Developing An International Horizon Scanning Approach

Carlie LaLone, Ph.D.
Research Bioinformaticist
U.S. Environmental Protection Agency

SETAC Pellston Workshop Series

- Named for the UM Biological Station in Pellston, MI where the 1st Pellston Workshop took place in 1977
- **High visibility topics/challenges in environmental sciences/regulation, often international in scope**
- Attendance by invitation only; typically 40-50 experts representing the tripartite nature of SETAC
- "Sequestered" setting with long hours discussing/writing
- Usually 4-5 topic-oriented workgroups, each producing a chapter/journal article
- **Selection of topics typically made by Steering Committee, but this can limit scope for broad issues**

Evolution of the Adverse Outcome Pathway Conceptual Framework

2007 — *National Research Council Report "Toxicity Testing in the 21st Century: a Vision and a Strategy"*

2009 — *Pellston Workshop "A Vision and Strategy for Predictive Ecotoxicology in the 21st Century"*

2010 — *Initial Publication describing the AOP Framework by Ankley et al. (Environ. Toxicol. Chem. 29:730-741).*

2012 — *The Organisation of Economic Cooperation and Development launches international AOP development programme.*

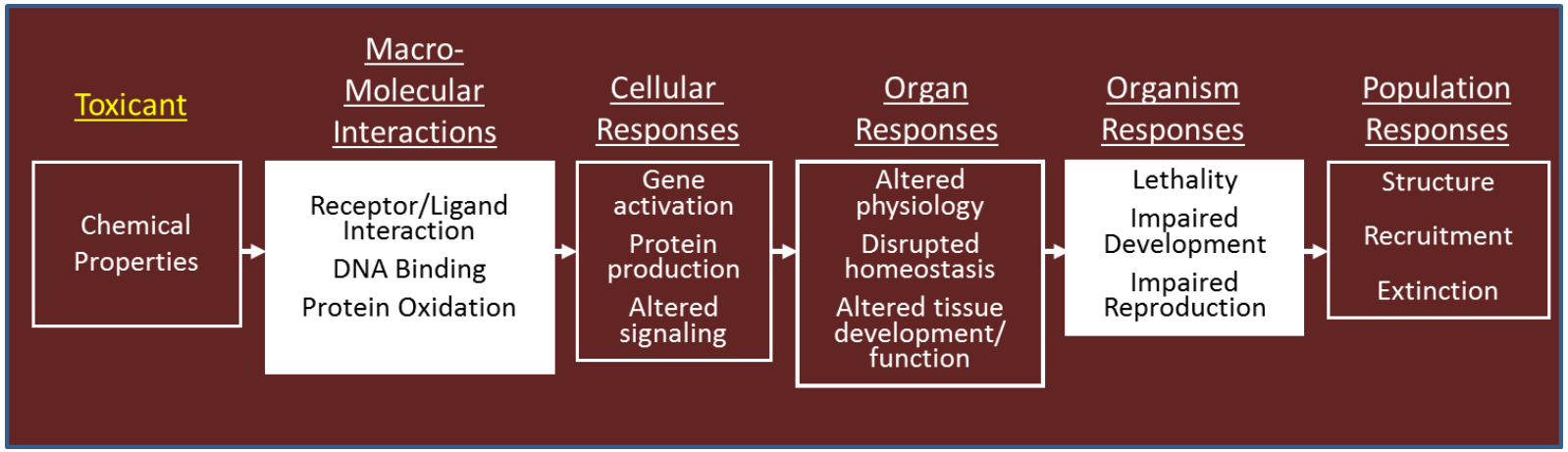
2013 — *The Organisation of Economic Cooperation and Development Publication "Guidance Document on Developing and Assessing AOPs"*

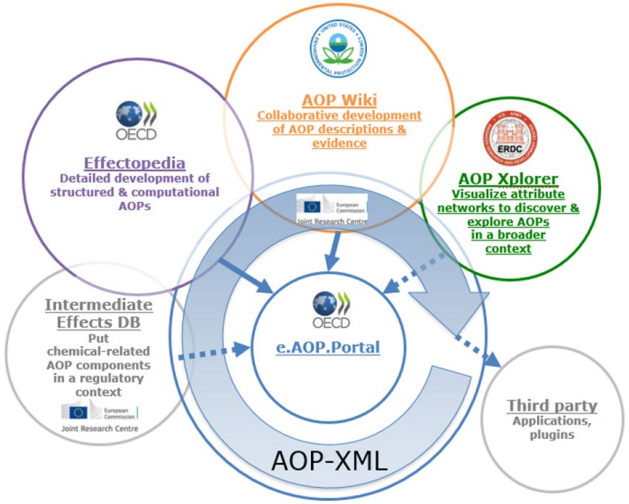
2014 — *Release of the AOP Wiki*

Soma Lombardo Workshop: "Advancing AOPs For Integrated Toxicology and Regulatory Applications"

2015 — *Joint Research Centre, Ispra Workshop: "AOP-informed predictive modeling approaches for regulatory toxicology"*

An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome, at a level of biological organization relevant to risk assessment.
(Ankley et al. 2010. Environ. Toxicol. Chem., 29(3): 730-741.)





Users' handbook supplement to OECD guidance document for developing and assessing AOPs.

Relatively small community guiding the direction of the AOP framework

Horizon Scanning!!

