

Putting SEURAT-1 in an International Context



SEURAT-1 Symposium
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The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

Shared Overall Goal



ToxCast/Tox21 and SEURAT share an overall goal of intelligent integration of new computational and experimental approaches for assessing chemical safety

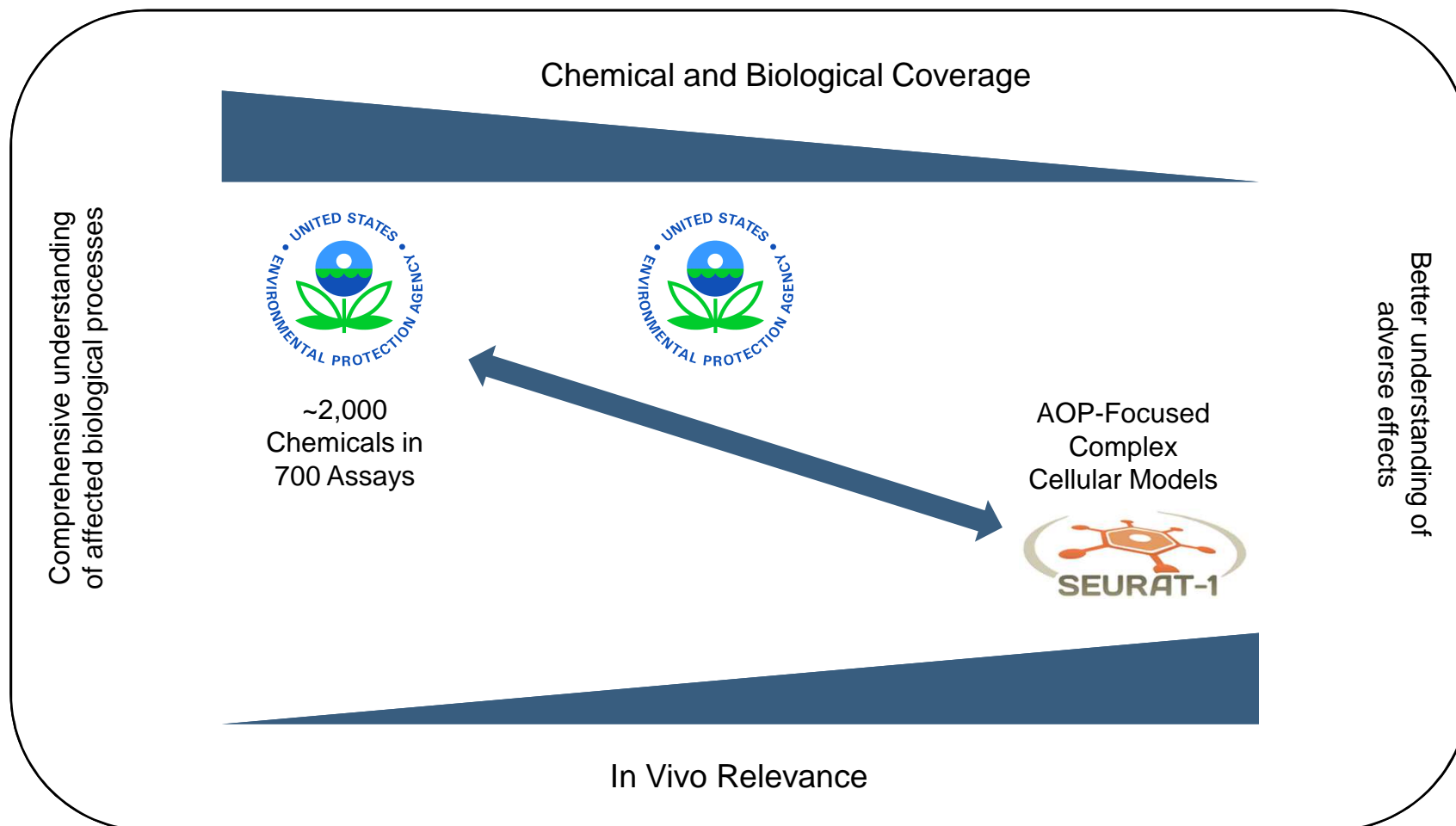
- ~~Identify every chemical potential~~ human *in vivo* toxicity
- ~~Knowledge of~~ mode-of-action
- ~~Quantitative understanding of adverse response,~~
~~with associated uncertainty and variability~~ how much
does that amount change between people,
lifestages, etc.

