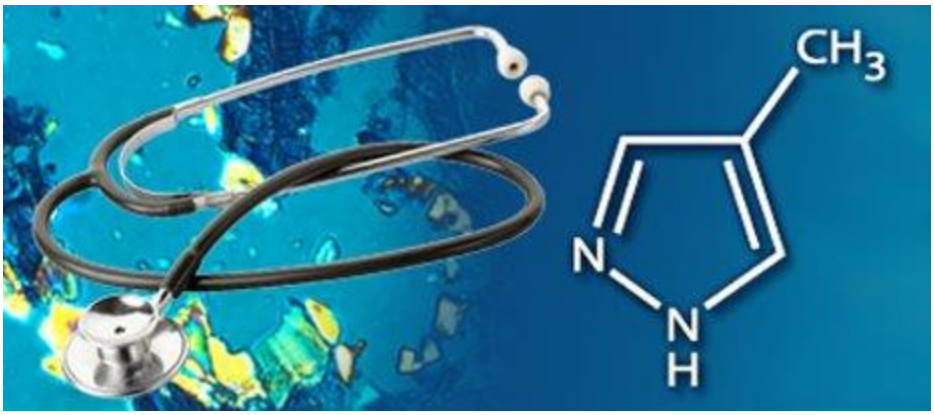


Fomepizole, also known as 4-methylpyrazole, is a medication used to treat methanol and ethylene glycol poisoning

CTTSS Spring Newsletter: May 2019

Message From the 2018-2019 President: Dr. John-Michael Sauer

It has been a great year for me serving as the President of the Clinical and Translational Toxicology Specialty Section (CTTSS). We had significant impact at the annual Society of Toxicology meeting by supporting several symposia and workshops. We also supported a webinar this year that integrated our current understanding of nonclinical and clinical data together around the hepatotoxicity associated with acetaminophen. Thank you to all the presenters and participants.

During our annual specialty section meeting at the Society of Toxicology meeting there was a strong call for us to communicate better and increase our membership ranks. The leadership of the CTTSS has taken your input seriously and has developed a communication plan that includes the revamping our SOT specialty section webpage, more frequent newsletters, and outreach to non-CTTSS SOT members. The leadership team for the CTTSS is also considering external outreach to clinicians through Society of Toxicology's Clinician-Scientist Engagement (CSE) Task Force.

We have a strong incoming leadership team for CTTSS under Dr. Jennifer Burkey that is committed to the success of our specialty section. I look forward to a great year and see everyone at SOT next year in Anaheim, CA.

Message From the 2019-2020 President: Dr. Jennifer Burkey

Greetings! I look forward to serving as your president for the next year, and I look forward to CTTSS continuing to be an active and useful specialty section. Our luncheon at the 2019 annual meeting highlighted an interest in having more communication and outreach to the membership. As a result, we will continue the excellent work of the past and make an extra effort to increase communication regarding the activities of this unique group of preclinical and clinical toxicologists. With your help, we hope to put out more newsletters to inform the group of topics of interest, reach out to those who may benefit from the networking opportunities of the section, and increase the value of the specialty section to all members, new and old.

Dr. Hartmut Jaeschke,

winner for the Translational Impact Award,

speaks at CTTSS luncheon

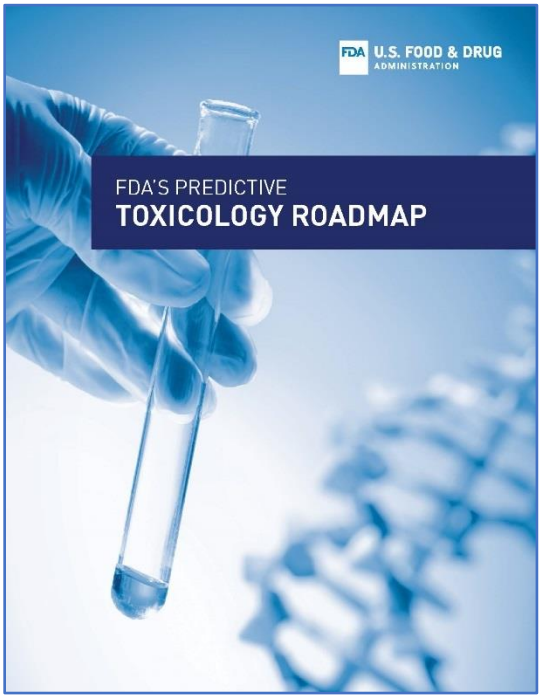
As it is tradition, this year's Translational Impact Award recipient was asked to present a brief lecture at our annual reception. Our honoree, Dr. Hartmut Jaeschke, University of Kansas Medical Center, gave a talk on "Mechanisms of Bile Acid Toxicity in Obstructive Cholestasis: The Impact of Translational Research." The presentation was as much about the science of bile acid toxicity as it was about the lessons learned from exploring several dead-end roads. The journey began in the early 1990s when it was recognized that exposing rat hepatocytes to 50-100 µM glycine-conjugated bile acids triggers apoptotic cell death. This exciting finding about a novel form of cell death and new intracellular signaling pathway was quickly embraced by the scientific community and by the end of the decade hydrophobic bile acid-induced apoptosis became a widely accepted mechanism for cholestatic liver injury. The only caveat was that *in situ*, rat hepatocytes are never exposed to the tested concentrations of glycine-conjugated bile acids. In the experimental model of obstructive cholestasis in mice (bile duct ligation), it was shown that the focal liver injury (bile infarcts) are caused by neutrophils. Reactive oxygen species derived from neutrophils trigger extensive cell necrosis not apoptosis. The predominant bile acids in

