



## **Global Collaboration Coffee** ***When and How We Can Stop Using Animals in Toxicology***

**Tuesday, March 16, 8:00 AM-10:30 AM**

We are featuring an expert panel with diverse perspectives and excellent information to share on this important topic. This annual event organized by IUTOX and hosted by SOT helps IUTOX Member Societies and other international attendees put ideas into action to advance information sharing and to solve common problems with available resources.

## **Global Collaboration Coffee** ***When and How We Can Stop Using Animals in Toxicology*** **Tuesday, March 16, 8:30 AM-10:00 AM**

### **Question & Answer Transcript**

From Emanuela Corsini to Everyone: 07:53 AM

Welcome everybody and thanks for join the Global Collaboration Coffe, we are going to start in ten minutes with Chat and Networking. The Presentations and discussion will start at 8:15.

From Silvia to Everyone: 08:04 AM

Cheers from Brazil

From Rowena Raeburn (Afton Chemical) to Everyone: 08:05 AM

Hi from the UK!

From Amaia Irizar to Everyone: 08:05 AM

Greetings everyone

From Valentina Schiavone (ZeClinics) Spain to Everyone: 08:05 AM

Italian from Spain!

From Dahea You to Everyone: 08:06 AM

Good morning!

From Maureen Gwinn to Everyone: 08:06 AM

Good morning from the US!

From Mary Ellen Cosenza to Everyone: 08:07 AM

Good morning from California

From Isabelle Plante to Everyone: 08:15 AM

I am here also Jayadev

From Shakil Saghir to Everyone: 08:29 AM

Any insight into what six tests will replace the current six-pack? Will these be in the same price range and timeline to complete?

From Rowena Raeburn (Afton Chemical) to Everyone: 08:36 AM

Question for Dr Casey, but also anyone else on the panel: what are your thoughts on UVCBs?

There is evidence that some of the currently available in vitro methods can either be under-predictive (skin/eye irritation) or not applicable (skin sensitization) to UVCBs. Using computational methods is also more complicated for these substances. Until there are methods available that are more relevant/applicable it is going to be difficult to move away from animal testing for these substances, even for acute testing.

From Shakil Saghir to Everyone: 09:02 AM

For Donna Mendrick: What assays are currently accepted by FDA and which studies they replace?

From Sandra Coecke EC JRC to Everyone: 09:06 AM

To all speakers: Great inspirational complementary thoughts!!!!

What is our common goal:

#Embrace together use of the right research and innovation NAMs tools and abandon those tools that did a part of the job 3 decennia ago?

#Gofor #globalrevolution by applying our science understanding in 2021 versus complying with requests that comply with trusting what we used for half a century ago but do NOT protect/account for nature's created diversity of response and defence mechanisms to external adverse triggers

WHAT ARE TODAY'S TOP 3 GLOBAL BARRIERS TO TOTAL CHANGE OF THE TOOLBOX?

From Ron Hines to Everyone: 09:06 AM

Great presentations, and I continue to find this effort exciting and promising. However, one aspect that I have not seen addressed is the pacing problem, i.e., that technology is advancing far faster than rule-making and legislation. Involving regulators helps with the former, but what about the latter? Some existing legislation actually serves as a barrier to non-animal testing. How do we convince legislators to change existing laws and ensure that future legislation encouraged alternative approaches?

From Betina Lew to Everyone: 09:09 AM

How do we overcome the issue of different geographies not being opened to animal alternatives?

From Valentina Schiavone (ZeClinics) Spain to Everyone: 09:15 AM

Completely agree. In addition to finding and harmonizing protocols with alternative models, we should update and harmonize legislation among countries. It is the only way to align the times and really go for replacement. State of art of this point?

From Mary Gulumian South Africa to Everyone: 09:16 AM

What is said by all esteemed presenters may apply to chemicals and therefore will inspire hope for reducing animal testing. But somehow we are finding it difficult for nanotechnology. The problems encountered include the assay systems and the prediction of short- versus long-term effects using non-animal testing. Moreover, the big data generated may not be used for predictive toxicology for the reasons that those generated may have the issue of interference of nanomaterials tested in these assay systems. For these reasons, present efforts by OECD are challenging to say the least.

