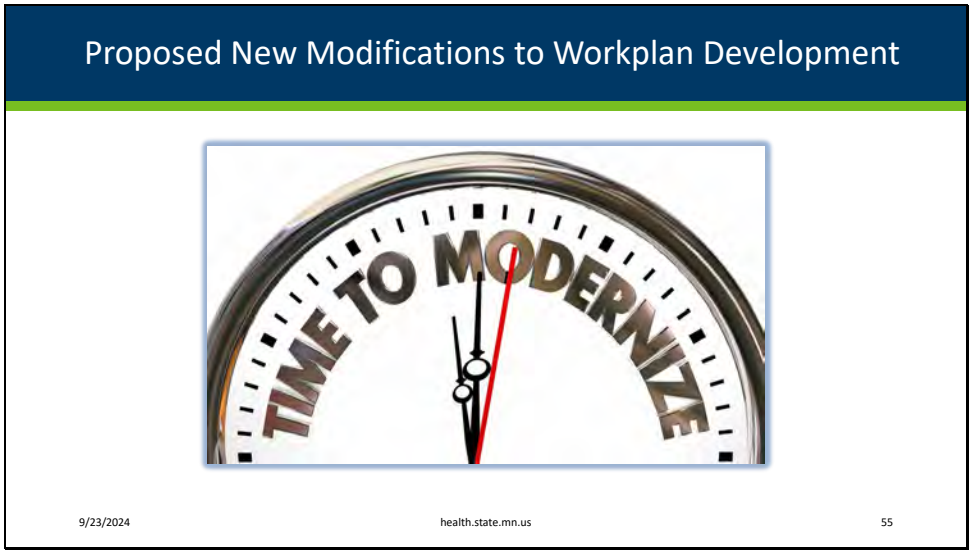
the CEC program. We like to hear what our partners are thinking about and seeing as a possible issue in Minnesota waters. The first step in priotization is nomainations—and we have external nominations that come in or internal nominations that also happen. We review them to make sure that they belong in the CEC program and that it isn't more appropriate for them to be in the Health Risk Limits program.

Second, we do a concurrent screen for both exposure and toxicity. And as you see here, there's a little dead end up at the top right that I already mentioned for data poor chemicals on the toxicity side. And we do have a process through which we revisit chemicals that that land on the not feasible list where we revisit it every few years to look for newly available information to try and get it to go through the screening process and added to our fully screened pool of chemicals that are available for toxicological reviews.

Once they've gone through that screening, we combine the scores for exposure and toxicity and then we use it to rank the nominations. And this happens alongside the historical nominations in our pool. Once a chemical has been screened fully and scored, it goes into that pool and it doesn't come out of the pool unless we have a reason to remove it or it's already been addressed through a chemical review in the CEC program or the HRL program, or by some other way that health-based water guidance can be developed. We do occasionally rescreen things that have been screened but are not rising to the top.

Since this process was developed, there have been a number of developments both here at MDH and in larger risk assessment community.

Slide 53: Proposed New Modifications to Workplan Development



Slide Text and Image Description

Image: Time to modernize graphic

Summary

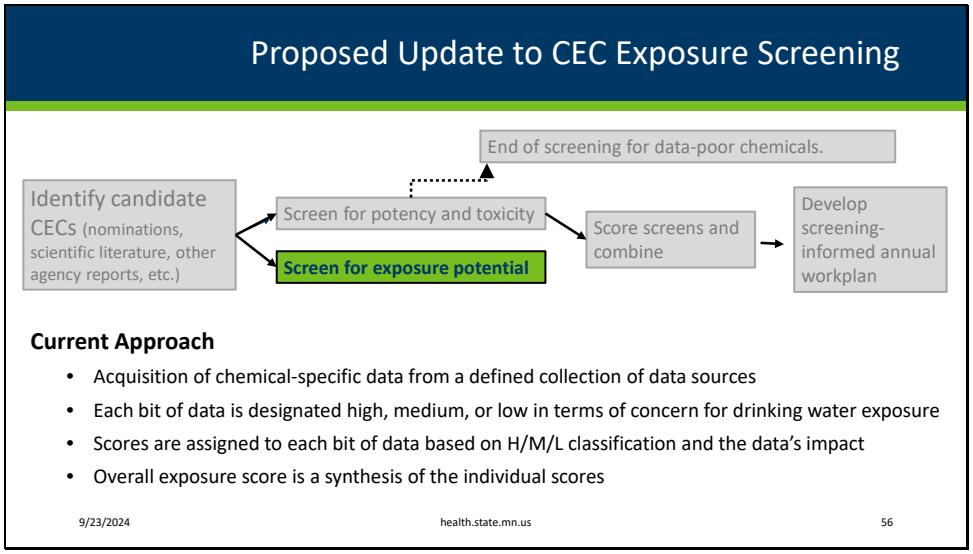
First is that the EPA and its partners began working to reduce reliance on animal testing. And as this process has moved along, NAMs have started to gain wider acceptance and there has already been a significant reduction in animal studies.