Horizon Scanning

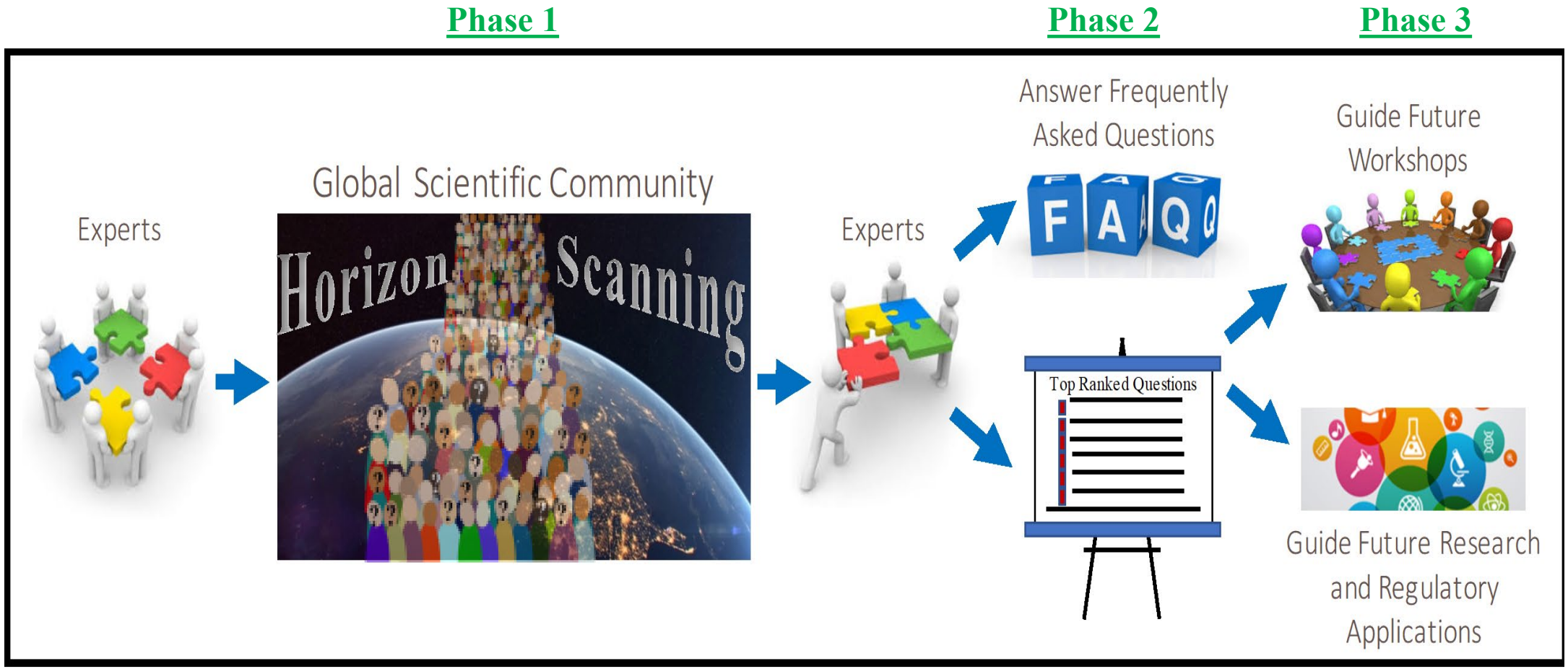
- Horizon scanning—**a method of systematically searching for and identifying emerging trends, opportunities, and limitations that might impact the future directions of a defined subject**
- Provides an opportunity to expand **input from few contributors to many**
- At a finer scale, research identification and prioritization exercises have been used to **identify important and actionable research questions** that can help align scientific effort with policy priorities

Example of Success:

Boxall, A.B., Rudd, M.A., Brooks, B.W., Caldwell, D.J., Choi, K., Hickmann, S., Innes, E., Ostapyk, K., Staveley, J.P., Verslycke, T. and Ankley, G.T., 2012. Pharmaceuticals and personal care products in the environment: what are the big questions?. *Environmental health perspectives*, *120*(9), pp.1221-1229.

Cited 997 times!!!!!

Setting the Stage for the Pellston Workshop



Adverse Outcome Pathways

What Outstanding Challenges Must Be Addressed?

The Society of Environmental Toxicology and Chemistry (SETAC) is initiating Horizon Scanning effort chaired by Drs. Carlie LaLone and Markus Hecker to advance the science and application of the Adverse Outcome Pathway framework. For further information, click here.

This initiative was proposed and approved as a first step in developing themes for an upcoming SETAC Pellston Workshop: **Advancing the Adverse Outcome Pathway Concept – An International Horizon Scanning Approach**.

In this survey we ask you to **please propose questions that consider key outstanding challenges or limitations that must be addressed in order to realize the full potential of the adverse outcome pathway framework in research and regulatory decision making**. Please consider developing questions pertinent to your field, sector, and/or geographic location.

We recommend that you submit your questions using a **computer keyboard or tablet**, rather than smart phone.

Click below to proceed and submit your questions.

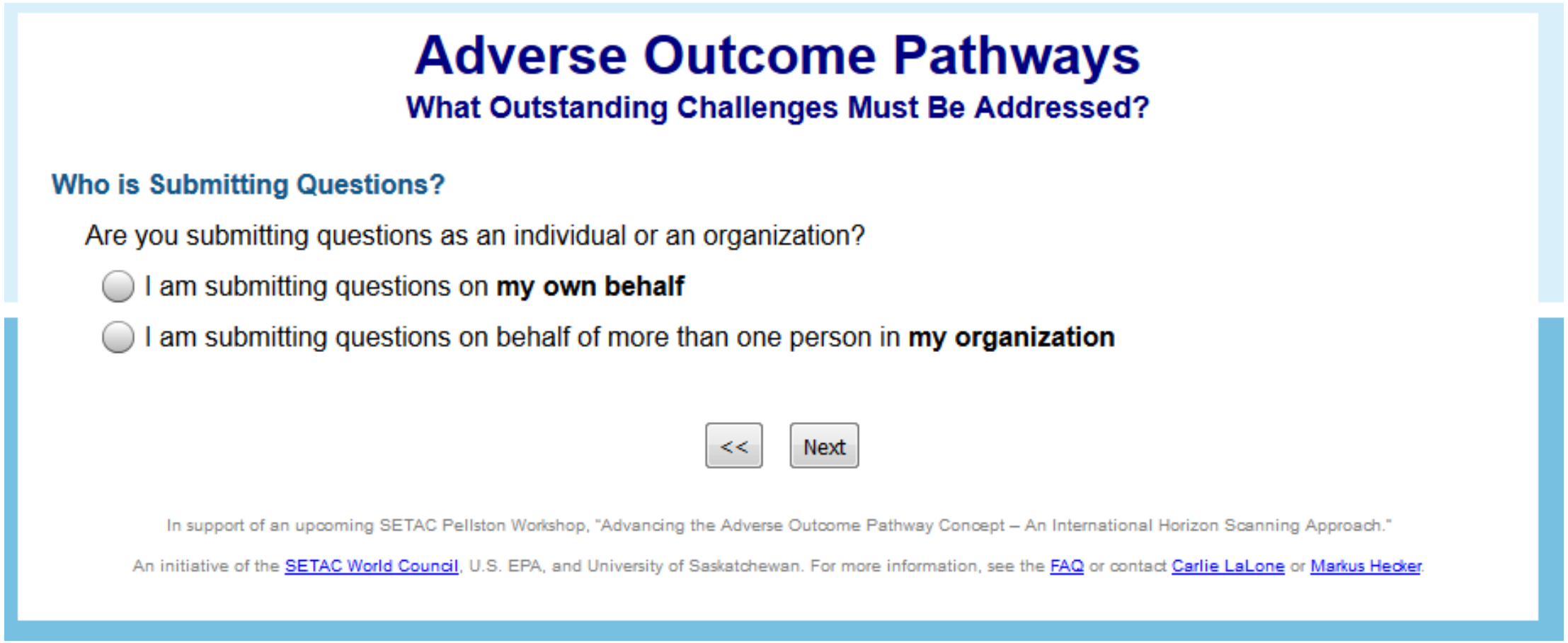
Open March 7th-June 30th 2016

Next

In support of an upcoming SETAC Pellston Workshop, "Advancing the Adverse Outcome Pathway Concept – An International Horizon Scanning Approach."