rodents are taurine-conjugated cholic acid and muricholic acid, which even in high mM concentrations do not cause cell death. Instead, these hydrophilic bile acids induce the formation of MIP-2 and other neutrophil chemokines in murine hepatocytes and enhance the expression of intercellular adhesion molecules. Furthermore, the release of osteopontin from cholangiocytes and its cleavage in bile by matrix metalloproteases generates another neutrophil chemoattractant. Cleaved osteopontin and chemokines are the main signals for neutrophil recruitment during obstructive cholestasis when bile leaks into the parenchyma. Although this novel mechanism of cholestatic liver injury was investigated in an *in vivo* model, there was concern whether the hydrophilic bile acid milieu in mice may be relevant for humans. To assess this, translational studies were initiated. First, changes of the bile acid profile in serum and bile of patients with obstructive cholestasis were compared to non-cholestatic patients. Second, primary human hepatocytes exposed to serum or biliary concentrations of individual bile acids as well as a mixture of these bile acids clearly showed that serum concentrations during cholestasis of up to 25 µM of glycochenodeoxycholic acid and other glycine-conjugated bile acids did not cause cell death. In contrast, concentrations of 500 µM and above (i.e., biliary levels) triggered time-dependent necrotic cell death. Third, the *in vitro* findings were verified by measuring cell death biomarkers for apoptosis and necrosis in serum of patients with obstructive cholestasis. These translational studies indicated that even the elevated serum levels of bile acids during obstructive cholestasis in patients are insufficient to cause liver injury. However, leakage of bile from ruptured cholangioles during the obstruction directly triggers cell necrosis through the exposure to glycine-conjugated hydrophobic bile acids characteristic for humans (Woolbright et al., Toxicol Appl Pharmacol 283:168-77, 2015). These findings also demonstrate that neither the sophisticated signaling mechanisms of bile acid-induced apoptosis in rat hepatocytes investigated for several decades nor the exclusive inflammatory liver injury mechanisms in bile duct-ligated mice have much relevance for the pathogenesis of obstructive cholestasis in humans. This example shows that translational studies are vital for setting the framework for studying disease mechanisms relevant for humans.

FDA's Efforts to Advance *In Vitro* Assays

FDA and New Technologies

Donna L. Mendrick, PhD, Associate Director for Regulatory Activities, FDA/NCTR



FDA published a Predictive Toxicology Roadmap (https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM587831.pdf) in December 2017. The roadmap was written by the FDA's Toxicology Working Group which is comprised of senior level scientists from all regulatory Centers and NCTR. New tools and approaches are being used to predict or answer safety questions and the FDA has been and remains committed to learning about these. It was decided that we needed a comprehensive strategy to communicate with FDA and advance these new approaches since each regulatory Center operates under different legal authorities and has unique products (e.g., implantable devices vs. food) yet overlapping issues (e.g., carcinogenicity).

Therefore, we developed a roadmap for integrating predictive toxicology methods into safety and risk assessments. It provides a six-part framework:

1. Organizing. The new Organizing Committee will enhance communication within the FDA and leverage FDA resources to advance new methods.
2. Training. Continue ongoing education in new methods
3. Commitment. We will continue our commitment and support for incorporating data from newly qualified methods into regulatory submissions. We encourage sponsors to submit scientifically

valid approaches for using a new method early in the regulatory process and to engage in frequent communication with FDA.