But, Also Different Objectives



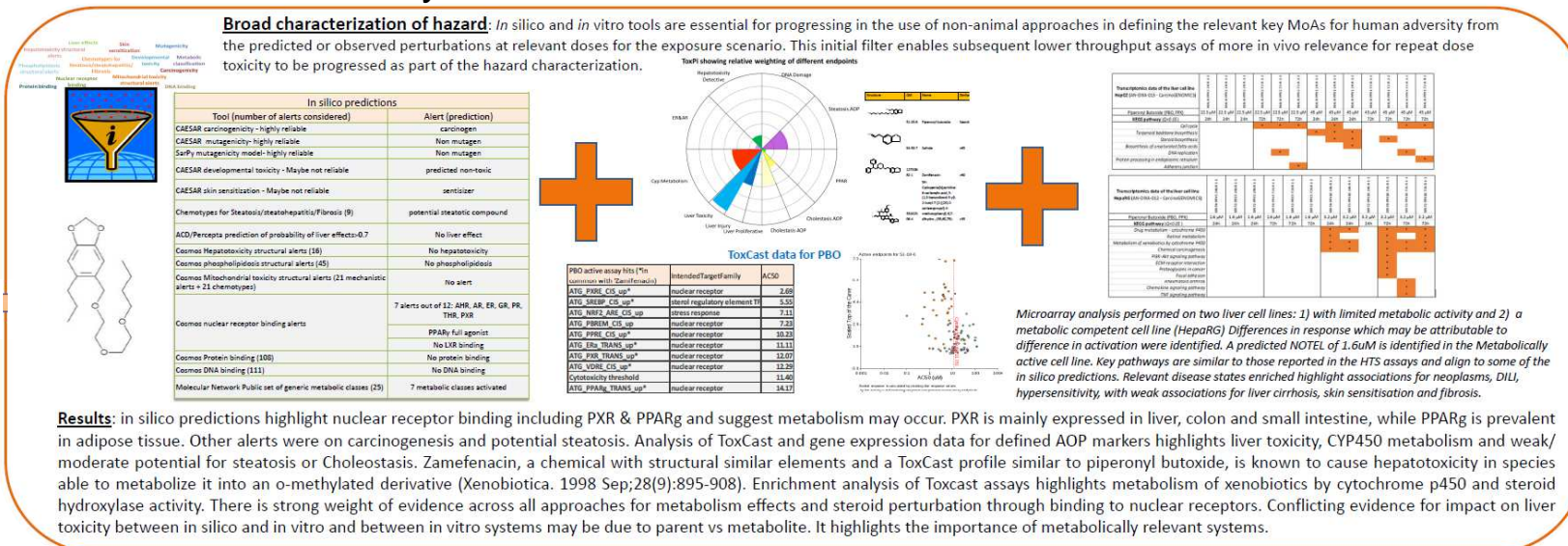
- SEURAT primarily focused on non-animal replacements for repeat dose systemic toxicity, while ToxCast/Tox21 has broader objectives that include other endpoints (e.g., cancer, repro) and regulatory decision contexts (e.g., chemical prioritization)
- SEURAT was inspired by the needs and chemistries of the cosmetics industry, while ToxCast/Tox21 serves a broader chemical and regulatory spectrum
- SEURAT operates in a region with hazard-centric chemical assessments, while ToxCast/Tox21 operates in a risk-based regulatory environment

Complementary Approaches to Assay Development and Testing



Integration of ToxCast and SEURAT Data in Case Studies

Ab Initio Case Study



Read Across Case Study

Review

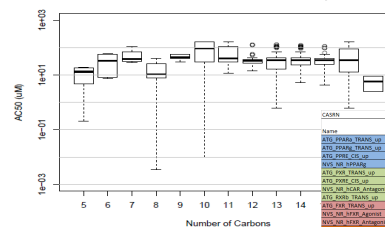
A Section 508-conformant HTML version of this article is available at <http://dx.doi.org/10.1289/ehp.1409342>.