An initiative of the SETAC World Council, U.S. EPA, and University of Saskatchewan. For more information, see the FAQ or contact Carlie LaLone or Markus Hecker.

Intro page with links to key information



411 accessed the website
147 individual submissions
11 group submissions

Adverse Outcome Pathways

What Outstanding Challenges Must Be Addressed?

Requested Information

Which sector do you work in?

- [ ] Academia (faculty)
- [ ] Academia (staff)
- [ ] Academia (student)
- [ ] Government (research)
- [ ] Government (management/policy)
- [ ] Industry (consulting)
- [ ] Industry (manufacturing)
- [ ] Industry (other)
- [ ] Non-governmental organization
- [ ] Other (please specify)

In which country do you live?

- ( ) Afghanistan
- ( ) Akrotiri
- ( ) Albania
- ( ) Algeria
- ( ) American Samoa
- ( ) Andorra
- ( ) Angola
- ( ) Anguilla
- ( ) Antarctica
- ( ) Antigua and Barbuda
- ( ) Argentina
- ( ) Armenia
- ( ) Aruba
- ( ) Ashmore and Cartier Islands
- ( ) Australia
- ( ) Austria
- ( ) Azerbaijan
- ( ) Bahamas, The
- ( ) Bahrain
- ( ) Bangladesh
- ( ) Gambia, The
- ( ) Gaza Strip
- ( ) Georgia
- ( ) Germany
- ( ) Ghana
- ( ) Gibraltar
- ( ) Glorioso Islands
- ( ) Greece
- ( ) Greenland
- ( ) Grenada
- ( ) Guadeloupe
- ( ) Guam
- ( ) Guatemala
- ( ) Guernsey
- ( ) Guinea
- ( ) Guinea-Bissau
- ( ) Guyana
- ( ) Haiti
- ( ) Heard Island and McDonald Islands
- ( ) Holy See (Vatican City)
- ( ) Niue
- ( ) Norfolk Island
- ( ) Northern Mariana Islands
- ( ) Norway
- ( ) Oman
- ( ) Pakistan
- ( ) Palau
- ( ) Panama
- ( ) Papua New Guinea
- ( ) Paracel Islands
- ( ) Paraguay
- ( ) Peru
- ( ) Philippines
- ( ) Pitcairn Islands
- ( ) Poland
- ( ) Portugal
- ( ) Puerto Rico
- ( ) Qatar
- ( ) Reunion
- ( ) Romania
- ( ) Russia

Put most valuable information we wanted to collect prior to the main question collection page

Adverse Outcome Pathways

What Outstanding Challenges Must Be Addressed?

Submit a Question

Please propose questions that consider **key outstanding challenges or limitations that must be addressed in order to realize the full potential of the adverse outcome pathway framework** in research and regulatory decision making.

Consider developing questions pertinent to your field, sector, and/or geographic location.

Question Criteria:

- Address important knowledge gaps
- Factual answer that does not depend on value judgement
- Cover a spatial and temporal scale that realistically can be addressed by expert groups
- Cannot be answered by "yes," "no," or "it all depends" answers

Please limit the question itself to 300 characters.

If you would like to provide rationale for your question or references (to 3000 characters) please use the space below.

You can submit up to a total of 20 candidate questions. Would you like to submit another question?

Yes No

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340 questions

This was helpful and many did provide rationale

Adverse Outcome Pathways

What Outstanding Challenges Must Be Addressed?

Requested Information

How long have you worked in fields related to toxicology?

- ◯ 5 years or less
- ◯ 6 to 10 years
- ◯ 11 to 20 years
- ◯ 21 to 30 years
- ◯ More than 30 years
- ◯ Not applicable

Please select your area of primary expertise.

- ☐ Aquatic toxicology
- ☐ Aquatic ecology
- ☐ Terrestrial or wildlife toxicology
- ☐ Terrestrial or wildlife ecology
- ☐ Environmental or analytical chemistry
- ☐ Ecological risk assessment
- ☐ Human health risk assessment
- ☐ Human toxicology
- ☐ Risk management, risk communication, and/or science policy
- ☐ Other (please specify)

How many peer-reviewed journal articles have you published relevant to adverse outcome pathway framework? (does not specifically have to include AOP descriptions, but relevant to this body of work)

- ◯ 0 articles
- ◯ 1 to 2 articles
- ◯ 3 to 5 articles
- ◯ 6 to 10 articles
- ◯ 11 to 25 articles
- ◯ 26 to 50 articles
- ◯ 51 to 100 articles
- ◯ Over 100 articles

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Put least valuable information after the main question collection page in case the participant didn't finish the questionnaire

Adverse Outcome Pathways

What Outstanding Challenges Must Be Addressed?

Requested Information

Are you a member of these societies? (if you are active in others, please provide up to a maximum of 3)

- [ ] Society for Ecotoxicology and Chemistry (SETAC)
- [ ] Society of Toxicology (SOT)
- [ ] American Chemical Society (ACS)
- [ ] Other (please specify) _____
- [ ] Other (please specify) _____
- [ ] Other (please specify) _____

Are you a member of any SETAC advisory groups? Please check all that apply.

- [ ] Europe: Dung Organism Toxicity Testing
- [ ] Europe: Environmental Monitoring Advisory Group on Pesticides
- [ ] Europe: Extreme Stress Events and Ecosystem Recovery
- [ ] Europe: Mechanistic Effect Models for Ecological Risk Assessment of Chemicals
- [ ] Europe: REACH
- [ ] Global: Animal Alternatives in Environmental Science
- [ ] Global: Aquatic Macrophyte Ecotoxicology
- [ ] Global: Bioaccumulation Science
- [ ] Global: Ecological Risk Assessment
- [ ] Global: Ecosystem Services
- [ ] Global: Ecotoxicology of Amphibians and Reptiles
- [ ] Global: Endocrine Disruptor Testing and Risk Assessment
- [ ] Global: Exposure Modeling
- [ ] Global: Global Soils
- [ ] Global: Life Cycle Assessment (LCA) Global Coordinating Group
- [ ] Global: Metals
- [ ] Global: Nanotechnology
- [ ] Global: Pharmaceuticals
- [ ] Global: Sediments
- [ ] Global: Sustainability
- [ ] North America: Chemistry
- [ ] North America: Human Health Risk Assessment

<< Next

Adverse Outcome Pathways

What Outstanding Challenges Must Be Addressed?

Follow-Up

If you would like to be acknowledged for the questions you submitted, please provide your name and/or organization below. If you choose not to provide your name, your questions will be anonymous.

