



# Annual Report

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**MICHIGAN STATE  
UNIVERSITY**

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# ABOUT CRIS

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The Center for Research on Ingredient Safety at Michigan State University (CRIS) is one of the few organizations in the world willing to tackle the hard questions about ingredient safety in our everyday products.



We are unique in that we work with academia, government, non-governmental organizations, and industry to understand the safe use of ingredients. To be a CRIS Partner, an entity must be willing to submit to our code of ethics of complete transparency and always put the consumers' best interests regarding ingredient safety first.

But how do we ensure these entities have our best interests at heart? How do we know that what they are saying about the ingredients in our everyday products is true?

CRIS fills that void. We use expert knowledge to research, fact-check, and supply the global community with the latest science-based information about the ingredients in our food, beverages, and cosmetics.

We leverage the expertise of established investigators who have devoted their lives' work to science, and we demystify dense academic journal findings and governmental reports so you can make informed decisions about the science in our lives.

While this may make us unpopular with some groups, we believe that transparency and truth are requirements to earn your trust, and the confidence of the global community.

# MISSION & VISION

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Our mission is to conduct research and provide insight into the safety of ingredients in food and consumer products to support evidence-informed decisions by consumers, industry, and policymakers.

Our vision is to ensure credible, relevant information on ingredient safety is accessible to a wide range of decision-makers.

# CORE VALUES

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We operate using our core values:

- Integrity
- Responsibility
- Transparency
- Inclusivity
- Engagement
- Diversity

# THE OBJECTIVE

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We at the Center for Research on Ingredient Safety at Michigan State University (CRIS) strive to become the go-to source for information on ingredient safety.



# OUR COMMITMENT & OUR ETHICS

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We at the Center for Research on Ingredient Safety at Michigan State University (CRIS) believe that science and research should speak for itself. That is why we wrote transparency and accountability into our bylaws and governance practices from CRIS's inception to ensure that we

- produce and disseminate unbiased and credible research data and analysis on the safe use of ingredients in food and consumer products.
- offer unbiased and transparent evaluation of new technology that can be applied to evaluate ingredient safety.
- expand the opportunity to conduct basic and applied research on the safety and toxicology of ingredients in food and consumer products to support the management of potential safety issues.

This also means that the established investigators conducting research at CRIS have final say on all scientific research, including

- driving the research agenda.
- research design, methods, and conduct.
- interpreting and publishing findings in peer-reviewed journals.

To ensure impartiality, all research outcomes from CRIS-conducted projects must undergo the peer review process and are published. Research findings are not shared, including with members, or communicated until accepted for publication in the peer-reviewed literature. All of our research methods and processes are available openly and freely for any person to evaluate.

While our partners can participate in CRIS advisory committees, all final research and communication decisions are made by the CRIS team using the CRIS bylaws and established governance.

Additionally, we follow the code of ethics outlined by Michigan State University.

# OUR MEMBERS

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# OUR TEAM

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The Center for Research on Ingredient Safety at Michigan State University (CRIS) consists of a core team of individuals who provide leadership, management, research, educational opportunities, and direction for CRIS activities. In addition to our core team, we're connected to a global network of scientists and researchers available to support CRIS research.

These activities are guided by input from CRIS advisory committees. However, all final decisions are made by the CRIS team.



**Norbert Kaminski, Ph.D.**

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# A NOTE FROM THE DIRECTOR

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As our membership continues to grow, we've decided to launch an annual report to showcase some of our accomplishments at CRIS over the previous year. In this inaugural report, you'll find highlights of CRIS's accomplishments.

In 2022, we secured new funding and a partnership with Corewell Health to assist us in the validation of a human developmental immunotoxicity assay. Toward this end, we will assess the effects of lead exposure on the developing immune system during early life stages, using umbilical cord-derived stem cells, and on maternal health. Our partnership allows us to broaden the assessment of the assay with the long-term goal of assay's qualification and its application for assessing ingredients and contaminants safety.