Our program already frequently struggles with having enough data to develop health-based risk and water guidance values for many CECs due to a lack of data. We've been thinking about how our processes would look with reduced availability of data from animal studies and a reliance more on the type of data generated by NAMs.

We can envision a future for risk assessment where there will not be enough traditional toxicology data for standard risk assessment methods. Animal studies, in particular for most CECs are already at a premium for developing a standard chemical review, and we currently do not have a process to support incorporating NAMs data. Because we can see the possibility that most CECs will no longer be eligible for full review due to an across-the-board reduction in traditional tox studies, we feel compelled to proactively prepare for that eventuality.

The second change is that thanks to an increase in Clean Water Funds, the CEC initiative was able to hire a computational toxicologist. It is important for moving us forward as a program and for our valuable Minnesota-specific risk assessments.

Slide 54: Proposed Updated to CEC Exposure Screening



Slide Text and Image Description

Image: Graphic from Slide 52, with "Screen for exposure potential" highlighted

Text:

Current Approach

- Acquisition of chemical-specific data from a defined collection of data sources
- Each bit of data is designated high, medium, or low in terms of concern for drinking water exposure
- Scores are assigned to each bit of data based on H/M/L classification and the data's impact
- Overall exposure score is a synthesis of the individual scores

Summary

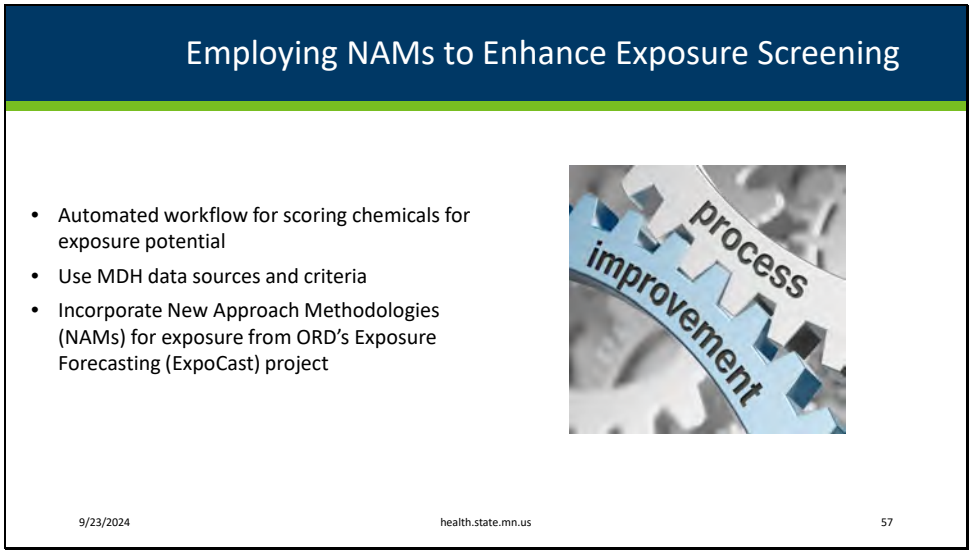
A couple of slides back, Sarah presented this diagram which until today I never heard described as the Cadillac of chemical screening processes and I kind of like that term. I've highlighted in green the area I'm focusing in on the next couple of slides: the screening for exposure potential.
We anticipate an expanding role for exposure assessment in the future and so we're looking into ways that we can make the exposure screening process work better. We're looking for ways to be more proactive as we identify chemicals that Minnesotans may be exposed to, especially in their drinking water.