Chemical Safety Assessment Using Read-Across: Assessing the Use of Novel Testing Methods to Strengthen the Evidence Base for Decision Making

Elisabet Berggren,¹ Patric Amcoff,² Romualdo Benigni,³ Karen Blackburn,⁴ Edvard Carney,⁵ Mark Cronin,⁶ Hubert Deluyker,⁷ Francoise Gautier,⁸ Richard S. Judson,⁹ Georges E.N. Kass,⁷ Detlef Keller,¹⁰ Derek Knight,¹¹ Werner Lilienblum,¹² Catherine Mahony,¹³ Ivan Rusyn,¹⁴ Terry Schultz,¹⁵ Michael Schwarz,¹⁶ Gerrit Schüürmann,^{17,18} Andrew White,¹⁹ Julien Burton,¹ Alfonso M. Lostia,¹ Sharon Munn,¹ and Andrew Worth¹

¹Joint Research Centre, European Commission, Ispra, Italy; ²Cosmetics Europe, Brussels, Belgium; ³OECD (Organisation for Economic Co-operation and Development), Paris, France; ⁴Procter & Gamble, Cincinnati, Ohio, USA; ⁵The Dow Chemical Company, Midland, Michigan, USA; ⁶Liverpool John Moores University, Liverpool, United Kingdom; ⁷EFSA (European Food Safety Authority), Parma, Italy; ⁸Oréal, Asnières-sur-Seine, France; ⁹U.S. Environmental Protection Agency, Washington, DC, USA; ¹⁰Henkel AG & Co, Düsseldorf, Germany; ¹¹ECOA (European Chemicals Agency), Helsinki, Finland; ¹²SCS (Scientific Committee on Consumer Safety), Luxembourg; ¹³Procter & Gamble, Egham, UK; ¹⁴Texas A&M University, College Station, Texas, USA; ¹⁵The University of Tennessee, Knoxville, Tennessee, USA; ¹⁶Tübingen University, Tübingen, Germany; ¹⁷Helmholtz Centre for Environmental Research, Leipzig, Germany; ¹⁸Institute for Organic Chemistry, Technical University Bergakademie Freiberg, Freiberg, Germany; ¹⁹Unilever PLC, Milton Keynes, United Kingdom