First Name:

Last Name:

Organization:

<< Next

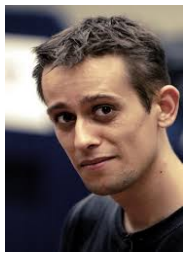
In support of an upcoming SETAC Pellston Workshop, "Advancing the Adverse Outcome Pathway Concept – An International Horizon Scanning Approach."

An initiative of the SETAC World Council, U.S. EPA, and University of Saskatchewan. For more information, see the FAQ or contact Carlie LaLone or Markus Hecker.

97 People provided their name

Steering Committee Reach out Personally to Network


Xiaowei Zhang
Nanjing University


Dries Knapen
University of Antwerp


Daniel Villeneuve
US EPA


Maurice Whelan
Joint Research Council


Edward Perkins
US Army


Scott Belanger
Procter and Gamble


Geoff Hodges
Unilever


Michelle Embry
HESI


Sharon Munn
Joint Research Council


Kate Willett
The Humane Society of the US

Workshop Co-chairs

Senior Advisor

Consultant

The Team


Carlie LaLone
US EPA


Markus Hecker
University of Saskatchewan


Greg Schiefer
SETAC


Nikki Mayo
SETAC


Tamar Schlekat
SETAC


Gerald Ankley
US EPA


Murray Rudd
Emory College

Advertise at professional meetings and through SETAC communications

- Globe Article
- Member email list
- SETAC News letter

WE NEED YOUR QUESTIONS TODAY!

WHAT QUESTIONS DO YOU HAVE ABOUT AOPS?
WHAT ARE THE CHALLENGES FOR THEIR APPLICATION?

Please take ~**5 minutes** and **submit** your thoughts via this **SETAC sponsored** survey:
https://AOP.sawtoothsoftware.com/login.html

Contact Carlie LaLone; LaLone.Carlie@epa.gov or Markus Hecker; Markus.hecker@usask.ca for details

Survey responses will guide an upcoming *SETAC Pellston Workshop* on AOPs

Join us in: Advancing the Adverse Outcome Pathway Concept – An International Horizon Scanning Approach

The Society for Environmental Toxicology and Chemistry (SETAC) is initiating a Horizon Scanning effort to advance the science and application of the Adverse Outcome Pathway (AOP) framework.

Objective:
To seek your participation in shaping the direction of the Adverse Outcome Pathway (AOP) Framework and its applications.

This Horizon Scanning approach will allow us to identify and begin to address recognized, on-going, and remaining issues relevant to the application of the AOP framework to chemical risk assessment in the context of both human and ecological health. Through **your participation,** as a member of the global scientific community, we ask that you:

Propose questions that consider key outstanding challenges or limitations that must be addressed in order to realize the full potential of the adverse outcome pathway framework in research and regulatory decision-making.

You can ***submit your questions*** using the following link (open March 7 – June 30, 2016):
https://AOP.sawtoothsoftware.com/login.html

Your questions are essential for developing themes to be addresses during an up-coming, expert-led, 2017 Pellston workshop. Workshop results will be publically disseminated in the form of publications and international presentations at professional meetings.

Background:
Regulatory agencies and industry worldwide are confronted with the challenging task of assessing the risks of thousands of chemicals to the environment and human health. Traditional toxicity testing strategies rely on whole animal studies, which, in addition to ethical concerns, are cost and time prohibitive. As a result, the utility of mechanistic-based approaches to support chemical safety evaluations have increasingly been explored. One approach that has gained traction for capturing available knowledge for describing the linkage between mechanistic data and apical toxicity endpoints required for regulatory assessments is the AOP framework (http://www.oecd.org/env/ehs/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm). A number of workshops and expert meetings held over the past years, however, illustrated the necessity of expert advice for moving the science of AOPs and their applications forward. This Horizon Scanning question solicitation effort is **your opportunity to have your voice heard** in the conversations surrounding the AOP framework and how it may be used, or could be better defined, for regulatory purposes.

We greatly appreciate your support of this initiative!

For further information please contact the co-chairs of this workshop, Dr. Carlie LaLone (lalone.carlie@epa.gov) and Dr. Markus Hecker (markus.hecker@usask.ca); Co-Chairs

Adverse Outcome Pathway (AOP) Horizon Scanning Effort

SETAC is holding a Horizon Scanning effort to advance the science and application of the AOP framework.

Please take ~5 minutes (prior to June 30th) and submit your thoughts via this survey:

https://AOP.sawtoothsoftware.com/login.html

The survey will prompt you to:

Propose questions that consider key outstanding challenges or limitations that must be addressed in order to realize the full potential of the adverse outcome pathway framework in research and regulatory decision-making.

In Promotion of the Horizon Scanning Effort:

Join one of the founders of the AOP Framework, **Dr. Gerald Ankley**, via **webinar** as he describes the evolution of the AOP construct from its origin to present day!!

Title: "Evolution of the AOP Framework as a Tool Supporting Chemical Risk Assessment In the 21st Century"