Our current process involves acquiring chemical specific data from a defined collection of data sources, and these individual bits of data can include many different things. For example, it could be detections of the chemical in drinking water at a certain concentration, or detections in surface water that's not used.

For drinking at a certain concentration or chemical properties that indicate that the chemical may be more likely to persist in the environment or be mobile if it's found, if there's a spill and it's found in groundwater. Each of these bits of data is designated as sort of a concern level that could be high, medium or low for drinking water. For example, a chemical is more soluble in water, is a slightly higher concern than a chemical that's not soluble in water. It's less likely.

To be in your drinking water at a high concentration or a chemical that is highly persistent in the environment and never breaks down might be a higher concern than a chemical that breaks down into less harmful degradation products and so scores are assigned to each of those bits of data based on whether it's high, medium or low in terms of its concern level, but also based on the impact of the data because not all these bits of data are of equal significance or importance. For example, if all we know about a chemical is that it's highly soluble in water and we don't know much about where it's found. Maybe it’s never been detected. That tells us a little bit, but it doesn't really raise our concern by a lot. On the other end of the spectrum, a detection of a chemical, if we know it's been found in drinking water in Minnesota, then we know it's likely that people are actually being exposed to the chemical in their drinking water and that obviously is a much higher impact potentially. And that gives that chemical a little bit of a of a boost and how we assess its exposure potential.

Slide 55: Employing NAMs to Enhance Exposure Screening



Slide Text and Image Description

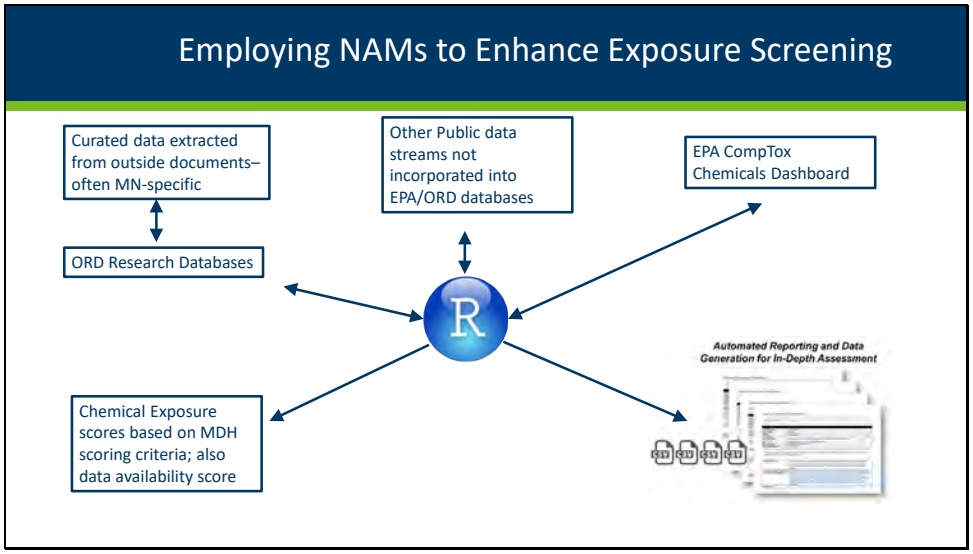
Image: process, improvement gears

- Text: Automated workflow for scoring chemicals for exposure potential
- Use MDH data sources and criteria
- Incorporate New Approach Methodologies (NAMs) for exposure from ORD's Exposure Forecasting (ExpoCast) project

Summary

The process works well for individual chemicals, but it's actually very time consuming. It can take many hours to evaluate a single chemical, and so we asked ourselves how can we use NAMs? Everyone's talking about NAMs. Are there NAMs that could enhance the exposure screening process?
We worked with EPA, some of their computational toxicologists, to develop an automated workflow for. Calculating those exposure scores that I talked about in the last slide. These methods use MDH data sources and criteria. And they incorporate these new approach methodologies.

