

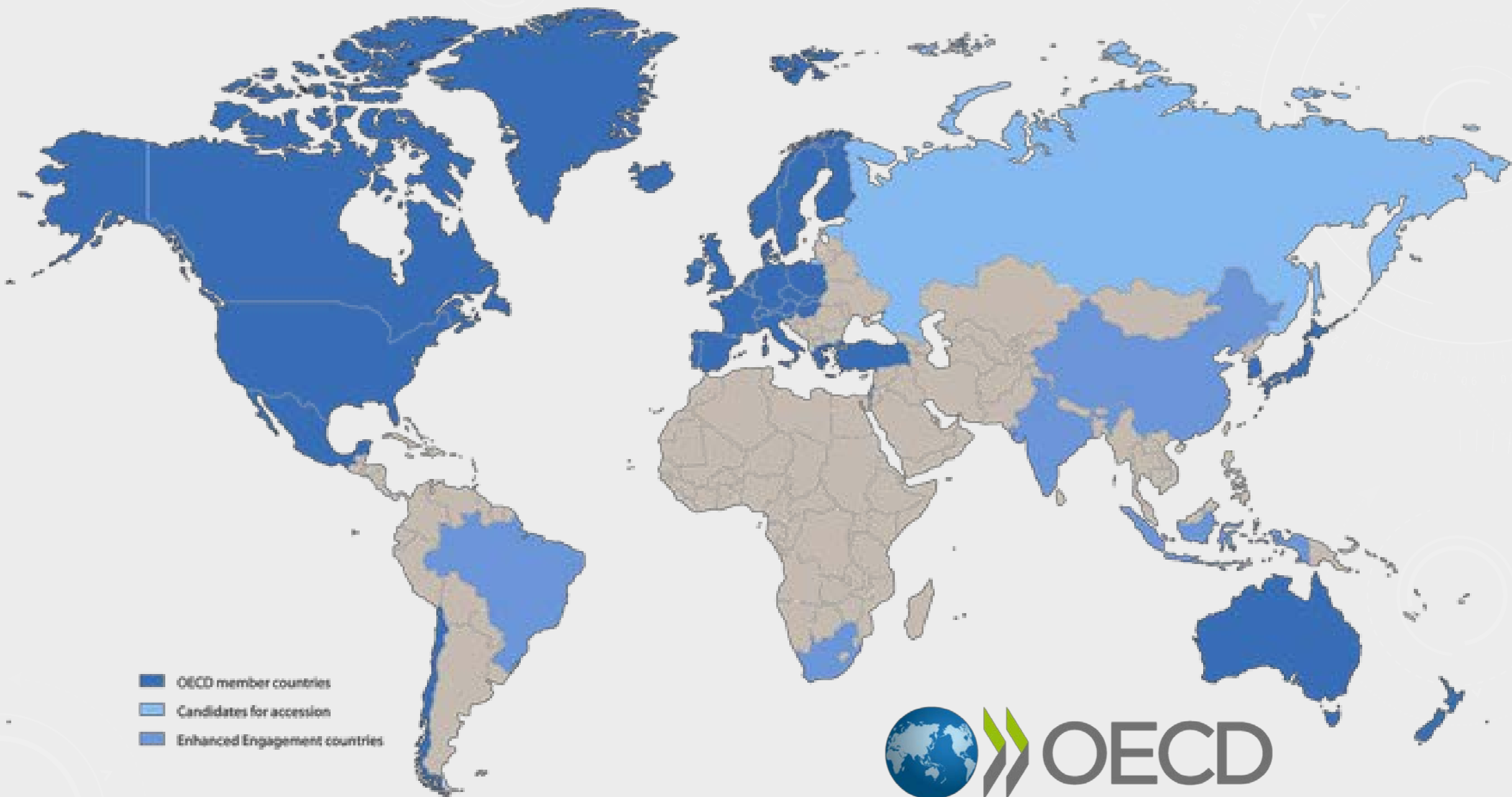


# END USER APPLICATIONS: OECD LANDSCAPE

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PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

PREDICTIVE MODELS FOR ACUTE ORAL SYSTEMIC TOXICITY WORKSHOP  
APRIL 12, 2018



- OECD member countries
- Candidates for accession
- Enhanced Engagement countries