Additionally, we formed a new alliance with Johns Hopkins University. We are participating in a developmental immunotoxicology working group established to further assist in the validation of our developmental immunotoxicity assays.

Results from a CRIS research project in which we have established a point-of-departure for CBD liver toxicity using a human hepatocyte spheroid model have been accepted for publication in the journal, *Toxicology and its* is now available in pre-publication form online.



*Photo: Dr. Norbert Kaminski*

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# A NOTE FROM THE DIRECTOR CONTINUED

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We saw 2022 return much of the normalcy we missed throughout the heart of the pandemic. As a result, I had the pleasure of continuing to broaden our CRIS reach through international travel to conferences as an invited speaker in Brussels, Belgium; Edinburgh, Scotland; and Dubai, United Arab Emirates, where I spoke on a breadth of topics, including endocrine-disrupting chemicals, titanium dioxide, and microplastics.

Continuing our international focus, we replied to the European Food Safety Authority regarding decision points on BPA. Our submission to the EFSA is publicly available and has also been recently published in the peer-reviewed journal, "Toxicological Sciences." Read it at [go.msu.edu/zCC5](http://go.msu.edu/zCC5).

In addition to our weekly blogs, we brought ingredient science to the public through our media engagements. Our titanium dioxide expertise through CRIS saw us featured on Newsy Channel, in Scientific American, and Canadian Broadcast Company.

2023 is already off to an excellent start, and we are excited about the developments we're seeing unfold. Thank you for your continued support of CRIS and CRIS activities.

We are thrilled to have your participation.



**Norbert Kaminski, Ph.D.**

Professor, Pharmacology & Toxicology  
Director, Center for Research on Ingredient Safety  
Director, Institute for Integrative Toxicology  
Michigan State University

*Research Highlights***NEW APPROACH METHODOLOGIES**

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**Background**

Historically, chemical toxicity testing has been accomplished primarily through the use of animal models. These models have proven to be costly, time-consuming, and often fail to adequately mimic human biology. Therefore, there has been increased interest and commitment by regulatory agencies within the United States and abroad in developing in vitro human-based methodologies, known as new approach methodologies (NAMs), to address the known shortcomings of the more traditional animal models.

Here at CRIS, we have similarly focused on developing and utilizing human-based NAMs for our toxicity assessments of chemicals.

Currently, we are utilizing NAMs for the determination of developmental immunotoxicology testing, as well as the determination of liver toxicity, using a co-culture model.



## Research Highlights

# NEW APPROACH METHODOLOGIES

## Developmental Immunotoxicology

The many different cell types that comprise the immune system arise from the pluripotent hematopoietic stem cell (HSC). This complex process takes place early in life during fetal development and then after birth within the bone marrow.

During the past eight years, the Kaminski laboratory has utilized human umbilical cord blood-derived HSC to study the effects initially of dioxin-like compounds on HSC to B cell lineage commitment. More recently, we discovered using a technique termed single-cell RNA sequencing that in addition to the presence of lineage-committed B cells, virtually all other major white bloods, with the exception of T cells, are present in this 28-day culture system.

Under the auspices of CRIS, we are proposing to utilize this culture system as a model for screening and identifying putative developmental immunotoxicants.

Studies describing the initial use of this model system for investigating the effects of dioxin-like compounds were first published in the *Journal of Immunology* in 2017. The more recent characterization of this model and the development of the various cell types that comprise the immune system is currently

pending peer-review.

In this CRIS Annual Report, we discuss the application and ongoing efforts toward validation of this model for investigative and regulatory purposes.