From Jeff Pitt to Everyone: 09:18 AM

Great session! How do we limit/remove the over-interpretation of in vitro data in terms of human safety/effects. A recent publication where carboxymethylcellulose was injected into zebrafish embryos blamed human obesity on CMC through CMC-induced genetic alteration. CMC is not absorbed or metabolized in humans and has no way to alter genes in humans. In fact, in vivo carcinogenicity studies have shown the opposite, that CMC reduces weight gain in rodents.

From Ron Hines to Everyone: 09:21 AM

Jeff - the examples you provide are great examples of the many problems encountered with extrapolation from one species to another - one of the drivers behind using human-based NAMs were possible.

From Jayadev Raju to Everyone: 09:22 AM

Fiona Sewell and Donna Mendrick have touched on this point specifically and by others for the need to build confidence and for acceptance. That part is the work of the regulators and the legal gurus on the other side of the rainbow spectrum to stop the use of animals in toxicology. Most jurisdictions are working to address animals in toxicity testing; I think harmonizing these ideas globally would work very well. Thank you all speakers! Cheers from Canada!

From PJ Devine to Everyone: 09:25 AM

I like Bob van de Water's mention of transparency. For the team you were talking about, where will data be placed (fully transparent)? For all speakers, how can we best share experiences, data and NAM details? We have data and publishing standards for transcriptomics and other big data, and we need something like that for NAMs.

From Idolan to Everyone: 09:25 AM

How can the gut microbiome be incorporated into cell culture systems? We are finding that the gut microbiome is involved in metabolism and this aspect needs to be included for accurately predicting toxicity of orally administered substances.

From Monica to Everyone: 09:25 AM

Currently even NAMs are for individual chemical assessment. If we use in silico/NAMs for screening, how do we address the whole product mixture assessment, as used by humans including repeated exposures? Would in vitro in 3D for example should be enough in stead of in vivo safety testing

From Me to Encore Tech: (Direct Message) 09:26 AM

Can you take down the presentation for Q&A?

Bring back up the ICT2022 slide afterwards

From Maureen Gwinn to Everyone: 09:26 AM

I think Elaine also touched on a key point that building understanding of NAMs in academia is also important. The culture change will need to be across all sectors to be successful.

From Encore Tech to Me: (Direct Message) 09:26 AM

done

From Ron Hines to Everyone: 09:26 AM

NAMs are being used for mixtures. For example, evaluating environmental mixtures in a cell-based system to evaluate endocrine disruption.

From Donna.Mendrick@fda.hhs.gov to Everyone: 09:27 AM

I recommend a paper by Avila et al. that was authored by CDER. It describes the data needed for drugs, the current state of the art with alternatives and data gaps. Avila et al.  
<https://doi.org/10.1016/j.yrtph.2020.104662>

From Me to Everyone: 09:27 AM

Feel free to enable your video cameras for the Q&A.

From Amaia Irizar to Everyone: 09:30 AM

Global harmonisation from the regulatory perspective is key as well as the understanding from the regulators of the need to apply NAMs for risk assessment in a way that it does not necessarily replace an already OECD in vivo assay in a paradigm shift to what has been done so far.

From Donna.Mendrick@fda.hhs.gov to Everyone: 09:32 AM

Unfortunately animals were used for testing COVID vaccines and drugs so we still have a long way to go

From Elaine Faustman to Everyone: 09:33 AM

George -- Very well stated!!

From Betina Lew to Everyone: 09:34 AM

exactly true, George

From PJ Devine to Everyone: 09:34 AM

Pharmaceutical industry needs to move forward with NAMs in step with regulators, if not push new methods forward. Regulations will need to be a bit more flexible, like the S5, which discusses where and how NAMs might fit in to the process.

From Matt Dent to Everyone: 09:35 AM

Completely agree George - I might also add that the new approach needs to be exposure led as well as hypothesis driven - otherwise we are stuck ticking boxes.

