

US EPA ARCHIVE DOCUMENT



21st Century Toxicology/
IATA Project

NAFTA (Q)uantitative Structure Activity Relationship Guidance Document

**Mary Manibusan, Environmental Protection Agency
and**

**Joel Paterson, Pest Management Regulatory Agency
November 30, 2012**

Presentation Overview:

Predicting Toxicity

- NAFTA Project Background: 21st Century Toxicology/IATA
- Tox21/IATA Tools: (Q)SAR Tools
- NAFTA (Q)SAR Guidance Document
 - Conceptual Framework
 - Comprehensive Scientific Peer review
 - Future Vision – Adverse Outcome Pathway
- Implementation plan – Next Steps

NAFTA Project Background

GOAL/OBJECTIVE:

- To develop common, North America wide approaches to the application of integrated approaches to testing and assessment (IATA) to the human health and ecological risk assessment of pesticides.
- IATA includes new technologies in molecular, cellular, and computational sciences that will supplement or replace more traditional methods of toxicity testing and help refine regulatory testing requirements for pesticides to the specific data needs of human health and ecological assessments.
- This joint project on “21st Century Toxicology: Integrated Approaches to Testing and Assessment” will ensure aligned, consistent and efficient applications of these approaches and tools in North America.
- **PROJECT DATES:** **Accepted: December, 2009**

(Q)SAR Current and Future Use

- (Quantitative) Structure Activity Relationship [(Q)SAR]: predicting activities/properties of untested chemicals based on similarity to chemicals with known activities/properties
- Longer history of academic, industrial, and regulatory development and use than many other Tox21/IATA tools
- Other projects at the OECD, ECB, US EPA, and Health Canada:
 - Making data sources available for use in (Q)SAR tools
 - Development of new tools
 - Application of (Q)SAR predictions to human health and environmental risk assessments
 - Preparation of (Q)SAR guidance documents
- To date, QSAR is commonly used to predict apical endpoints for regulatory applications
- Future direction of (Q)SAR – Predicting Precursor Events in the Adverse Outcome Pathways (AOPs)

NAFTA (Q)SAR Guidance Document

- **What is the Purpose?**
 - General guidance for evaluators reviewing (Q)SAR predictions in pesticide submissions or using (Q)SAR predictions to help identify data requirements
- **Who is the Targeted Audience?**
 - Pesticide evaluators, but also applicable to other types of regulatory risk assessment
 - Not for (Q)SAR experts/developers; Introduction to (Q)SAR tools and their application to regulatory risk assessment
- **What is its Functionality?**
 - Flexible framework; Not an SOP or step-by-step manual
 - Supplements, but does not replace, other (Q)SAR guidance (e.g., OECD, ECB, US EPA)
 - Applicable to human health-related and environmental uses of (Q)SAR
 - Emphasis on (Q)SAR as one component in weight-of-evidence

INTRODUCTION AND BACKGROUND INFORMATION

INTRODUCTION

(Section 2)

- Current applications of (Q)SAR in pesticide risk assessments
- Other regulatory applications of (Q)SAR
- Purpose of the NAFTA (Q)SAR Guidance Document

BACKGROUND INFORMATION ON (Q)SAR

(Section 3)

- Definition of (Q)SAR
- Types of (Q)SAR tools and approaches
- Importance of data quality in (Q)SAR model development
- Importance of mode/mechanism of action in (Q)SAR development
- Examples of (Q)SAR tools and their applications

APPLYING (Q)SAR PREDICTIONS TO PESTICIDES

PROBLEM FORMULATION AND (Q)SAR

(Section 4)

- Assessment context that (Q)SAR is being applied to
- Characteristics of the pesticide that is the subject of the prediction
- Characteristics of the (Q)SAR tool and the prediction
- Available empirical data including information on mode of action

COMBINING INFORMATION FROM MULTIPLE PREDICTIONS

(Section 6)

- Approaches to combining multiple predictions
- Advantages and disadvantages of combining predictions
- Selecting (Q)SAR tools for multiple predictions
- Evaluation of multiple predictions

EVALUATING THE ADEQUACY OF (Q)SAR PREDICTIONS

(Section 5)

- Scientific validity of a (Q)SAR tool
- Applicability of the (Q)SAR tool to the pesticide
- Relevance of the (Q)SAR tool to the assessment context
- Reliability of the (Q)SAR prediction
- Documentation of (Q)SAR tools and predictions

INTEGRATION OF (Q)SAR PREDICTIONS INTO WEIGHT OF EVIDENCE ASSESSMENTS

(Section 7)

- Incorporating (Q)SAR in hazard characterizations: Overview
- Problem formulation
- Evaluating empirical data versus (Q)SAR predictions
- Mode of action considerations
- Overall weight of evidence
- Hazard characterization and risk communication

CONCLUSIONS

CONCLUSIONS AND FUTURE VISION FOR (Q)SAR

(Section 8)