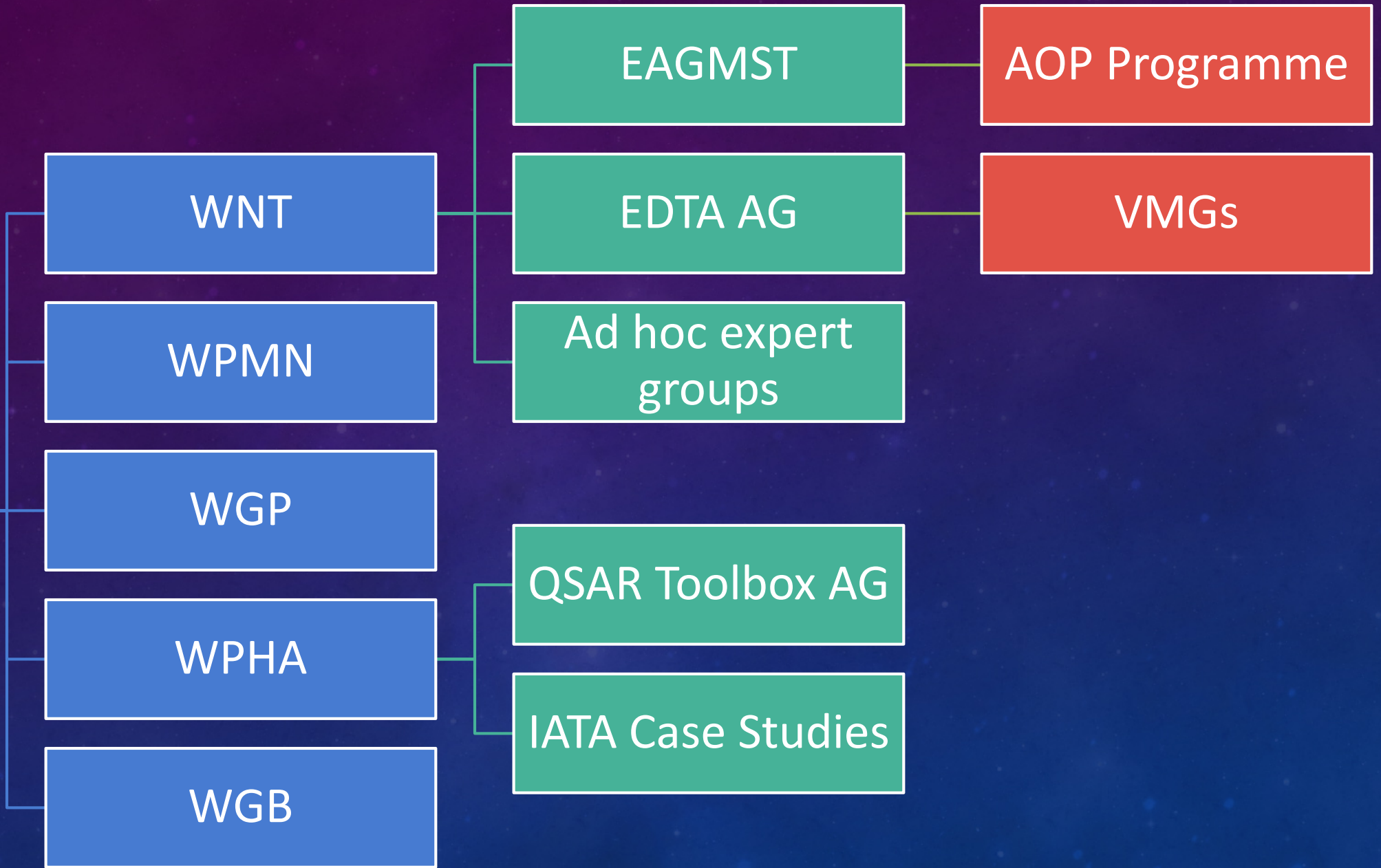
# OECD WORKING PRINCIPLES

- Everything requires consensus
- Treaty on Mutual Acceptance of Data
  - Applies to protocols, not interpretations
  - Does not preclude countries from asking for more
- Work towards harmonization in interpretation/classification
- Saves countries' resources
- “Learn by doing” approach

# OECD FUNCTIONS

- Test Guidelines
  - Adopts test guidelines for generating hazard characterization data according to country needs and via expert working groups
  - Writes accompanying guidance and validation reports
- Hazard Assessment
  - History of cooperative assessments, read across, now IATA case studies
  - Harmonized templates, data recording tools
  - Tools for hazard assessment and management of chemicals for developing countries
- Administers AOP Programme
  - Tools for recording AOP information
  - Series on AOPs: endorsed jointly