From Jeff Pitt to Everyone: 09:35 AM

Agree with Matt Dent

From Monica to Everyone: 09:35 AM

George - your session yesterday on communication was excellent; a key challenge is, if moving away from 'checkbox', many people loses how to communicate less than clear binary process. Regulatory process is unfortunately viewed as yes and no, rather than 'in depends' - any thought how to change a different way to risk communication?

From Betina Lew to Everyone: 09:36 AM

How can we lobby to influence other geographies ?

From Ron Hines to Everyone: 09:38 AM

To move away from a "yes/no" and "check-box" approach, need to move to probabilistic-based risk assessment.

From Thomas Hartung to Everyone: 09:38 AM

I fully agree with Ron Hines comment

From Jayadev Raju to Everyone: 09:39 AM

@ Ron Hines, good point

From Monica to Everyone: 09:39 AM

Thank you Donna - exactly, challenges from internal first!

From Alison Bernstein to Everyone: 09:39 AM

The communication piece is critical to ensuring that people trust the process. There is already a narrative in the public space that regulations are NOT keeping us safe. A proactive communication plan and public facing messaging is important.

From Valentina Schiavone (ZeClinics) Spain to Everyone: 09:39 AM

Thanks for all your interesting inputs. Respect what was mentioned before. We work with Zebrafish. The problem is solved doing GOOD SCIENCE and applying ETHICS. The first thing we have to do as scientists, it is to be realistic on the power of our alternative model. Anyway the integrated systems (several in vitro models) could partially solve this problem.

From Stephen Dertinger to Everyone: 09:41 AM

Articulated performance standards rather than lengthy OECD process...

From Ron Hines to Everyone: 09:41 AM

Also agree with George Daston's point, i.e., consider NAMs in more of a hypothesis view, rather than always considering as a replacement. If truly fit for purpose, does the NAM answer the question? But then, the problem with legislation. For example, TSCA reform in US states NAMs can be used "if the results are as good as or better than animal testing", thus legislating the comparison.

From Susan Emeigh Hart to Everyone: 09:42 AM

No argument here that safety evaluation should be more hypothesis/data/science driven -- the issue is how that can be "codified". Regulations by nature are "checkbox" driven (it's a lot easier) -- so the question becomes finding the right balance between the flexible and the rigid approach.

From Jayadev Raju to Everyone: 09:43 AM

Its hard to move away from the current risk assessment unless the regulatory process is redefined.

From PJ Devine to Everyone: 09:43 AM

I like George Daston's point that we shouldn't think about replacing in vivo studies with in vitro methods 1 for 1, but rather think about different ways of testing for safety. Also we cannot start from scratch but have to prove that the new strategies are better than what we have now. "Catching up" with in vivo data for NAMs/MPS validation will take a bit of time. Best use may be new therapeutic modalities where current in vivo testing is not relevant or useful.

From Amaia Irizar to Everyone: 09:43 AM

Probabilistic based risk assessment is right, the challenge is about how to communicate the output. Society feels comfortable with a checkbox approach that they believe has covered the key points and these have come up clean. Look at the example of the tendency for hazard based policy as opposed to risk assessment in the EU

From Karen Davis Bruno to Everyone: 09:47 AM

FDA does not box check. Data is necessary to support safety for first in human dosing!

Is there a MPS that recapitulates the complex physiological interactions present in vivo?

From Judy Strickland to Everyone: 09:48 AM

I agree that hazard assessment is a good way to start. In our survey of acute systemic toxicity needs of regulatory agencies in eight countries or regions, hazard assessment was the most frequent use (as compared to risk assessment, setting exposure levels, etc. ).

From Karen Davis Bruno to Everyone: 09:51 AM

How do you equate a tissue concentration to a plasma level per route (AUC)?

From Valentina Schiavone (ZeClinics) Spain to Everyone: 09:51 AM

Come to the workshop session (OECD Expert Group) on 18th March.. to continue the conversation that Dr. Bob van de Water opened! Any feedback is important!

From Amy Babcock to Everyone: 09:52 AM

Every regulator I know (local, state, and federal) is a scientist. Legislators, however, usually are not. The overlap between the science and the law is poorly understood (on both sides). If we focus on good science and can explain underlying biology, assumptions, unknowns, it will be a start in bridging the gap.