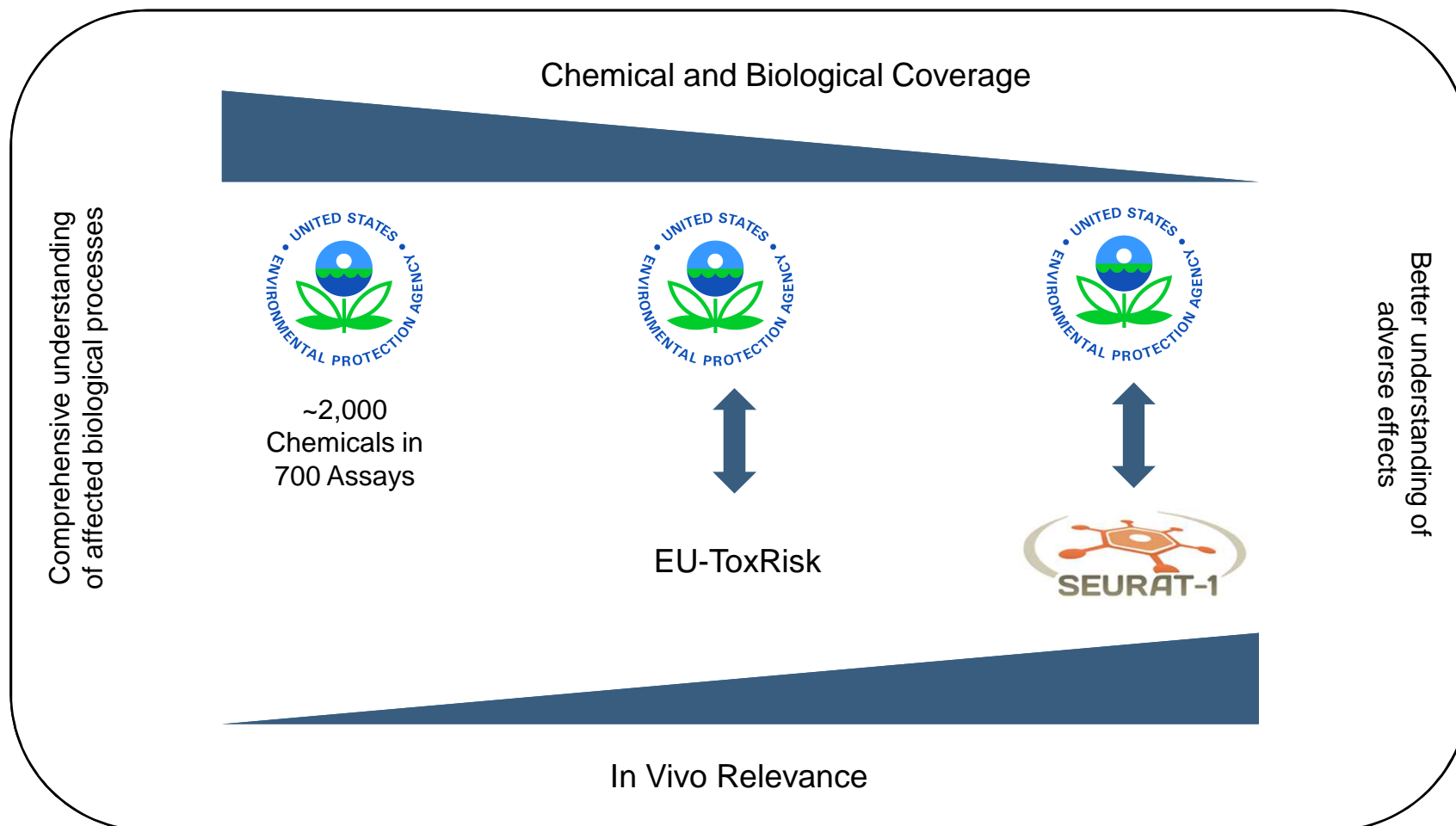
Alcohol Case Study



PFAA Case Study

Chemical	Perfluorooctanoic acid (PF8A)	Perfluorooctanoic acid (PF8A)	Perfluorooctanoic acid (PF8A)	Perfluorooctanoic acid (PF8A)	Perfluorooctanoic acid (PF8A)
ATG_PXR_CIS_up*	2.68	2.68	2.68	2.68	2.68
ATG_PXR_CIS_up*	3.55	3.55	3.55	3.55	3.55
ATG_PXR_CIS_up*	7.11	7.11	7.11	7.11	7.11
ATG_PXR_CIS_up*	7.23	7.23	7.23	7.23	7.23
ATG_PXR_CIS_up*	10.33	10.33	10.33	10.33	10.33
ATG_PXR_CIS_up*	11.11	11.11	11.11	11.11	11.11
ATG_PXR_CIS_up*	12.07	12.07	12.07	12.07	12.07
ATG_PXR_CIS_up*	12.29	12.29	12.29	12.29	12.29
ATG_PXR_CIS_up*	14.46	14.46	14.46	14.46	14.46
ATG_PXR_CIS_up*	14.17	14.17	14.17	14.17	14.17

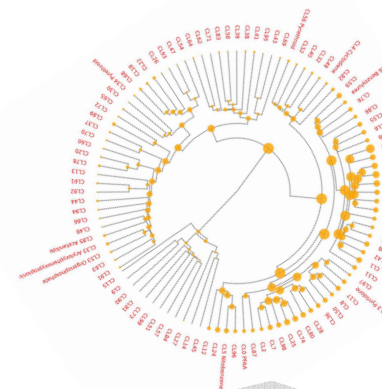
Complementary Approaches to Assay Development and Testing