- Toxicity Testing in the 21st Century: Shift in the Risk Assessment Paradigm
- Weight of Evidence Approach: Biological Plausibility
- Adverse Outcome Pathway: Conceptual Framework
- Expert Scientific Judgement and Peer Review

Guidance Document - Overview

- **Problem Formulation**

- Assessment context, characteristics of pesticide and (Q)SAR tool, empirical data including mode of action
- Immediate determination that prediction is not suitable/relevant or lead to more in-depth evaluation of adequacy

- **Evaluating the Adequacy of (Q)SAR Predictions**

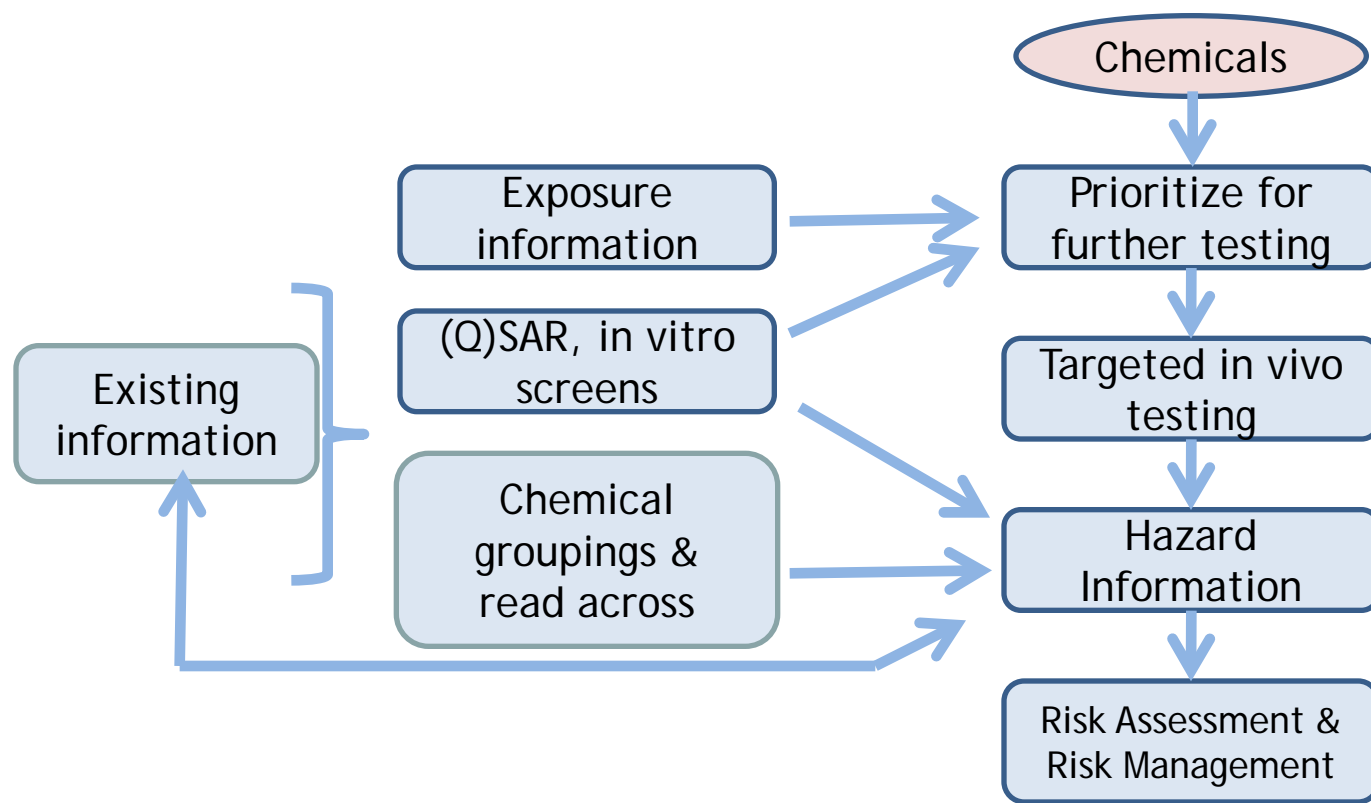
- Validity, applicability, relevance, and reliability of predictions
- Importance of OECD (Q)SAR Validation Principles
 - Defined Endpoint
 - Unambiguous Algorithm
 - Defined Domain of Applicability
 - Appropriate Measures of Goodness-of-fit, Robustness, and Predictivity
 - Defined Mechanism of Action, if Possible
- Documentation – sufficient level of transparency