When: June 22nd, 2016

Time: 9:00 AM U.S. Central Standard Time Zone

Webinar: https://epawebconferencing.acms.com/med_seminar

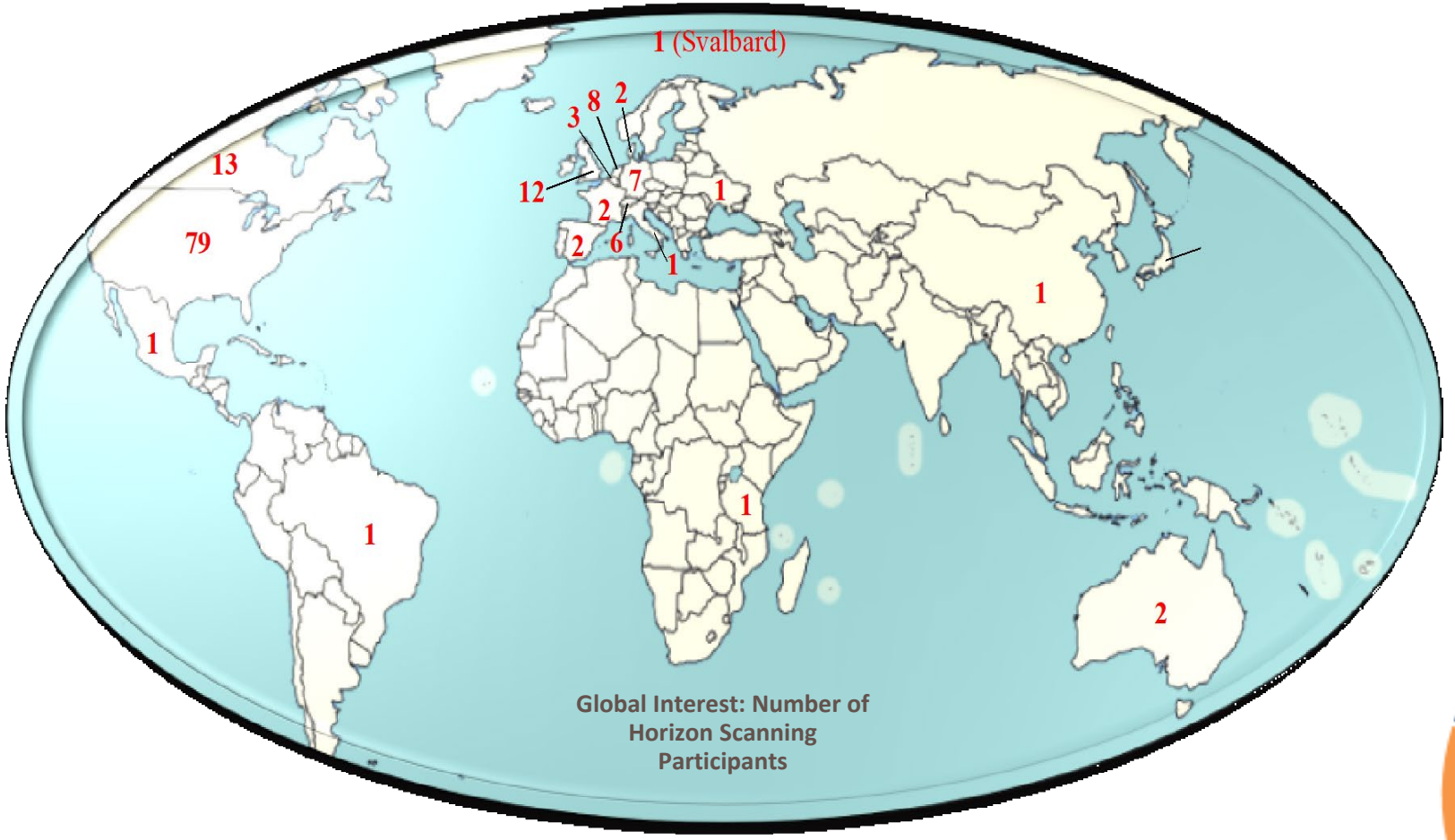
Enter as a Guest*

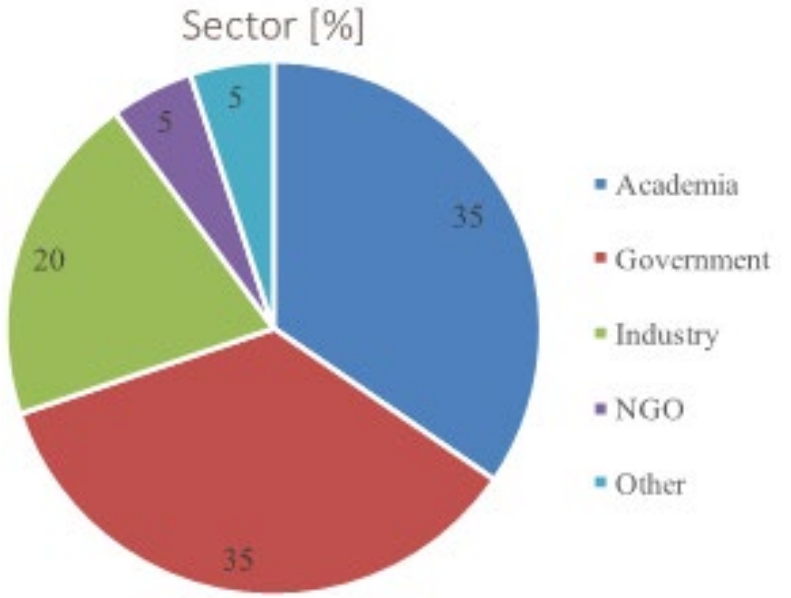
Conference line: 1-866-299-3188

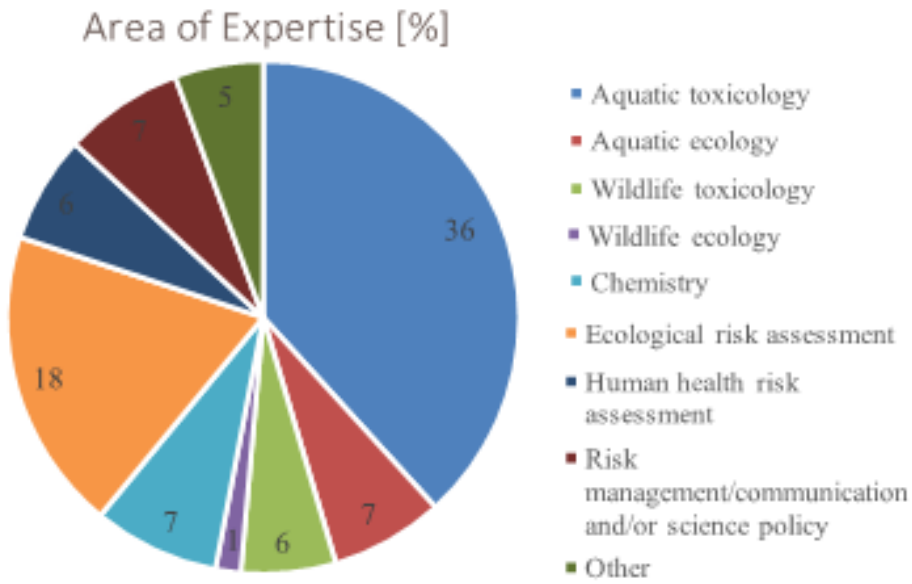
Conference code: 529 5035

Join Dr. Gerald Ankley via Webinar

Diversity of backgrounds: Participants by location, sector, and area of expertise