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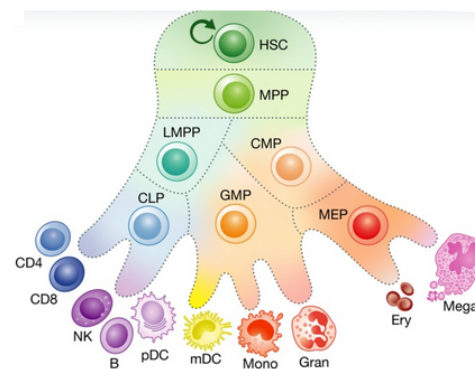


Image Source: Bao et al (2019), *EMBO Mol Med*

*Research Highlights***NEW APPROACH METHODOLOGIES**

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**Liver Co-Culture Model**

The liver is comprised of many different cell types that have varying functions, including hepatocytes, endothelial cells, Kupffer cells, and more. Although seen as the primary site of chemical metabolism, not all cells within the liver are able to metabolize chemicals to the same degree, resulting in differential sensitivities to certain toxic chemicals requiring metabolic activation.

At CRIS, we have developed a co-culture model system, in which we utilize a human hepatocyte cell line, that has been shown to closely mimic human liver metabolism, along with a human endothelial cell line, which is present in human livers, but has lower expression of chemical metabolizing enzymes. In this system, we can utilize toxicants that require metabolism, or bioactivation, to become toxic while determining if one cell type (i.e., hepatocytes or endothelial cells) over another is preferentially targeted by the toxicant.

Currently, CRIS is utilizing this NAM to determine differential genotoxicity to pyrrolizidine alkaloids.

**Pyrrolizidine Alkaloid Project**

Pyrrolizidine alkaloids (PAs) are a group of several hundred secondary metabolites that are produced by several thousand plant species that have been shown to be genotoxic. The primary target of PAs is endothelial cells, which can result in venal occlusive disease.

The presence of PAs in food products has been widely regulated internationally, as they are common contaminants in plant-based foods and spices. That said, the regulatory process of some agencies has approached PA contamination from the stance that all PAs are equally potent and genotoxic. Therefore, CRIS is utilizing our liver co-culture NAM to test this hypothesis, doing a structure activity analysis, to determine if there is differential potency amongst the different structural classes of PAs, which may call for a more nuanced approach in determining safety thresholds for these chemicals.



*Research Highlights***COLLABORATIVE ALLIANCES**

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**Utilizing Developmental Immunotoxicology Assay in Real-World Application**

As described earlier in this CRIS Annual Report, efforts are ongoing to validate the human DIT assay. One avenue toward this end has been to employ this assay system for identification of putative developmental immunotoxicants. Doing so is not a trivial task as most developmental immunotoxicants have been identified in mouse models and assumed to produce the same effects in humans, which is a big assumption. Therefore, the availability of “known” reference chemicals for assay validation is limited. One such developmental immunotoxicant identified in rodent models is lead.

In 2022, Drs. Zagorski and Kaminski submitted a grant proposal in collaboration with a clinical team in Grand Rapids, MI at the Corewell Health System proposing to recruit pregnant mothers to be screened for elevated blood lead levels and to consent to donate their umbilical cord blood hematopoietic stem cells (HSC). The HSC will be compared in parallel with HSC from pregnant mothers with no detectable blood lead using our DIT assay. The newborns will also be followed using medical chart reviews to determine if there is evidence of altered immune competence like increased infections (e.g., ear) or evidence of allergy in association with elevated blood levels.

Mothers will be recruited from the three zip codes in Kent County, Grand Rapids, which have a very high incidence of lead poisoning. Surprisingly, in a 2016 report the Michigan Department of Health and Human Services confirmed that no Michigan county, including counties in Flint, MI, has more lead-poisoned children than Kent County, and which is localized to three zip codes.

A total of 800 mothers will be screen for blood lead levels and approximately 40 mothers with high blood lead levels and 40 mothers with low or no detectible blood lead levels will be evaluated in our study.

This grant was selected in late 2022 for funding following peer review and will start in May 2023.



*Research Highlights*

# COLLABORATIVE ALLIANCE

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## Validation of Developmental Immunotoxicology Assay

With the explosion of NAMs, much of the current discussion in this area has been focused on what will be required to validate an in vitro assay for regulatory use. It is noteworthy that in the US, in vitro methods that are not fully “validated” may be fit-for-purpose for regulatory applications; however, this is determined on a case-by-case basis and is also dependent on the regulatory agency.