Slide 56: Employing NAMS to Enhance Exposure Screening



Slide Text and Image Description

- Chemical exposure scores based on MDH scoring criteria; also data availability score
- ORD Research databases
    - Curated data extracted from outside documents—often MN-specific
- Other public data streams not incorporated into EPA/ORD databases
- EPA CompTox Chemicals Dashboard
- Automated Reporting and Data Generation for In-Depth Assessment

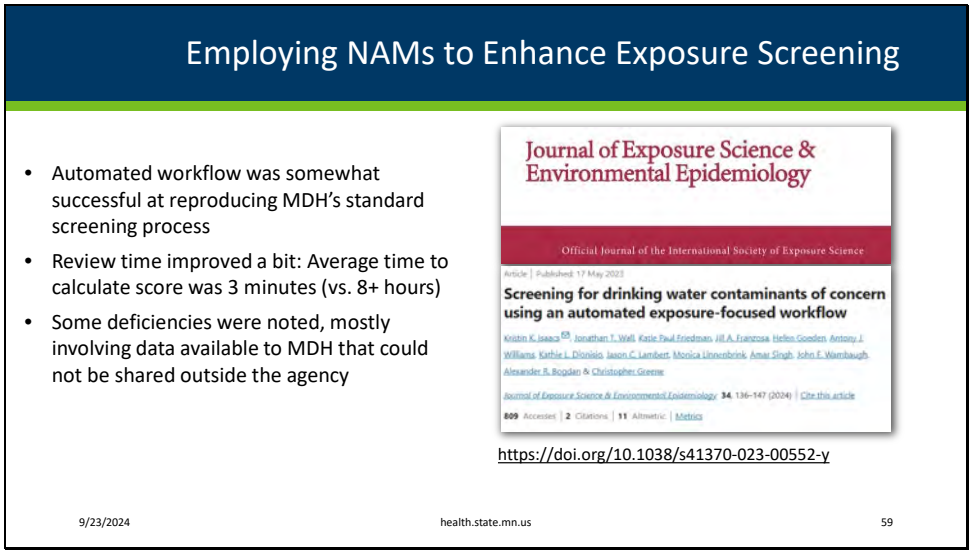
Summary

We discussed our exposure screening process with data scientists at EPA and they took our source documents that includes data tables from published reports and those had to be digitized in many cases and turned into a machine-readable format. We also developed interfaces for data sources outside, for example, the USGS EPA water quality portal resource or also Minnesota's specific data that was furnished to MDH in the past by the US Geological Survey, who does a lot of water monitoring in Minnesota and across the country. Then, of course, they also used the EPA CompTox chemicals dashboard as a data source.

They developed a software package developed in our programming language to query all these data sources and then apply to those t data, those criteria and scoring systems that we had already been using in our manual process over the last several years. We've developed that and then the software

package begins with a list of chemicals to be evaluated and then performs all its different data sources and calculating and then it puts out a set of chemical exposure scores using MDH's scoring criteria. And also a score that that indicates the level of availability of data and then it also produces a report for each chemical that summarizes what was found in the databases that were queried.

Slide 57: Employing NAMs to Enhance Exposure Screening



Slide Text and Image Description

Image: Screenshot of "Screening for drinking water contaminants of concern using an automated exposure-focused workflow" publication in *Journal of Expsoure Science and Environmental Epidemiology* *https://doi.org/10.1038/s41370-023-00552-y*

Text:

- Automated workflow was somewhat successful at reproducing MDH's standard screening process
- Review time improved a bit: Average time to calculate score was 3 minutes (vs. 8+ hours)
- Some deficiencies were noted, mostly involving data available to MDH that could not be shared outside the agency