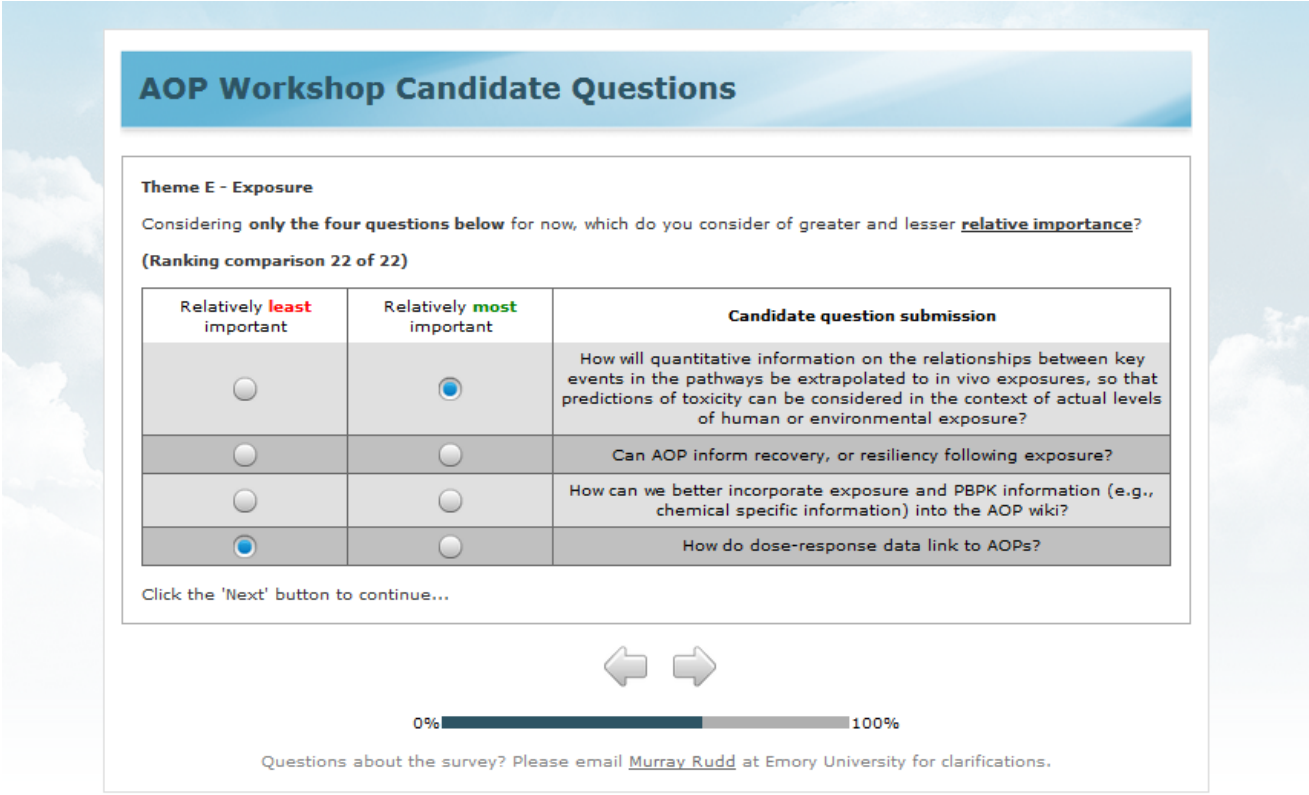
340 valid questions collected

Horizon Scanning to Expert Ranking/Prioritization Exercise

Best-Worst Ranking Exercise

Phase 2: Theme Development

Steering Committee rank and prioritize questions

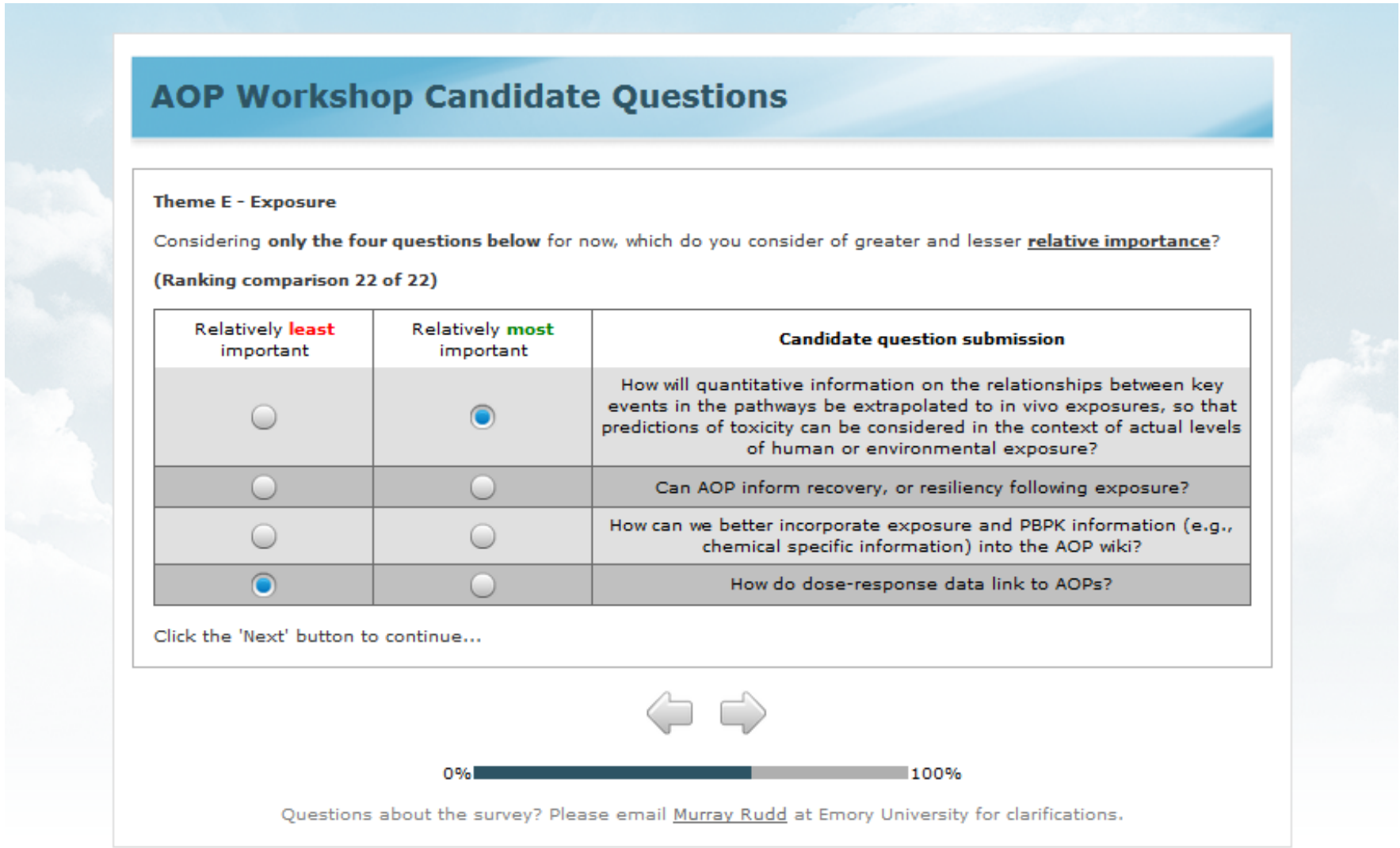


Developed broad topics for ranking exercise

1. AOP networks
2. qAOP
3. Collaboration and communication of AOPs
4. AOP discovery and development
5. Extrapolation
6. Exposure/toxicokinetics considerations
7. Application of AOPs

Removed questions that could be readily answered by an expert familiar with the AOP construct

Best-Worst Ranking Exercise – Steering Committee



AOP Workshop Candidate Questions

Theme E - Exposure

Considering **only the four questions below** for now, which do you consider of greater and lesser **relative importance**?