CRIS has been participating in a Developmental Immunotoxicology Working Group comprised of immunotoxicologists from government, industry and academia led by Dr. Fenna Sille at Johns Hopkins University to identify and validate DIT assays.

The DIT assay developed at Michigan State University is presently the lead candidate for validation.

Presently four laboratories have agreed to participate in an inter-laboratory validation, which will include Dr. Fenna Sille’s laboratory at the Johns Hopkins, Burleson Research

Technologies Inc, Health Canada and CRIS at Michigan State University.

In the upcoming May workshop of the working group, first steps toward validation will be discussed, which will include which reference standards to employ and logistics to conduct the validation.

We will have more information to share later in the year.



*Research Highlights*

# 2022 RESEARCH

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## CBD Liver Toxicity

### 2022 Submission (2023 publication)

Evaluation of the Potential Hepatotoxicity of CBD using a Human Hepatocyte Spheroid Model.

#### Abstract

The United States Food and Drug Administration recently approved the use of cannabis sativa derived cannabidiol (CBD) in the treatment of Dravet Syndrome and Lennox-Gastaut Syndrome, under the trade name, Epidiolex. In double-blinded, placebo-controlled clinical trials, elevated ALT levels were observed in some patients, but these findings could not be uncoupled from the confounds of potential drug-drug interactions with co-administration of valproate and clobazam.

Given the uncertainty of the potential hepatotoxic effects of CBD, the objective of the present study was to determine a point of departure for CBD, using human HepaRG spheroid cultures, followed by transcriptomic benchmark dose analysis. Treatment of HepaRG spheroids with CBD for 24 and 72 hours, resulted in EC50 concentrations for cytotoxicity of 86.27  $\mu\text{M}$  and 58.04  $\mu\text{M}$ , respectively. Subsequent transcriptomic analysis at these timepoints demonstrated little alteration of gene and pathway data sets at a CBD concentration at or below 10  $\mu\text{M}$ . Although this current analysis was conducted using liver cells, interestingly the findings at 72 hours post CBD treatment showed suppression of many genes more commonly associated with immune regulation.

Indeed, the immune system is a well-established target for CBD based on immune function assays. Collectively, in the present studies a point of departure was derived using transcriptomic changes produced by CBD in a human cell-based model system, which has been shown to accurately translate to human hepatotoxicity modeling.

Read the full paper: [go.msu.edu/BCC5](https://go.msu.edu/BCC5)



*CRIS Activities*

# COMMITMENT TO WEIGHT OF EVIDENCE

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## Committed to Weight of Evidence

As responsible stakeholders and thought leaders in the toxicological field, we are committed to advocating for the use of Weight of Evidence (WoE) methodologies in chemical risk assessments and support efforts to promote their adoption by regulatory agencies and other stakeholders.

To that end, we've used our unique, collaborative structure to form a new Weight of Evidence Committee. The WoE committee's goal is to develop a common understanding of the principles and best practices for implementing WoE methodologies and will build a central platform to provide guidance and facilitate knowledge-sharing.

## Weight of Evidence in Practice

At CRIS, we've engaged in constructive dialogue on chemical ingredient research with an emphasis on WoE.

In particular, we've responded to the European Food Safety Authority's call for comments on the ingredient Bisphenol A (BPA).

You can read our response at [go.msu.edu/zCC5](https://go.msu.edu/zCC5)





*CRIS Activities*

# ENGAGEMENTS NATIONAL & INTERNATIONAL

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## CRIS Annual Meeting & Science Symposium

The 2022 CRIS Science Day focused on developmental immunology and immunotoxicology as well as on the effects of nanoplastics on human health.