Guidance Document Overview

- **Integrating (Q)SAR Predictions into Hazard Assessments**
 - Emphasis on (Q)SAR as one component of a weight of evidence assessment
 - Need to evaluate empirical data versus (Q)SAR predictions
 - Consideration of mode of action
- **Conclusions and Future Vision**
 - Shift in the risk assessment paradigm – 21st Century Toxicity Testing
 - Building (Q)SAR into Adverse Outcome Pathways (AOP)
 - Importance of expert scientific judgment and peer review
- **Where to go to Learn More About (Q)SAR...**
 - Links to web sites and guidance documents from ECB, OECD, US EPA, US FDA
- **Case Study Examples**
 - Application of (Q)SAR to pesticides and other chemicals
 - Examples of toxicity and ecotoxicity predictions
 - Validation, use of models, read-across, integrating (Q)SAR into weight of evidence

Guidance Document – Future Vision

Goal: Enhance Integrated Testing and Assessment with New Technologies and Knowledge of AOPs



Comprehensive Scientific Peer Reviews

- **Technical Document Writing Team**
 - US EPA/OCSP and Health Canada/PMRA
- **Technical Contributions and Internal Peer review**
 - US EPA/OPP, US EPA/OPPT, US EPA/ORD, US FDA, Health Canada/HECSB
- **External Peer Review by Key Experts in (Q)SAR**
 - Dr. Andrew Worth, European Joint Research Centre
 - Dr. Kirk Arvidson, US Food and Drug Administration
 - Dr. Bob Diderich and Dr. Terry Schultz, OECD
 - Dr. Mark Bonnell, Environment Canada

An OECD QSAR Guidance Document: Formal OECD Project

- A proposal to develop an OECD QSAR Guidance Document that will address chemicals more broadly, beyond pesticides.
 - NAFTA QSAR Guidance Document serve as the starting basis for a generic guidance document applicable to all chemicals
- The proposal was presented to OECD by EPA in June, 2012 and accepted.
- Project leadership provided by OPPT and Health Canada/Environment Canada

Next Steps

- ✓ Approval by NAFTA Executive Board
- Website Loading in November 2012
<http://www.epa.gov/pesticides/science/testing-assessment.html>
- Formation of an Expert QSAR Group
- Development of QSAR Training Modules
- Emphasize “Learn by Doing”

Acknowledgements:

NAFTA Project Lead: Mary Manibusan, USEPA/OPP

NAFTA Project Lead: Joel Paterson, Health Canada/PMRA

Dr. Ray Kent, USEPA/HED

Dr. Jonathan Chen, USEPA/AD

Dr. Chris Russom, USEPA/ORD

Dr. Pat Schmieder, USEPA/ORD

Dr. Tom Steeger, USEPA/EFED

Dr. YinTak Woo, USEPA/OPPT (OECD Chair)

Dr. Sunil Kulkarni, Health Canada/HECSB (OECD Chair)

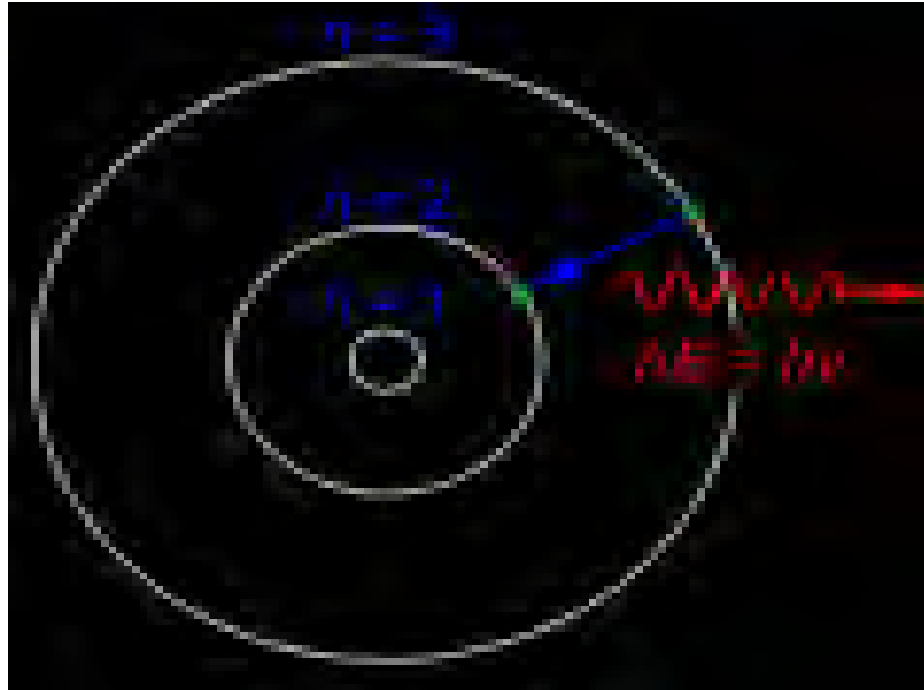
Dr. Kelly Mayo, USEPA/OPPT

Dr. Jenny Tao, USEPA/AD

Dr. Edwin Matthews, USFDA

Ms. Christine Olinger, USEPA/HED

Dr. Edward Scollon, USEPA/HED



“Prediction is difficult, especially if it’s
about the future.”
(Niels Bohr 1885-1962)