Complementary Approaches in Read Across



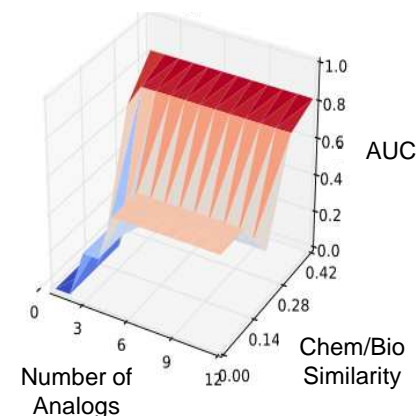
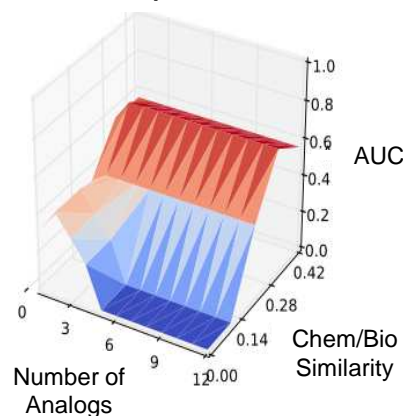
Defining regulatory application through case studies



Chemicals
Clustered Based
on Chemotype,
Structure, or
Biological
Descriptors

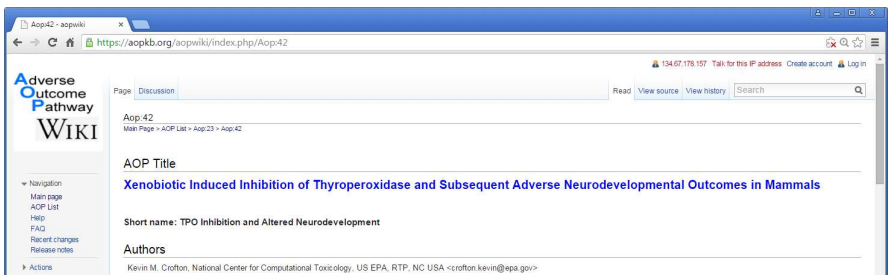
Developmental

Multi-Gen



Research to quantitatively define uncertainty
based on similarity and analog availability₆

Similar Approaches and Focus on AOPs

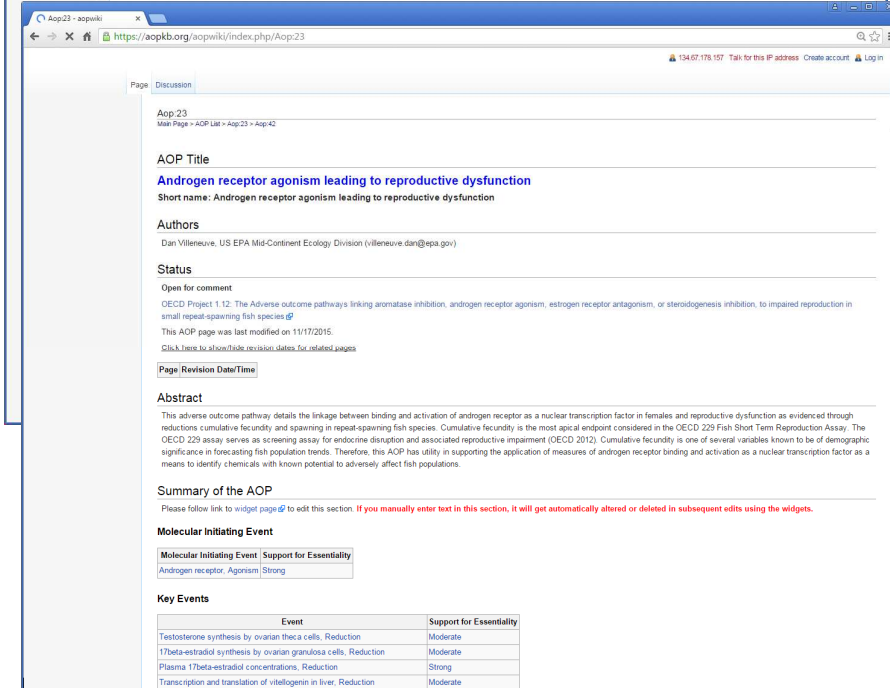


Aop:42
Main Page > AOP List > Aop:23 > Aop:42

AOP Title
Xenobiotic Induced Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals

Short name: TPO Inhibition and Altered Neurodevelopment

Authors
Kevin M. Crofton, National Center for Computational Toxicology, US EPA, RTP, NC USA <crofton.kevin@epa.gov>



Aop:23
Main Page > AOP List > Aop:23 > Aop:42

AOP Title
Androgen receptor agonism leading to reproductive dysfunction

Short name: Androgen receptor agonism leading to reproductive dysfunction

Authors
Dan Villeneuve, US EPA Mid-Continent Ecology Division (villeneuve.dan@epa.gov)

Status
Open for comment

OECD Project 1.12: The Adverse outcome pathways linking aromatase inhibition, androgen receptor agonism, estrogen receptor antagonism, or steroidogenesis inhibition, to impaired reproduction in small repeat-spawning fish species

This AOP page was last modified on 11/17/2015.
[Click here to show/hide revision dates for related pages](#)

Page Revision Date/Time

Abstract
This adverse outcome pathway details the linkage between binding and activation of androgen receptor as a nuclear transcription factor in females and reproductive dysfunction as evidenced through reductions cumulative fecundity and spawning in repeat-spawning fish species. Cumulative fecundity is the most apical endpoint considered in the OECD 229 Fish Short Term Reproduction Assay. The OECD 229 assay serves as screening assay for endocrine disruption and associated reproductive impairment (OECD 2012). Cumulative fecundity is one of several variables known to be of demographic significance in forecasting fish population trends. Therefore, this AOP has utility in supporting the application of measures of androgen receptor binding and activation as a nuclear transcription factor as a means to identify chemicals with known potential to adversely affect fish populations.

Summary of the AOP
Please follow link to widget page to edit this section. **If you manually enter text in this section, it will get automatically altered or deleted in subsequent edits using the widgets.**

Molecular Initiating Event

Molecular Initiating Event	Support for Essentiality
Androgen receptor, Agonism	Strong

Key Events

Event	Support for Essentiality
Testosterone synthesis by ovarian theca cells, Reduction	Moderate
17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Moderate
Plasma 17beta-estradiol concentrations, Reduction	Strong
Transcription and translation of vitellogenin in liver, Reduction	Moderate



Aop:27
Main Page > AOP List > Aop:23 > Aop:42 > Aop:27

AOP Title
Cholestatic Liver Injury induced by Inhibition of the Bile Salt Export Pump (ABCB11)

Short name: Cholestatic Liver Injury induced by inhibition of the Bile Salt Export Pump (ABCB11)

Authors
Mathieu Virken, Brigitte Landesmann, Marina Goumenou, Stefanie Virken, Imran Shah, Hartmut Jaeschke, Catherine Willett, Maurice Whelan and Vera Rogiers.



Aop:38
AOP List > Aop:23 > Aop:42 > Aop:27 > Aop:38

AOP Title
Protein Alkylation leading to Liver Fibrosis

Short name: Protein Alkylation to Liver Fibrosis

Authors
Brigitte Landesmann
Systems Toxicology Unit and EURL ECVAM, Institute for Health and Consumer Protection
European Commission Joint Research Centre
Brigitte.LANDESMANN (at) ec.europa.eu

Status
Under development: Do not distribute or cite.
OECD Project 1.14: The Adverse Outcome Pathways from protein alkylation to liver fibrosis.
This AOP page was last modified on 11/17/2015.
[Click here to show/hide revision dates for related pages](#)