Featuring:

- Fenna C.M. Sillé, Ph.D., Johns Hopkins Bloomberg School of Public Health
- Eliver Ghosn, Ph.D., Emory University School of Medicine
- Juan Carlos Zúñiga-Pflücker, Ph.D., University of Toronto
- Isha Khan, Ph.D. Candidate, Michigan State University
- Robert Ellis-Hutchings, Ph.D., Dow Chemical
- Christie Sayes, Ph.D., Baylor University
- Baoshan Xing, Ph.D., University of Massachusetts Amherst
- Helena Bottemiller Evich, Founder and Editor-in-Chief of FoodFix.co



Watch the symposium: [go.msu.edu/92C5](https://go.msu.edu/92C5)

## National Speaking Engagement



### JIFSAN-CFS3

#### *Annual Symposium*

CRIS Director, Dr. Norbert Kaminski, was invited to give a talk on science communication, focusing on the role academics take on educating consumers.

JIFSAN-CFS3 is a Center of Excellence to promote research, education and outreach in food safety, security and applied nutrition. Their goal is to be a premier source of scientific information that enables the development of sound public health policy and reduces the incidence of food-related illness.

*CRIS Activities*

# ENGAGEMENTS NATIONAL & INTERNATIONAL

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## International Speaking Engagements

### Brussels, Belgium

#### *Fourth Annual Meeting on Endocrine Disrupting Chemicals*

Directorate General for Environment, in collaboration with ANSES, the French National Agency for Food, Environmental and Occupational Health & Safety, held second segment of the Fourth Annual Forum on Endocrine Disruptors on September 21-22, 2022, in Brussels, Belgium.



CRIS Director, Dr. Norbert Kaminski, was invited to present results at this meeting as his laboratory conducted the immunotoxicology evaluations for the BPA/CLARITY study that was organized and funded by the FDA's, National Center for Toxicological Research, the NIEHS National Toxicology Program.

Interestingly, in November of 2021, the European Food Safety Authority (EFSA) released a draft scientific opinion on BPA exposure and health outcomes to the public. EFSA concluded that the most sensitive outcome category to BPA exposure is the immune system.

You can read the CRIS response to the EFSA: [go.msu.edu/yCC5](https://go.msu.edu/yCC5)

### Edinburgh, Scotland

#### *Microplastic and Seafood: Human Health Symposium*

The Microplastic and Seafood: Human Health Symposium was held September 13-14, 2022. The symposium was jointly hosted by Herriot-Watt



University, Seafish (UK), Seafood Industry Research Fund (US) The National Fisheries Institute (US), and Fisheries Research and Development Corporation (AU).

The objective was to bring together an international group of scientists to discuss the current state-of-the-science on the impact of water borne micro- and nanoplastics on seafood and what is currently known concerning the toxicology of these materials.

There were a number of key takeaways from the symposium. Perhaps the most important being that using state-of-the-art analytical techniques, investigators were only able to detect miniscule amounts of micro-and nanoplastics in the tissues of wild caught fish.