# Joint Meeting



# OECD AND QSAR: LONG HISTORY OF COOPERATION

- 1992: Report of the OECD Workshop on Quantitative Structure Activity Relationships (QSARs) in Aquatic Effects Assessment
- Report on the Regulatory Uses and Applications in OECD Member Countries of (Q)SAR Models in the Assessment of New and Existing Chemicals, No. 58 (2006)
- March 2008: First release of the OECD QSAR Toolbox
  - Intended to provide tools for regulatory use
  - Databases, grouping/category formation, read across, profilers, metabolism predictors
- Guidance Document for using the OECD (Q)SAR Application Toolbox to develop Chemical Categories according to the OECD Guidance on Grouping of Chemicals, Series on Testing and Assessment No. 102, (2009)
  - Many training materials created/offered since
  - Webinars, hands-on training as well
- Additional updated/new documents related to QSAR available
- Toolbox version 4.2 released Feb 2018

## No. 69: GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE) STRUCTURE-ACTIVITY RELATIONSHIP [(Q)SAR] MODELS (2007)

[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2007\)2&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2007)2&doclanguage=en)

- A validated (Q)SAR is a model considered to be reliable for a particular purpose based on the results of the validation process in which the domain of application and the level of uncertainty required is defined.
- A valid (Q)SAR is a model considered to be adequate for the intended purpose either because reliability has been demonstrated by historical use or by a validation process
- To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:
  - 1) a defined endpoint
  - 2) an unambiguous algorithm
  - 3) a defined domain of applicability
  - 4) appropriate measures of goodness-of-fit, robustness and predictivity
  - 5) a mechanistic interpretation, if possible
- Interpretation Guidance for principles
- QSAR Method Reporting Format

# FACILITATING REGULATORY ACCEPTANCE

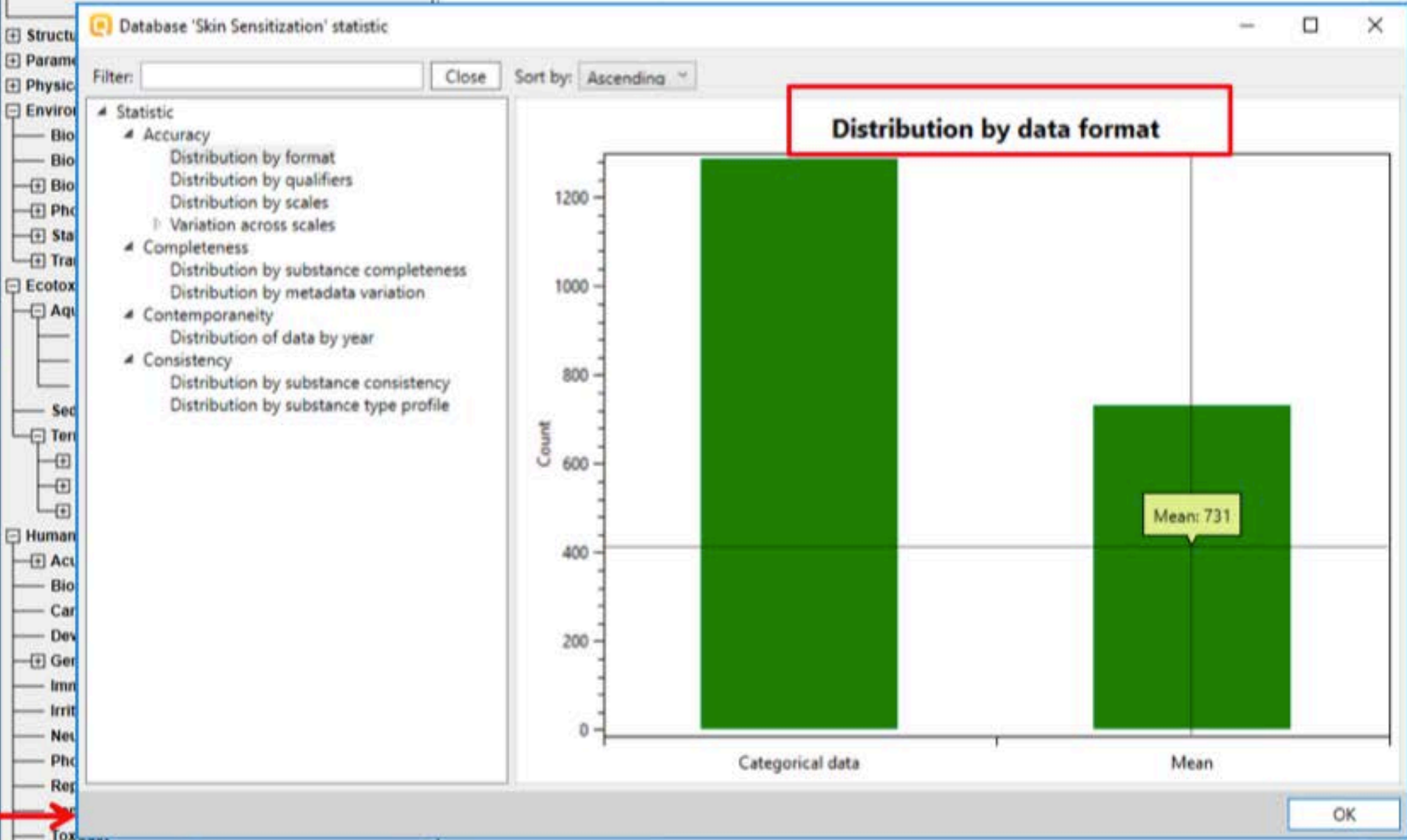
- Understand what is needed
- Explain decisions you have made
- Documentation and transparency
- Offer hands-on training
- Demonstrate how your tool meets their needs
- Be sure you are reflecting the chemistries of concern
- Use case studies
- Mechanistic relevance increases trust
- Use pictures!