Page Revision Date/Time

Abstract
Hepatotoxicity in general is of special interest for human health risk assessment. Liver fibrosis in particular is an important human health issue associated with chemical exposure and predictive assays are lacking. It is a typical result of chronic or repeated-dose toxic injury and one of the considered endpoints for regulatory purposes. It is a long-term process in which inflammation, tissue destruction, and repair occur simultaneously, together with sustained production of growth factors and fibrogenic cytokines due to a complex interplay between various hepatic cell types, various receptors and signaling pathways which lead to an imbalance between the deposition and degradation of extracellular matrix (ECM) and a change of ECM composition. Due to this complex situation an adequate cell model is not available and an in-vitro evaluation of fibrogenic potential is therefore not feasible. A sufficiently detailed description of the AOP to liver fibrosis might support chemical risk assessment by indicating early (upstream) markers for downstream events and facilitate a testing strategy without the need for a sophisticated cell model. The systematic and coherent display of currently available mechanistic-toxicological information can serve as a knowledge-based repository for identification/selection/development of in vitro methods suitable for measuring key events and their relationships along the AOP and to facilitate the use of alternative data for regulatory purposes. Identified uncertainties and knowledge gaps can direct future research by priority setting and targeted testing. The key event descriptions can be used for hazard identification and read-across to assess the toxic potential of an untested substance.
This AOP describes the linkage between hepatic injury caused by protein alkylation and the formation of liver fibrosis. The MIE is protein alkylation, leading to structural and functional cell injury and further to cell death, the first KE. Apoptotic hepatocytes undergo genomic DNA fragmentation and formation of apoptotic bodies. Upon engulfment of apoptotic bodies Kupffer cells (KCs) are activated, the next KE along the pathway. Activated KCs are the main source of TGF-β1, the most potent profibrogenic cytokine. TGF-β1 expression therefore is considered a KE that causes the next KE, hepatic stellate cell (HSCs) activation, meaning the transdifferentiation from a quiescent vitamin A-storing cell to a proliferative and contractile myofibroblast, the central effector in hepatic fibrosis. Activated HSCs cause progressive collagen accumulation, which together with changes in ECM composition signifies the KE on tissue level. The excessive accumulation of extracellular matrix proteins progressively affects the whole organ and alters its normal functioning, which corresponds to liver fibrosis, the adverse outcome.
There are two further events that play an important role in driving fibrogenesis, namely oxidative stress and chronic inflammation. Both are on-going processes being present throughout the pathway and interconnected with most of the KEs. Hence, they are not classified as KEs themselves and described in the individual KE and KER descriptions. The inflammatory response plays an important role in driving fibrogenesis, since persistent inflammation precedes fibrosis. Inflammatory signaling stems from injured hepatocytes, activated KCs and HSCs. Inflammatory and fibrogenic cells stimulate each other in amplifying fibrosis. Chemokines and their receptors provoke further fibrogenesis, as well as interacting with inflammatory cells to modify the immune response during injury. Oxidative stress, as

Strong International Collaboration

JOINT RESEARCH CENTRE

European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)

> "SEURAT-1 meets Tox21": international cooperation in safety assessment of chemicals using animal-free methods

"SEURAT-1 meets Tox21": international cooperation in safety
assessment of chemicals using animal-free methods June, 2013



Making Progress Towards the Shared Goal

Summarized from FR Notice

- EPA is planning to adopt *in vitro* high throughput assays and computational models for detecting and measuring ER agonist and antagonist bioactivity as an alternative for three current Tier 1 assays: 1) ER binding *in vitro* assay; 2) ER transcriptional activation *in vitro* assay (ERTA); and 3) *in vivo* uterotrophic assay.

35350
Federal Register / Vol. 80, No. 118 / Friday, June 19, 2015 / Notices

may claim all or part of a response confidential. EPA will disclose information that is covered by a claim of confidentiality only to the extent permitted by, and in accordance with, the procedures in TSCA section 14 and 40 CFR part 2.

Burden statement. The annual public reporting and recordkeeping burden for this collection of information is estimated to average 31.5 hours per response. Burden is defined in 5 CFR 1320.3(b).