4. Collaboration. We will continue to form collaborations across sectors to support new predictive methods. One example is the DARPA/FDA/NCATS partnership to develop microphysiological systems (aka organs on a chip).
5. Research. FDA will identify data gaps to ensure the most promising technologies are pursued. For example, CDER, CBER, CDRH, CFSAN, CVM, and NCTR are using 3D systems such as microphysiological systems obtained from commercial companies, academic collaborators or those made in house.
6. Oversight. The Toxicology Working Group will track the progress of these recommendations and report to the Chief Scientist annually.

This Roadmap identifies issues that need to be addressed for FDA-regulated products (e.g., identifying potential target organs of toxicity) and areas that could benefit from improved predictability (e.g., recognizing idiosyncratic toxicities). It also lists promising new technologies in use at the FDA such as organs on a chip and computational toxicology.

There was a public meeting at the FDA on September 12, 2018 to solicit comments on our Roadmap. The webcast and slides can be found at:
(https://www.fda.gov/scienceresearch/aboutscienceresearchatfda/ucm601090.htm)

FDA remains very active in many inter-agency (e.g., ICCVAM) and international organizations (e.g., OECD) looking at alternative approaches. FDA is committed to advancing new approaches to safety and risk assessment.

SOT 2019 Annual Meeting highlights

CTTSS Travel Award winners for 2019

This year we were able to provide travel awards for two individuals, a graduate student and a postdoctoral student in the clinical field of study. Congratulations to our award winners!

Grad student Ms. Elizabeth Corteselli, University of North Carolina “Supplementation with omega-3 Fatty Acids Potentiates Oxidative Stress in Human Airway Epithelial Cells Exposed to Ozone”.

Post doc awarded Dr. Timo Wille, Bundeswehr Institute of Pharmacology and Toxicology “In Vitro And Ex Vivo Models in Medical Chemical Defense Research”.

SOT sessions endorsed by CTTSS presented in 2019

Our section has the honor of reviewing and endorsing sessions for the annual meeting every year. This year several of the sessions we endorsed or co-endorsed were accepted for presentation at the annual meeting. We hope you had the opportunity to attend at least one of these sessions, and next year we will make sure to let you know about CTTSS endorsed sessions ahead of the annual meeting!

Invitation by CRC to author Focus on Toxicology series on Translation Toxicology

Our specialty section has been invited by the editor of the CRC Focus on Toxicology Series to author a short monograph (longer than a review, but shorter than a complete book, in the 20,000 to 50,000 word range). This could be composed of 3 or 4 review articles, for example. The overarching topic would be translational toxicology, so the specific topics for each of the articles is flexible. Each article could have one or more authors and the monograph can review up to four related topics. Once started, the goal would be to turn the monograph around quickly, in 3 months or so, as an e book, and then print on demand.

The proposal for a monograph should include the topic audience, a TOC, the proposed contributors, and those who might be interested in the book (target audience). If interested in participating, please contact jburkey@c-path.org.

IT TAKES A VILLAGE!

Your research, that is. Especially if it's in line with Clinical and Translational Toxicology. So why not use our newsletter as a way to reach out to potential collaborators? Our suggestion is we start a "Looking For..." section (please, no personals). Consider submitting to this new section in our newsletter to find potential collaborators who would fit your criteria.

Next newsletter/coming soon:

Predictive Safety Testing Consortium accomplishments

Calling all Clinicians… recruiting clinicians to the CTTSS

Fomepizole in clinical use!

Sessions endorsed by CTTSS for 2020 Annual Meeting

Leadership: 2018-2019 Officers	**2019-2020 officers**
John-Michael Sauer	**Jennifer L. Burkey**
President	President
Jennifer L. Burkey	**Sally Bradberry**
Vice President	Vice President
Sally Bradberry	**Yvonne Dragon**
Vice President-Elect	Vice President-Elect
William Mattes	**William Mattes**
Secretary/Treasurer	Secretary/Treasurer
Hartmut Jaeschke	**Tracy Chen**
Senior Councilor	Senior Councilor
Tracy Chen	**Mitchell McGill**
Junior Councilor	Junior Councilor
Phillip A. Wages	**Emma Bowers**
Postdoc Representative	Postdoc Representative
Courtney N. Jamison	**Jephte Akakpo**
Student Representative	Student Representative
Donna L. Mendrick	**John-Michael Sauer**
Past President	Past President