	Chemical 1	Chemical 2	Chemical 3	Chemical 4	
Structure	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx	
Property 1	● → ○		● → ○		SAR/Read-across
Property 2	● → ○		○ ← ●		Interpolation
Property 3	○ ← ●		● → ○		Extrapolation
Activity 1	● → ○		● → ○		SAR/Read-across
Activity 2	● → ○		○ ← ●		Interpolation
Activity 3	○ ← ●		● → ○		Extrapolation

● Existing data point   ○ Missing data point

What do we mean by regulatory acceptance?





Databases

Sort by: Name

Legend

All Unselect All Invert About

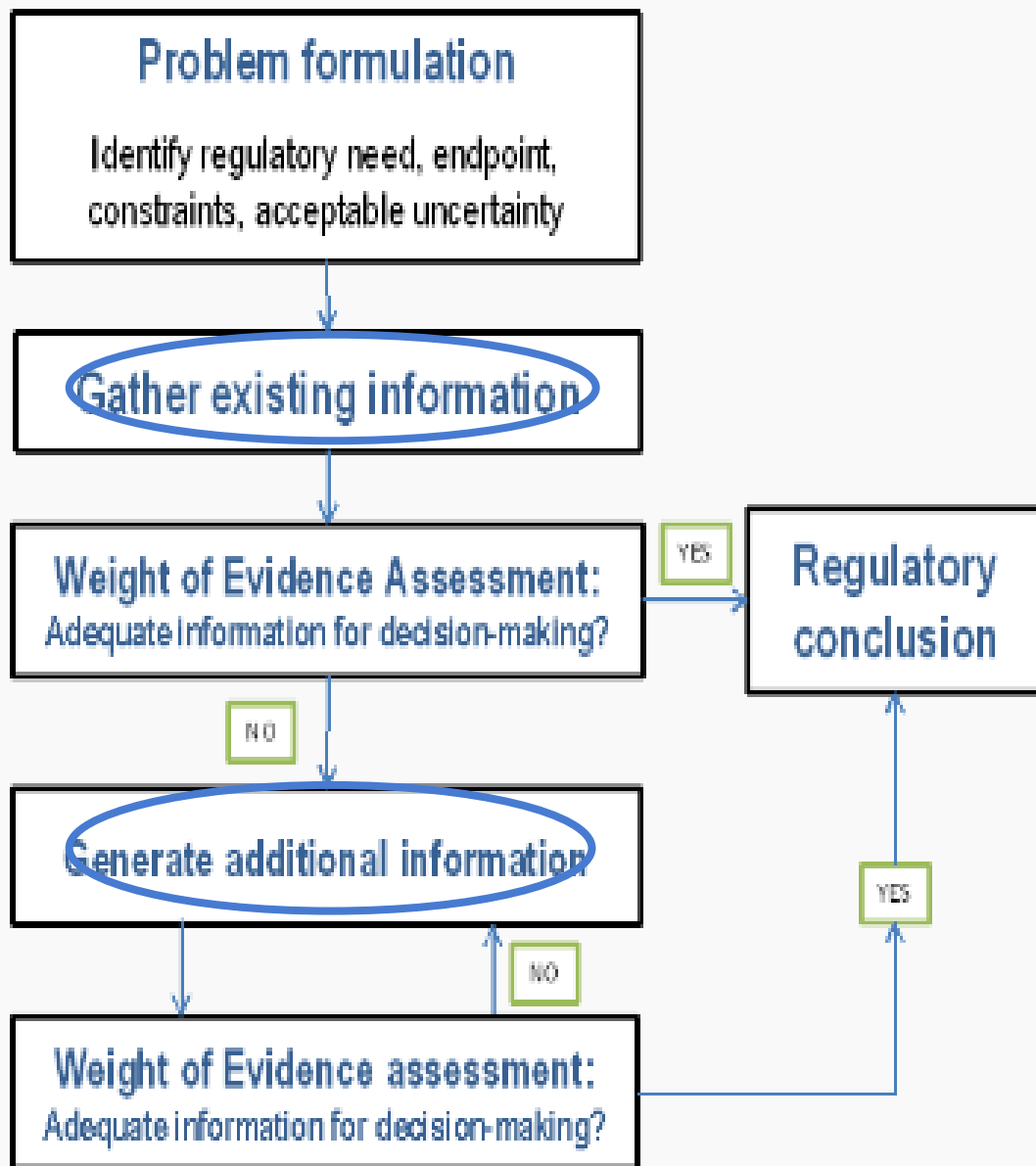
about

Select All

Unselect All

Invert

**Database statistic**



# BASIC IATA

- Test Guidelines
- “Non-guideline” methods (GD 211)
- Integrated Testing Strategies
- QSARs
- Read Across
- Defined Approaches
- Modeling results
- “Information”