Summary

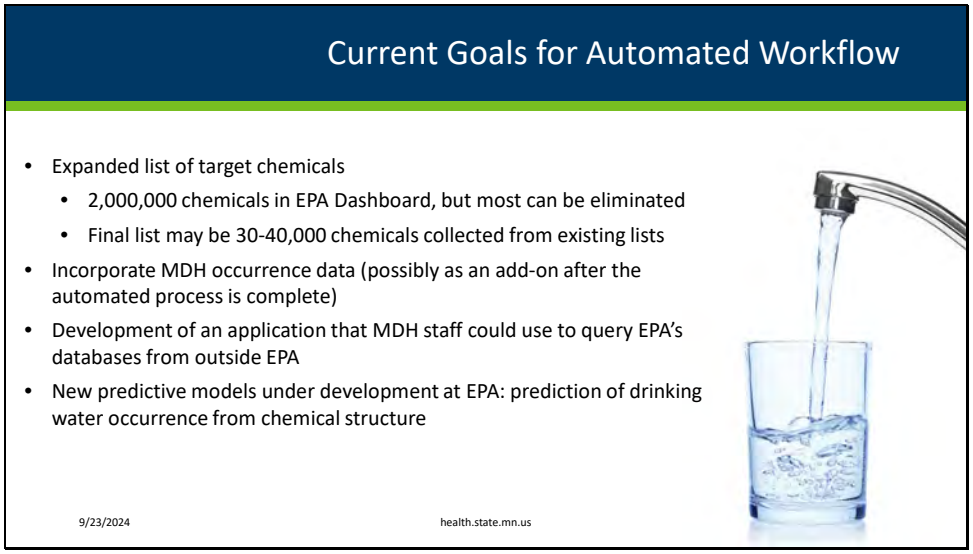
We applied this process to a trial set of chemicals of about 1800 chemicals, and 82 of those chemicals were ones that were previously scored and evaluated by MDH using our manual process. By doing this, we hoped to be able to compare the old method that was done by hand and the new method done by machine and see if there was a reasonable agreement.

The first thing we found was that it improved a bit because the average time to calculate a chemical score went down from 80 or more hours down to about 3 minutes per chemical on average. This is a significant change in the speed with which we can evaluate chemicals.

However, some deficiencies in the analysis were noted, and many of those involve data that were available to MDH for our manual process, but they could not be shared outside our agency, and we're currently working on workarounds that we can either provide that data or apply that data in house, after the automated process is complete.

We also found that agreement between the two methods, the manual and the automated, was a lot better for chemicals that had high degree of data availability. That's not surprising, but it does point to the continuing need to make use of the available data that we have for the chemicals that we're trying to evaluate and try to do our best to accommodate data and extract what we can from the available data that are out there.

Slide 58: Current Goals for Automated Workflow



Slide Text and Image Description

Image: running water flowing from a faucet to a drinking glass.

Text:

- Expanded list of target chemicals
    - 2,000,000 chemicals in EPA Dashboard, but most can be eliminated
    - Final list may be 30-40,000 chemicals collected from existing lists
- Incorporate MDH occurrence data (possibly as an add-on after the automated process is complete)
- Development of an application that MDH staff could use to query EPA's databases from outside EPA
- New predictive models under development at EPA: prediction of drinking water occurrence from chemical structure

Summary

I will talk briefly about some of the goals for this automated workflow. We're currently working on expanding the list of target chemicals so that we can run them through this process and develop potential exposure scores for a long list of chemicals. There's a vast number of chemicals in EPA's chemistry dashboard, but most of those can be eliminated. We're aiming at a final list, maybe 30,000 or

40,000 chemicals, and those are generally collected from existing lists within EPA as Chemical dashboard. There are several hundred and those can be things like chemicals found in biosolids or chemicals found in leaking underground storage tanks or ingredients used in cosmetics. My colleagues at EPA and I are going through some of those lists to pull out lists that are relevant, even indirectly relevant to drinking water. These lists are going to be primary contributors to a final list of thirty to forty thousand chemicals we'd like to run through the process.

We currently have a list we've windowed it down to about 60,000, but we do want to narrow that down a little bit more because even using their system that can process these chemicals, that still would be on the order of a few months of computational time to evaluate the chemicals. So we may try to narrow down the list a little bit. At least prioritize because that would be a pretty major computational effort on their part.

EPA is also developing an application that potentially MDH staff could use to query EPA's databases from outside EPA that would enable us to run our own script or software that would with our own list of chemicals, if something new came on the scene that we didn't already have an evaluation for, or if we had a new list that we wanted to run through, we would be able to do that ourselves using EPA's tools. And another advantage to this system that we're trying to develop with EPA is that the whole list can be rerun periodically to reflect any changes in the source data from the chemical dashboard as new data get added there. We could say on an annual basis, rerun our long list of chemicals just to make sure there's been no changes either methodology or new data coming in on some of these chemicals.

Finally EPA is working on some models that are intended to predict drinking water occurrence or occurrence potential based on chemical structure. That's another aspect that may be added to this automated workflow is just a flag at the end of the analysis, like has this been identified based on chemical structure as a potential drinking water contaminant and it might warrant a bit more attention than a chemical that had not been identified that way.