(Ranking comparison 22 of 22)

Relatively **least** important	Relatively **most** important	**Candidate question submission**
○	●	How will quantitative information on the relationships between key events in the pathways be extrapolated to in vivo exposures, so that predictions of toxicity can be considered in the context of actual levels of human or environmental exposure?
○	○	Can AOP inform recovery, or resiliency following exposure?
○	○	How can we better incorporate exposure and PBPK information (e.g., chemical specific information) into the AOP wiki?
●	○	How do dose-response data link to AOPs?

Click the 'Next' button to continue...

0% 100%

Questions about the survey? Please email Murray Rudd at Emory University for clarifications.

Challenge to get all Steering committee to participate

Output from Best-Worst Ranking Exercise

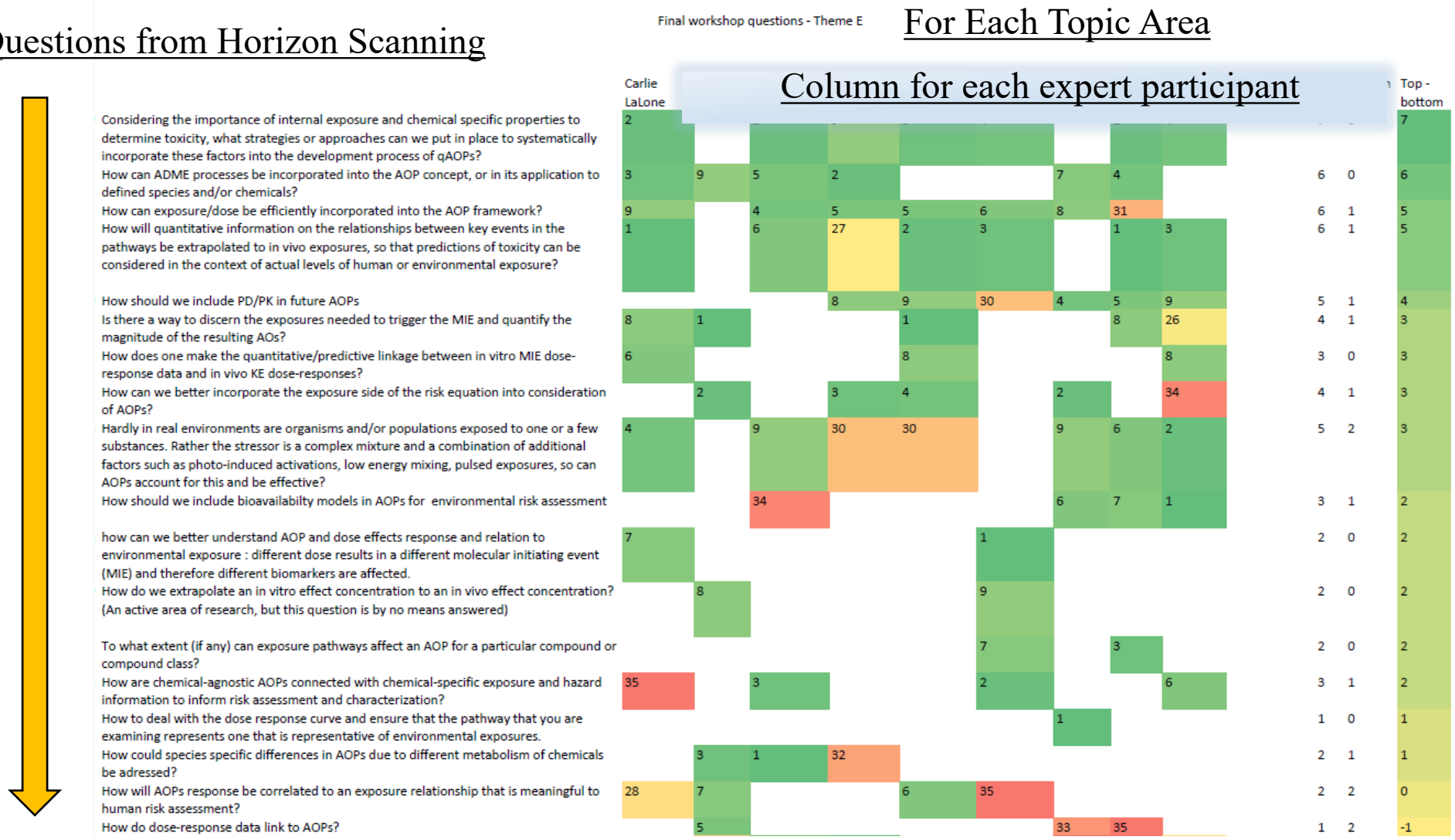
Questions from Horizon Scanning

For Each Topic Area

Column for each expert participant

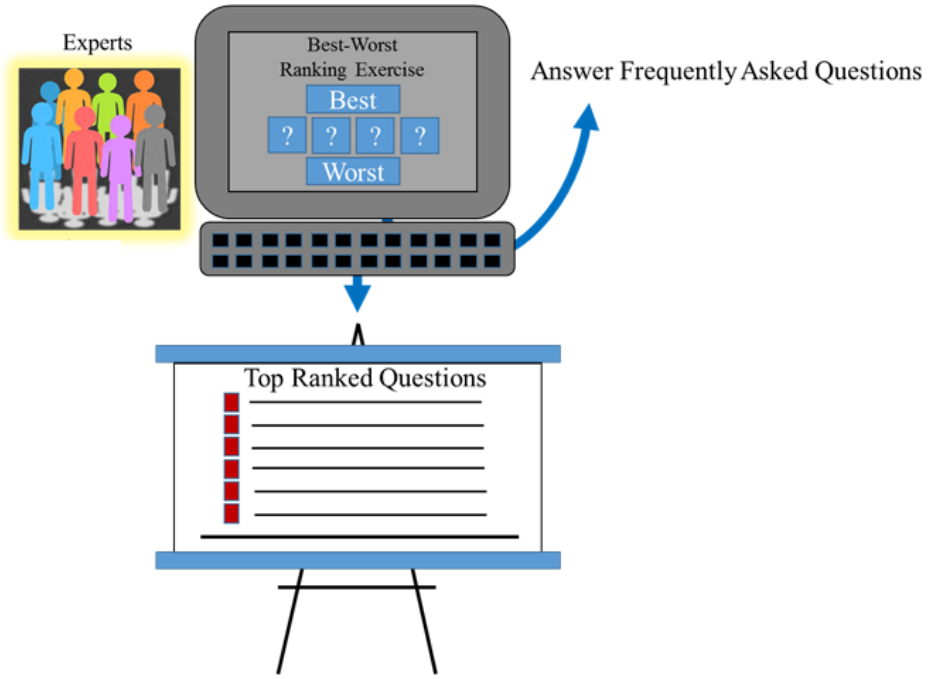
Highest Ranked

Lowest Ranked



Initial Question Categorization

- Developed broad topics to bin questions for ranking exercise
  1. AOP networks
  2. qAOP
  3. Collaboration and communication of AOPs
  4. AOP discovery and development
  5. Extrapolation
  6. Exposure/toxicokinetics considerations
  7. Application of AOPs



- Removed questions that could be readily answered by an expert familiar with the AOP construct – Included and answered in overview manuscript**: Advancing the Adverse Outcome Pathway Framework – An international Horizon Scanning Approach** (2017) Environmental Toxicology and Chemistry
  - Example: What is the origin of the AOP framework? Has the concept been peer reviewed? Is there potential profit for the concept proposers? How does the concept differ from established, peer-reviewed concepts of adverse effects? Does the concept include possibilities of beneficial outcomes?