<http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm>

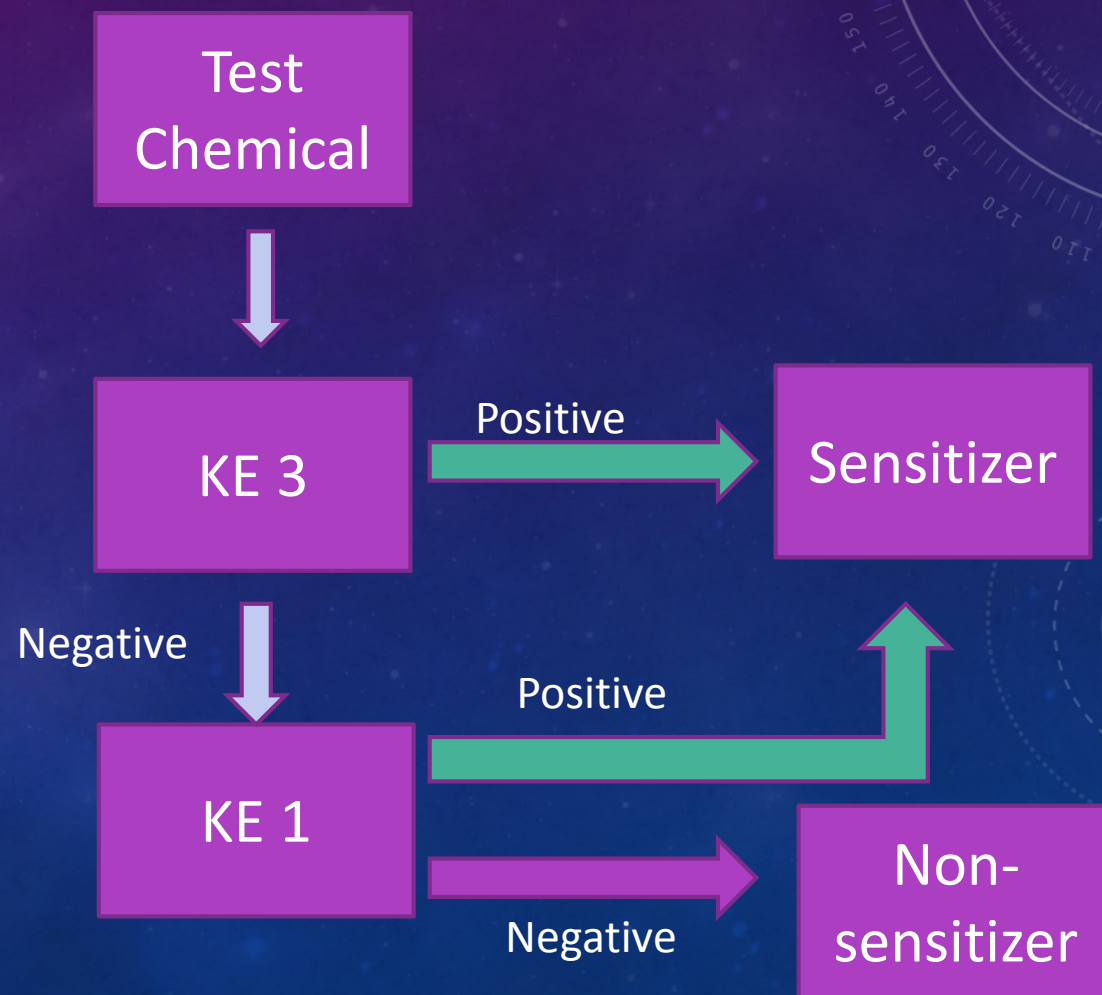
Review Year	No.	Title	Type of Assessment	Endpoint	Status
2017	1	Estrogenicity of Substituted Phenols	Prioritization and hazard characterization	Endocrine disruption	Under review
2017	2	Prioritization of chemicals using the Integrated Approaches for Testing and Assessment (IATA)-based Ecological Risk Classification	Prioritization of chemicals	Ecotoxicity	Under review
2017	3	Case study on grouping and read-across for nanomaterials genotoxicity of nano-TiO2	Grouping (Read-across)	Genotoxicity	Under review
2017	4	A Case Study on the Use of Integrated Approaches for Testing and Assessment for Sub-Chronic Repeated-Dose Toxicity of Simple Aryl Alcohol Alkyl Carboxylic Esters: Read-Across	Grouping (Read-across)	Repeated dose toxicity	Under review
2016	1	Repeated-Dose Toxicity of Phenolic Benzotriazoles	Grouping (Read-across)	Repeated dose toxicity	<a href="#">Published</a>
2016	2	Pesticide Cumulative Risk Assessment & Assessment of Lifestage Susceptibility	Cumulative risk assessment	Neurotoxicity	<a href="#">Published</a>
2016	3	90-Day Rat Oral Repeated-Dose Toxicity for Selected n-Alkanols: Read-Across	Grouping (Read-across)	Repeated dose toxicity	<a href="#">Published</a>
2016	4	90-Day Rat Oral Repeated-Dose Toxicity for Selected 2-Alkyl-1-alkanols: Read-Across	Grouping (Read-across)	Repeated dose toxicity	<a href="#">Published</a>