From Jayadev Raju to Everyone: 09:52 AM

Thank you Valentina, will do.

From Vivek Mathrani to Everyone: 09:55 AM

It's important for NAM validation and the objectivity of its implications to be developed. However, the results will be continued to be leveraged based on stakeholder values (to what extent the precautionary principle informs decision-making).

From Valentina Schiavone (ZeClinics) Spain to Everyone: 09:55 AM

Thank to you! We must join in a common effort!

From Mary Gilbert to Everyone: 09:56 AM

I agree with Dr. Mattes - hard to validate against humans in absence of human data. Animal database is rich and should be used

From Jayadev Raju to Everyone: 09:57 AM

Animal data is data rich indeed! Thank you @William Mattes

From Betina Lew to Everyone: 09:58 AM

should we have another webinar to keep the discussion going outside of the annual meeting?

From Vivek Mathrani to Everyone: 09:58 AM

Fantastic discussion. We could do this all week.

From Kathryn Page to Everyone: 09:58 AM

Agreed

From Jayadev Raju to Everyone: 09:59 AM

Absolutely Betina

From Rose-Marie Jenvert to Everyone: 09:59 AM

The problem if you use animal data as a reference this that this does not always reflect the human response. A very good example is nickel allergy were LLNA classify nickel as a non-sensitizers and we all know that nickel is known a skin sensitizer in humans.

From Me to Emanuela Corsini: (Direct Message) 10:00 AM

IUTOX could certainly host a quarterly panel

From Stephen Dertinger to Everyone: 10:00 AM

Devil you know aspect is something you'll continue to deal with...

From William Mattes to Everyone: 10:01 AM

I agree about situations where there is NOT an animal model for a human response.

From Jayadev Raju to Everyone: 10:01 AM

Rose-Marie, there will always be challenges for specific cases, predictive animal data cannot be discounted.

From William Mattes to Everyone: 10:02 AM

I'm always reminded about "nausea": rats don't vomit and dogs vomit all the time.

From Jayadev Raju to Everyone: 10:02 AM

:) @William Mattes

From Kathryn Page to Everyone: 10:02 AM

For some endpoints we have the ability to use both validation against animal data, and explain any differences or challenges by using the mechanistic data

From Donna.Mendrick@fda.hhs.gov to Everyone: 10:03 AM

May I suggest that this session be written up for publication

From Betina Lew to Everyone: 10:04 AM

that is a great idea Donna

From Me to Everyone: 10:04 AM

Donna Mendrick, the chat will be documented, and I will work to get a transcription of the presentation

From Kelly Hanson, SRC Inc. to Everyone: 10:04 AM

Thank you @Rachel Frohberg!

From Mary Ellen Cosenza to Everyone: 10:04 AM

Great idea to publish this info.

From Maureen Gwinn to Everyone: 10:05 AM

@Donna great idea!

From Valentina Schiavone (ZeClinics) Spain to Everyone: 10:05 AM

In order to speed us the implementation, we should put more resources on that

From Martin Stephens to Everyone: 10:05 AM

Hi all. I've had noisy workmen here at the house during the session, so I haven't logged on live. My question: has the revolution in new methods engendered a reevaluation of the kinds of information we need to properly regulate chemicals? Do we need, to echo Warren's presentation, data that replicate in vivo studies with 45 cell types, etc., etc.? Or should we rethink what we really need?

From Idolan to Everyone: 10:13 AM

The in vitro assays need to be accepted as alternatives to an in vivo assay for the check the box activity. Assays that come to mind are the in vitro micronucleus test and the Ames test. In the food space, we generally do not have to do carcinogenicity tests in vivo if the results of these two tests are negative.

From Kathryn Page to Everyone: 10:13 AM

I think we can push ownership back to companies too; I know many in the consumer products industry vow to not do testing on animals where there are replacements available. However, I think regulators (and us all) need to do a better job of sharing what alternatives are available; I have seen recently where people are doing WAY more testing to meet regulatory data requirements that is necessary.