Slide 59: 2024 CEC Initiative Workplan

Slide Text and Image Description

- Trifluoroacetate (TFA)
- Cobalt
- o-toluidine
- Germanium
- 5,6-Dimethly-1-H-Benzotriazole
- 4 Nonylphenols : (NP2EO, NP1EO, NP2EC, NP3EC)
- Nodularin
- Metformin

Summary

This is our 2024-2025 CEC initiative work plan. For full disclosure, I'll say we only had one nomination this year—it was trifluoroacetate. The rest are existing from our previous rankings. We believe there's enough toxicity data to be able to develop one of our usual types of guidance, such as risk assessment advice, health-based values or health risk limits for trifluoroacetate and salts, cobalt, o-toluidine, and germanium.

And then these that have the asterisks, these are data poor chemicals, and these come off of the “not feasible list”. And what we did to develop this list was to look at what was on the not feasible list and rule certain classes of chemicals out and then look at rescreening everything else that was left. These were left standing after that rescreening: 5-6 dimethyl-1-H-benzotriazole, the 4 nonylphenols, nodularin, and metformin.

The possible outcome as far as guidance development goes is pretty much unknown at this point in time. These did not have enough information to do a full review. Any guidance development would have to be supported by NAMs and other new sources of data. These are kind of like I would say, maybe test chemicals that we're going to use to point out where the holes are and what's going to be a problem with incorporating these new data sources. There you have it the 2024 CEC initiative work plan.

Slide 60: Q+A

Slide Text and Image Description

Minnesota Department of Health logo

Image: raised hands

Summary

Question: Anything on how much the acceptance and defensibility has been tested by industry interests for NAMS approaches?

Answer: Acceptance and defensibility by industry—it varies. I'm not going to say it's perfect, nor is it imperfect. A lot of industries have embraced their own versions of NAMs for their own internal testing. Those are often proprietary and several components have been accepted, and of course these are still approaches that need further evaluation overall.

Question: US EPA has recently developed a protocol for short term in vivo rodent studies to predict chronic non-cancer toxicity from changes in gene expression (ETAP). EPA has concluded that this protocol is likely to be sufficiently predictive of chronic systemic toxicity and requires less time and resources than traditional repeated dose studies. Is MDH evaluating ETAP as well as NAMs?

Answer: We've read the MOPA ETAP with great interest! We have our eye on ETAPs and are interested to see where they go.

Question: As NAMs has inherent uncertainty, would human health risk guidance consider this uncertainty in any derived numeric values that are considered protective or even over-protective?

Answer: Absolutely that will be considered as we develop these systems. And a reminder that the guidance methodology we use was designed to protect most sensitive populations so it would be aligned with our current practice to build a NAMs methodology would also do that.

Question: Where can we find the MDH occurrence data?

Answer: MNDWIS data is internally available only, there is not a public interface. However, there are a number of sources available for the public:

- www.waterqualitydata.us that is sort of a clearinghouse for publicly available EPA, USGS data.
- MDH also has an interactive map of PFAS detections.
- it is not MDH's data but there is ample PFAS groundwater data collected by the MPCA that can be found on both the Minnesota Groundwater Contamination Atlas and Groundwater Environmental Data Access websites.

Question: Is there a way to find a list of all chemicals that have been reviewed by MDH in the past say decade or so? Where do we find upcoming chemicals for review by the MDH?

Answer: We post our guidance but not sorted by type of guidance or year it was created at the Human Health-Based Water Guidance Table page.

- Chemicals currently under review are found here.