2016	5	Chemical Safety Assessment Workflow Based on Exposure Considerations and Non-animal Methods	Safety assessment workflow	Repeated dose toxicity	<a href="#">Published</a>
2015	1	In Vitro Mutagenicity of 3,3' Dimethoxybenzidine (DMOB) Based Direct Dyes	Grouping (Read-across)	Mutagenicity	<a href="#">Published</a>
2015	2	Repeat Dose Toxicity of Substituted Diphenylamines (SDPA)	Grouping (Read-across)	Repeated dose toxicity	<a href="#">Published</a>
2015	3	Hepatotoxicity of Allyl Ester Category	Grouping (Read-across)	Repeated dose toxicity	<a href="#">Published</a>

## No. 270: REPORT ON CONSIDERATIONS FROM CASE STUDIES ON INTEGRATED APPROACHES FOR TESTING AND ASSESSMENT (IATA)

- Demonstrates general lessons on how to increase acceptance of and confidence in read across predictions
- Demonstrates use of transcriptomic and ToxCast data to facilitate prediction or reduce uncertainty
- Specific examples of reduced uncertainty

# WHAT IS A DEFINED APPROACH?

- Defined information sources
  - Experimental methods
  - Characteristics
  - Predictions
- Fixed data interpretation procedure
  - Algorithm for interpreting data
  - Manual or automated
- Offers potential for mutual acceptance of in silico predictions via DA TG



THANK YOU FOR YOUR ATTENTION!

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