*Communications Highlights*

# GLOBAL OUTREACH

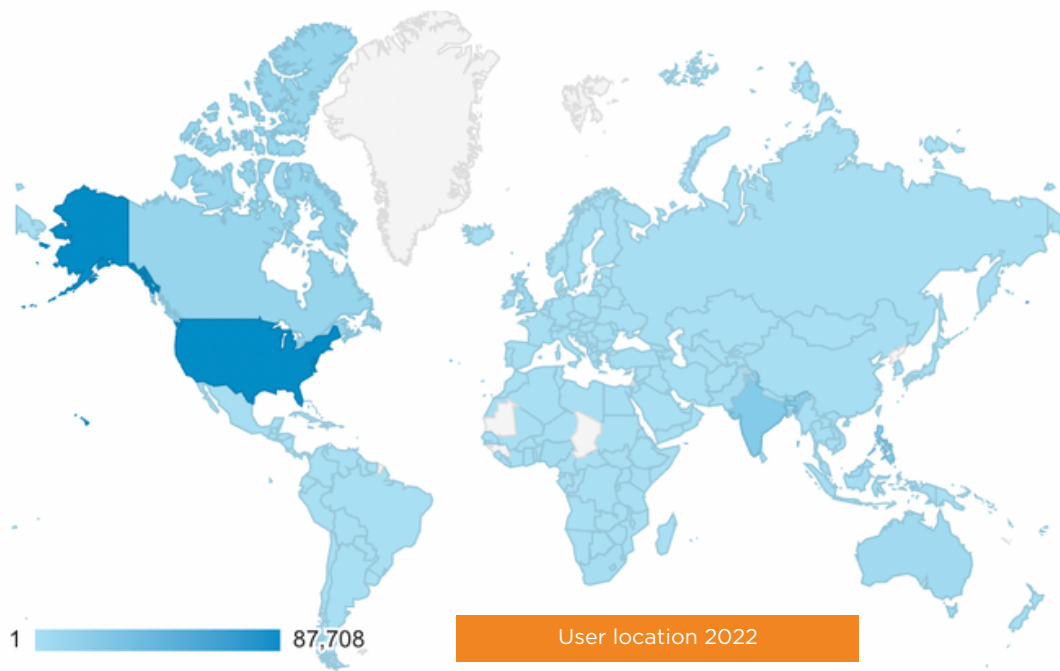
**Global strategy.**

**Global reach.**

**Global impact.**

Everyone deserves to know that the products they use and consume daily are safe. Our global approach to sharing information has a global impact, as evident by our website visitors that span nearly every country on the planet.

Below, you can see our user locations from January 1, 2022-December 31, 2022. The darker shade represents our user density.



Communications Highlights

# CRIS REACHES GOALS

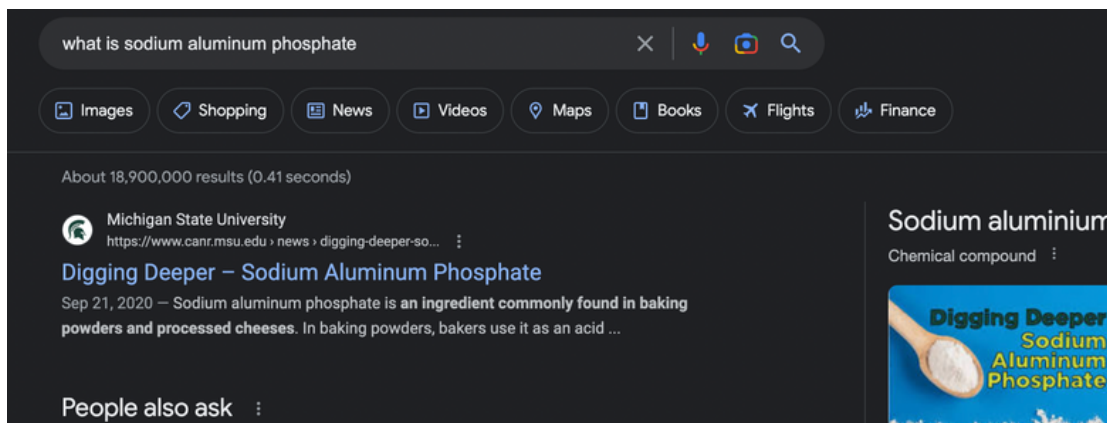
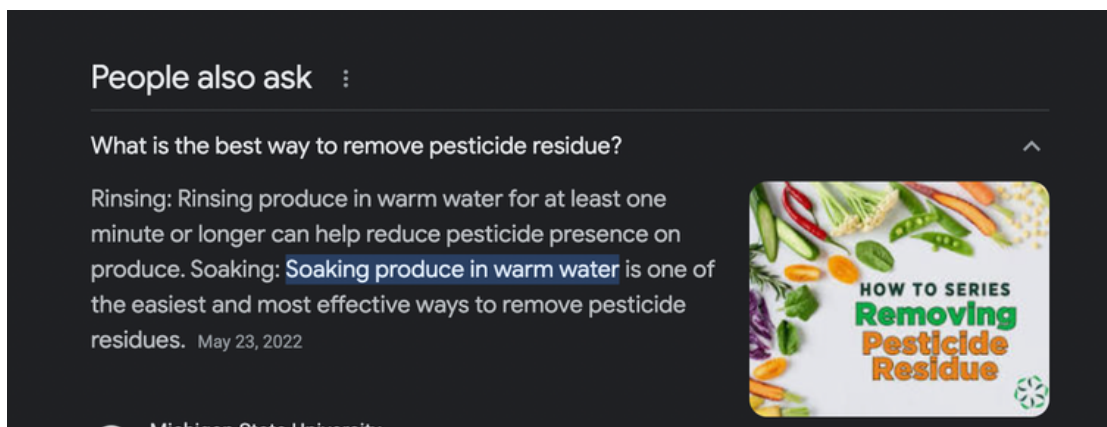
## Achieving Goals