The ICR, which is available in the docket along with other related materials, provides a detailed explanation of the collection activities and the burden estimate that is only briefly summarized here:

Respondents/Affected Entities: Entities potentially affected by this ICR are companies that manufacture, process or import chemical substances, mixtures or categories.

Estimated total number of potential respondents: 1.

Frequency of response: On occasion.

Estimated total average number of responses for each respondent: 1.

Estimated total annual burden hours: 31.5 hours.

Estimated total annual costs: \$2,388. This includes an estimated burden cost of \$2,388 and an estimated cost of \$0 for capital investment or maintenance and operational costs.

III. Are There Changes in the Estimates from the Last Approval?

There is a decrease of 916 hours in the total estimated respondent burden compared with that identified in the ICR currently approved by OMB. This decrease reflects additional both adjustment changes from a reduction in the assumed number of PAIR reports filed annually, and program changes resulting from mandatory electronic submissions of PAIR reports. In recent years (FY 2011–FY 2014), EPA has received no PAIR submissions and, for the purposes of this analysis, EPA assumes an annual rate of one submission per year. At the time OMB last renewed this ICR, EPA estimated an average of 33 reports from 14.8 submitters based on fiscal year 2006–2010 data. The ICR supporting statement provides a detailed analysis of the change in burden estimate. This change is both an adjustment and a program change.

IV. What is the Next Step in the Process for this ICR?

EPA will consider the comments received and amend the ICR as appropriate. The final ICR package will then be submitted to OMB for review

and approval pursuant to 5 CFR 1320.12. EPA will issue another **Federal Register** document pursuant to 5 CFR 1320.5(a)(1)(iv) to announce the submission of the ICR to OMB and the opportunity to submit additional comments to OMB. If you have any questions about this ICR or the approval process, please contact the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

Authority: 44 U.S.C. 3501 *et seq.*

Dated: June 10, 2015.

James Jones,
Assistant Administrator, Office of Chemical Safety and Pollution Prevention.
[FR Doc. 2015–14946 Filed 6–18–15; 8:45 am]
BILLING CODE 5560–50–P

ENVIRONMENTAL PROTECTION AGENCY
[EPA–HQ–OPPT–2015–0305; FRL–9928–69]

Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This document describes how EPA is planning to incorporate an alternative scientific approach to screen chemicals for their ability to interact with the endocrine system. This will improve the Agency's ability to fulfill its statutory mandate to screen pesticide chemicals and other substances for their ability to cause adverse effects by their interaction with the endocrine system. The approach incorporates validated high throughput assays and a computational model and, based on current research, can serve as an alternative for some of the current assays in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery. EPA has partial screening results for over 1800 chemicals that have been evaluated using high throughput assays and a computational model for the estrogen receptor pathway. In the future, EPA anticipates that additional alternative methods will be available for EDSP chemical screening based on further advancements of high throughput assays and computational models for other endocrine pathways. Use of these alternative methods will accelerate the pace of screening, decrease costs, and reduce animal testing. In addition, this approach advances the goal of providing sensitive, specific, quantitative, and

efficient screening using alternative test methods to some assays in the Tier 1 battery to protect human health and the environment.

DATES: Comments must be received on or before August 18, 2015.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPPT–2015–0305, by one of the following methods:

- **Federal eRulemaking Portal:** <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
- **Mail:** Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460–0001.
- **Hand Delivery:** To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>.

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: For technical information contact: Jane Robbins, Office of Science Coordination and Policy (OSCP), Office of Chemical Safety and Pollution Prevention, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460–0001; telephone number: (202) 564–6625; email address: robbins.jane@epa.gov.

For general information contact: The TSCA Hotline, ADVL-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554–1404; email address: TSCA-Hotline@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

This action is directed to the public in general, and may be of interest to a wide range of stakeholders including those interested in endocrine testing of chemicals (including pesticides), and the EDSP in general. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. What is the agency authority for taking this action?

The EDSP is established under section 408(p) of the Federal Food, Drug and

Need to Continue the Journey Together