Unfortunately we don't have human data for all endpoints

As Fiona said earlier, it depends what endpoint you are talking about

From Sandra Coecke EC JRC to Everyone: 10:15 AM

Chemical's hazard and RA and global introduction of NAMs with confidence seems to be a difficult one..BUT look as mentioned by @ThomasHartung... look at the boost of NAMs in SARS-CoV-2 understanding of kinetics and dynamics. .there the mechanistic understanding has helped to look at elucidation of infection dynamics, target organ system effects, comparison with clinical features , understanding symptomatology, post-mortem pathology data, use of newest generation of in silico models in therapeutic interventions etc...interesting to see how UNDER PRESSURE NAMs were picked up and often not questioned but added to the gathering of understanding of the action of an external new stresser like SARS-CoV-2 ..a miracle indeed happened in our back yard...

From Amaia Irizar to Everyone: 10:15 AM

There are two parts in the 'validation' discussion, one is actually looking a specific assay or method measuring an endpoint that the OECD has been doing. The other is how to use several methods together to actually try to answer what a complex endpoint previously addressed by a bioassay (RT-dev-repro) by looking at AOPs. What is the best forum to 'validate' these new approaches for complex endpoints if OECD is not sufficient?

From Monica to Everyone: 10:16 AM

On future meetings, I encourage more case studies - not only success but not so successful cases - across test materials and endpoints. Theoretically we all agree moving away from in vivo, but tangible examples will allow reduce anxiety

From jackfowle to Everyone: 10:19 AM

Warrens your comments are spot on!

From Kathryn Page to Everyone: 10:19 AM

Great idea Monica. I will try to get something on the calendar through IVAM

From Babasaheb Sonawane to Everyone: 10:20 AM

I like Betina's suggestion to have another webinar.

From Stefan Pfuhler to Everyone: 10:22 AM

Agree with Warren - Hazard ID based regulation could be an impediment to implementation of NAM. We start seeing a push to do Classification based on in-vitro-only data, and that goes in the way of the use that Thomas has emphasized - Haz ID as first screen

From Jayadev Raju to Everyone: 10:24 AM

Good point @ Donna Mendrick

From Kathryn Page to Everyone: 10:26 AM

Re-emphasizing what many have already said, that some of the "fall back" onto animal testing is that its easy (check box). NAMs requires us to think about what studies we are doing and why each time. This means that we really need an emphasis on education to show all options available and how to use.

I like the idea of a meeting with case studies and discussion; I will try to get something set up through SOT IVAM

From Monica to Everyone: 10:28 AM

One comment - as we move away from animal testing, we should expand our interaction and collaboration with clinical research community; so far, we mostly work in silo

From Monica to Everyone: 10:28 AM

One comment - as we move away from animal testing, we should expand our interaction and collaboration with clinical research community; so far, we mostly work in silo

From Me to Encore Tech: (Direct Message) 10:28 AM

thank you!

From Maureen Gwinn to Everyone: 10:28 AM

Thank you. Great points from all, and great discussion.

From Me to Encore Tech: (Direct Message) 10:29 AM

next slide

back one

Thank you :)

From Vivek Mathrani to Everyone: 10:29 AM

Thanks for chairing, Emanuela. Great discussion.

From Sandra Coecke EC JRC to Everyone: 10:29 AM

thank you all..such an inspiring session of hope to keep #going #growing & # challenging together

From Jana Iscla to Everyone: 10:30 AM

Thanks to everyone, it was a great discussion

From Jayadev Raju to Everyone: 10:30 AM

Good to see everyone of you, miss seeing and listening to you in person. But thank you for this exciting session

From Rose-Marie Jenvert to Everyone: 10:30 AM

Thank you all for sharing your knowledge and for the great discussions!

From Sue Leary to Everyone: 10:30 AM

Thank you all; appreciate the direct discussion. Inspired!

From Betina Lew to Everyone: 10:30 AM

thanks Emanuela for chairing and moderating the debate

From Jayadev Raju to Everyone: 10:30 AM

Thank you Emanuela

From Valentina Schiavone (ZeClinics) Spain to Everyone: 10:30 AM

Thanks!

From Jochem Louisse to Everyone: 10:30 AM

thanks!