### Google Search Placement

#### Top Ranking

Our unwavering commitment to consistent and organic growth has been reflected in the growing popularity of our community-focused blog posts, many of which have reached the top search engine results. Our approach is based on utilizing social listening to help shape our post ideas and to ensure that we meet our audience where they are, rather than where we assume they should be.

As we continue to use search engine optimization and social listening to optimize our content, we have witnessed a continued increase in community-driven activity to our posts. Our dedication to providing valuable and engaging content to our audience remains at the forefront of our efforts.



*Communications Highlights*

# CRIS IN THE MEDIA & NEWS

Our strategy of making content accessible to everyone and search engine optimized allows the media to engage with us quickly.

News media and journalists continue to reach out to CRIS experts for interviews and to seek clarification on important food, household, and cosmetic-related issues impacting society.

In 2022, we were featured on Newsy Channel (now Scripps News), in Scientific American, on Canadian Broadcast Corporation, and American Public Broadcast Service.





*Communications Highlights*

# TOP STORIES OF 2022

1. Preservatives, keeping our food fresh and safe
2. Disinfecting with Bleach
3. Sodium Aluminum Phosphate
4. Preservatives, cosmetic ingredients
5. Natural and Artificial Flavors
6. Expiring Cosmetics
7. Food Dye
8. Polyvinyl Alcohol
9. GRAS ingredients
10. Flavored Seltzer Water





# CRIS EXTERNAL SCIENTIFIC ADVISORS

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**Jason Aungst, PhD**  
U.S. Food & Drug Administration



**Alan Boobis, PhD**  
Imperial College of London



**Kevin Boyd, PhD**  
The Hershey Company



**Leon Bruner, DVM PhD**  
Michigan State University



**Samuel Cohen, MD, PhD**  
University of Nebraska Medical Center



**Alex Eapen, PhD**  
Cargill



**Suzanne Fitzpatrick, PhD**  
U.S. Food & Drug Administration



**A. Wallace Hayes, PhD**  
Harvard, University of South Florida



**Steven Hermansky, PhD**  
U.S. Food & Drug Administration



**James E. Klaunig, PhD**  
University of Indiana



**Brent Kobielush, PhD**  
ConAgra Brands



**Larry Lichter**  
McCormick Company, Inc.



**Kelly Magurany, MS**  
NSF International



**Steve Mavity**  
Bumble Bee Foods



**Nathaniel J. Parizek, PhD**  
Sherwin-Williams



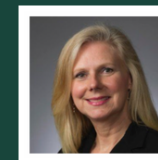
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**Michael Rizzo, PhD**  
PepsiCo, Inc.



**Robert Sills, DVM PhD**  
National Institute of Environmental Health Sciences



**Pam Spencer, PhD**  
ANGUS Chemical Company



**Kristie Sullivan, MPH**  
Physicians Committee for Responsible Medicine



**Katherine Thiel**  
Michigan Farm Bureau



**David Tonucci, PhD**  
SciFi Foods



**MICHIGAN STATE**  

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**UNIVERSITY**