In This Issue:

ET&C FOCUS

Focus articles are part of a regular series intended to sharpen understanding of current and emerging topics of interest to the scientific community.

Advancing the Adverse Outcome Pathway Framework—An International Horizon Scanning Approach

Carlie A. LaLone,[a,*] Gerald T. Ankley,[b] Scott E. Belanger,[b] Michelle R. Embry,[c] Geoff Hodges,[d] Dries Knapen,[e] Sharon Munn,[f] Edward J. Perkins,[g] Murray A. Rudd,[g] Daniel L. Villeneuve,[a] Maurice Whelan,[f] Catherine Willett,[i] Xiaowei Zhang,[j] and Markus Hecker[k,*]

Sessions at Professional Meetings:

- Session at the 2017 SETAC NA meeting in Minneapolis
- Session at the 2018 SOT meeting in San Antonio
- Session at the 2018 SETAC Europe meeting in Rome
- Session at the 2018 SETAC Asia Pacific meeting in Daegu

Publications:

LaLone, C.A., Ankley, G.T., Belanger, S.E., Embry, M.R., Hodges, G., Knapen, D., Munn, S., Perkins, E.J., Rudd, M.A., Villeneuve, D.L. and Whelan, M., 2017. Advancing the adverse outcome pathway framework—An international horizon scanning approach. *Environmental toxicology and chemistry*, *36*(6), pp.1411-1421.

Knapen, D., Angrish, M.M., Fortin, M.C., Katsiadaki, I., Leonard, M., Margiotta-Casaluci, L., Munn, S., O'Brien, J.M., Pollesch, N., Smith, L.C. and Zhang, X., 2018. Adverse outcome pathway networks I: development and applications. *Environmental toxicology and chemistry*, *37*(6), pp.1723-1733.

Villeneuve, D.L., Angrish, M.M., Fortin, M.C., Katsiadaki, I., Leonard, M., Margiotta-Casaluci, L., Munn, S., O'brien, J.M., Pollesch, N.L., Smith, L.C. and Zhang, X., 2018. Adverse outcome pathway networks II: network analytics. *Environmental toxicology and chemistry*, *37*(6), pp.1734-1748.

Pollesch, N.L., Villeneuve, D.L. and O'Brien, J.M., 2019. Extracting and benchmarking emerging adverse outcome pathway knowledge. *Toxicological Sciences*, *168*(2), pp.349-364.

Perkins, E.J., Ashauer, R., Burgoon, L., Conolly, R., Landesmann, B., Mackay, C., Murphy, C.A., Pollesch, N., Wheeler, J.R., Zupanic, A. and Scholz, S., 2019. Building and applying quantitative adverse outcome pathway models for chemical hazard and risk assessment. *Environmental toxicology and chemistry*, *38*(9), pp.1850-1865.

Coady, K., Browne, P., Embry, M., Hill, T., Leinala, E., Steeger, T., Maślankiewicz, L. and Hutchinson, T., 2019. When are adverse outcome pathways and associated assays "fit for purpose" for regulatory decision-making and management of chemicals?. *Integrated environmental assessment and management*, *15*(4), pp.633-647.

Carusi, A., Davies, M.R., De Grandis, G., Escher, B.I., Hodges, G., Leung, K.M., Whelan, M., Willett, C. and Ankley, G.T., 2018. Harvesting the promise of AOPs: An assessment and recommendations. *Science of the Total Environment*, *628*, pp.1542-1556.

Hecker, M. and LaLone, C.A., 2019. Adverse outcome pathways: moving from a scientific concept to an internationally accepted framework. *Environmental toxicology and chemistry*, *38*(6), pp.1152-1163.

Workshops:

- Science with impact in an era of information overload (June 2021)

Theme (Workgroup) 1: Adverse outcome pathway networks and their applications

Name	Sector	Location
Dries Knapen (leader)	Academia	Belgium
Dan Villeneuve (leader)	Government	US
Sharon Munn	Government	EU
Xiaowei Zhang	Academia	China
Jason O'Brien	Government	Canada
Ioanna Katsiadaki	Government	UK
Luigi Margiotta-Casaluci	Academia	UK
Marc Leonard	Industry	France
Marie Fortin	Industry	US
Michelle Angrish	Postdoc	US
L. Cody Smith	Grad Student	US

Theme (Workgroup) 2: Quantitative adverse outcome pathways and their applications

Name	Sector	Location
Stefan Scholz (leader)	Academia	EU
Ed Perkins (leader)	Government	US
Cameron Mackay	Industry	UK
Cheryl Murphy	Academia	US
Anze Zupanic	Academia	Switzerland
Brigitte Landesmann	Government	EU
Rory Conolly	Government	US
James Wheeler	Industry	UK
Roman Ashauer	Academia	UK
Nathan Pollesch	Postdoc	US

Theme (Workgroup) 3: Regulatory use of the adverse outcome pathway framework

Name	Sector	Location
Katie Coady (leader)	Industry	US
Patience Browne (leader)	OECD	EU
Michelle Embry	Industry	US
Tom Steeger	Government	US
Lidka Wijkhuizen-Maslankiewicz	Government	EU
Eeva Leinala	OECD	EU
Tom Hutchinson	Academia	UK
Thomas Hill	Postdoc	US

Theme (Workgroup) 4: Roadmap to expand awareness of, involvement in, and application of the AOP framework and AOP knowledgebase in the broader scientific and regulatory/environmental policy communities

Name	Sector	Location
Annamaria Carusi (leader)	Academia	UK
Gary Ankley (leader)	Government	US
Maurice Whelan	Government	EU
Kate Willett	NGO	US
Geoff Hodges	Industry	UK
Kenny Leung	Academia	Hong Kong
Beate Escher	Academia	EU
Mark Davies	Industry	UK
Giovanni De Grandis	Postdoc	EU