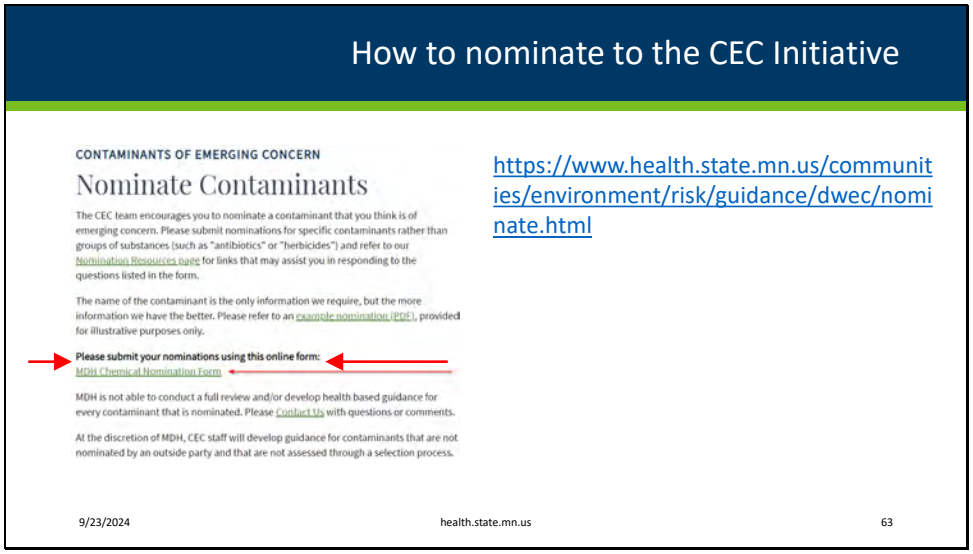
Question: Are there any PFAS that the department is really focusing on in the coming months or years (outside of those listed in the presentation)? Is there an established plan for when MN is planning on taking action on those contaminants?

Answer: The plan is in the works. TFA will likely go through a standard risk assessment process.

Question: Can you speak more to this data poor idea. Are the CECs more likely to be data poor?

Answer: This usually refers to the lack of toxicological impacts of the chemical when we say a contaminant is data poor; but yes, being data poor can be one of the characteristics that make a contaminant 'emerging' is that we don't yet have a lot of information about it.

Slide 61: How to nominate to the CEC Initiative



Slide Text and Image Description

Image: Screenshot of Contaminants of Emerging Concern Nominate Contaminants website (https://www.health.state.mn.us/communities/environment/risk/guidance/dwec/nominate.html)

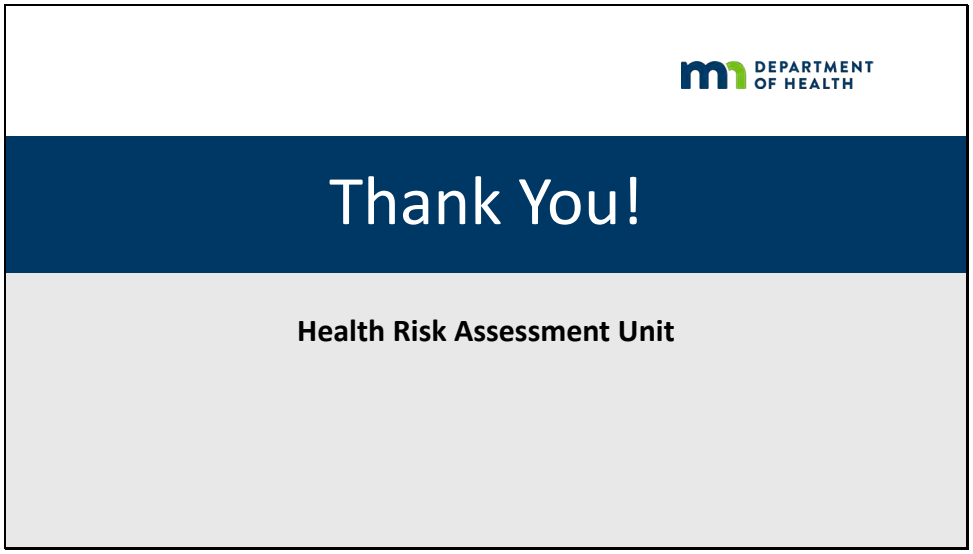
Summary

I want to thank everyone for asking such thoughtful questions throughout the presentation today.

You can nominate contaminants to the CEC initiative by visiting our website where you can submit your nominations using an online form. Please do take some time to visit our website. We've shared lots of different resources that are available there and accessible to the public.

And with that, thank you so much to everyone for attending today, for participating in our discussion, and for hearing from our Contaminants of Emerging Concern Initiative team members about the work that we are currently doing and where we are headed as we look to the future.

Slide 62: Thank You!



Slide Text and Image Description

Image: Minnesota Department of Health

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11/7/24

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