Industry Initiatives to Educate and Train Toxicologists in Green Toxicology

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May 24, 2018
NCAC Society of Toxicology Meeting
Washington D.C.
OVERVIEW

- Green Toxicology - Really?
- Value Proposition
- The Journey - Strides Towards Implementation
- Training & Education Activities
- Looking to the Future of Safer Products/Processes
- Q & A
R&D/Toxicologists Antagonist Relationship

Early perceptions of the toxicologist...

- Stall product development
- Find issues
- Kill good product ideas
- Toxicologists are not partners

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“Patch it” options under old paradigm

1. Kill the project - **GO**

2. Control Exposure
   a) Consumers - Restrict product uses
   b) Workers/professional users – require PPE
   c) Restrict end use concentrations in products below harmful levels

3. Prove that the harmful effects are not relevant for humans or under normal conditions of use.
Can we prevent undesirable toxicity instead of using control strategies?

*An ounce of prevention is worth a pound of cure.*
-- Benjamin Franklin

DISCOVER A BETTER WAY.
Goal: Move toxicological profiling earlier in the stage gate process

- R&D & Toxicologists are partners in product development
- Awareness – design choices can be associated with toxicity
- Molecular design for safety
  1. Less controls
  2. Less effort defending
- Inform regulatory safety assessment (i.e. tailor animal testing)
Challenges . . .

Cultivating effective partnerships

Training toxicologists to think about using new strategies/information streams. (Prevent rather than control)

Tools match needs of new product development
- Rapid
- Relatively inexpensive
- Small to no test material needed
DISCOVER A BETTER WAY.
Build Toolbox of Integrated Technology Platforms

In Vitro Biological Profiling

- Cell cultures
- Zebrafish
- Genomics

Cheminformatics

Exposure modeling

DATA INTEGRATION

PREDICT SAFETY
Apply Tiered Assessment Approach

**Tier 1 - Cheminformatics**

Tools: QSAR, Analog ID, Data mining (internal and publically available data)

**Tier 2 - In Vitro Biological Profiling**

In vitro predictive assays (selected based on specific question/need)

**Tier 3 - Standard Regulatory Toxicology**

Test guidelines (selection based on regulatory need)
If you build it, they will come.

W. P. Kinsella
Early Program Buildout – Large Company

R&D
- Worker safety (RSSDS)
- Formulations
- Product selection
- Early alerts
- Molecular design
- Sustainable alts assessment

Regulatory assessments
- Read-across
- Integrated Testing Strategies
- Hi throughput exposure modeling
- Emergency response modeling

Follow-up MoA
- Pathways-based quantitative risk assessment

- Applying now
- Near-term opportunity
- Long-term opportunity
Sustainable competitive advantage

- Design and select more sustainable products
- Evaluate safety more efficiently and accurately
- Less effort and expense defending commercialized molecules
- A major opportunity to improve public confidence
What will it take to get there?

- Internally, effective partnerships/training with R&D, toxicologists

- External engagement
  - Leverage technology
  - Expand acceptance to other toxicologists in gov’t agencies and key stakeholders (e.g. chemistry community, educators of next generation scientists, other industries)
Successful Implementation in a Large Company

- Worker safety (RSSDS)
- Formulations
- Product selection
- Early alerts
- Molecular design
- Sustainable alts assessment

- Read-across
- Integrated Testing Strategies
- Hi throughput exposure modeling
- Emergency response modeling

Follow-up MoA

Pathways-based quantitative risk assessment

- Applying now
- Near-term opportunity
- Long-term opportunity
Model transferable to a SME company?

**Big Company**
- Deep expertise
- More resources
- More $$ to invest

**SME Company**
- Little to no expertise
- Few resources
- Less $$ to invest
ANGUS New Product Introduction Stage Gate

Small Company Demographics
- 350 employees globally
- 2 toxicologists (3-5 years experience)
- Minimal experience in new screening methods.
Implement a Screening Level Assessment/Green Toxicology Evaluation Process

Candidate Chemical

Assess Data

Existing Data

Yes

No

Comp Tox

Data Gaps

Expert Judgment

Predict Effects

Mammalian Toxicity
- Oasis™-Toolbox/Times
- EPA Chemistry Dashboard™

EcoToxicity & Env. Fate
- Oasis™-Times/Catabol
- EpiWin™

Literature Reports
- Name
- Synonyms
- CAS Number
- Structure
- Sub-structure

Expert Judgment

Screening Level Assessment (SLA) Report

Comparison Table

Outcome
Early Screens: Toxicology “Red Flags”

CMRs
- Carcinogen
- Mutagen
- Reproductive/Developmental Toxicant

PBTs
- Persistent
- Bioaccumulative
- Toxic to the Environment
Safety Screening in Product Introduction Stage Gate

Concept Shaping and Analysis Innovation Pipeline

Decision to Initiate

Build the Business Case

Decision to Develop

Invent a Solution

Decision to Scale-up

Prepare to Launch

Decision to Launch

Post Launch Reviews

Screen
- Literature/data base search
- Physical/chemical properties
- In silico profiling
- Flag issues for in vitro screening

Test Flags (e.g.)
- In vitro skin/eye irritation
- In vitro skin sensitization
- Screening Ames

Acute Studies
- Acute ecotoxicity
- Acute mammalian
- Genetic toxicity studies
- Environmental Fate

Regulatory Toxicity Studies
- Subchronic studies (OECD 422)
- Developmental Toxicity studies
Green Toxicology Screening Strategies in Practice
It All Starts with a Structure!

Which one is safer?
## Comparison Table of Screening Level Assessments

<table>
<thead>
<tr>
<th>Chemical</th>
<th>CAS Number</th>
<th>Environment / Ecotox</th>
<th>Human Health Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Persistence</td>
<td>Bioaccumulation</td>
</tr>
<tr>
<td>200</td>
<td>h</td>
<td>l</td>
<td>l-m</td>
</tr>
<tr>
<td>213</td>
<td>h</td>
<td>m</td>
<td>h</td>
</tr>
<tr>
<td>214</td>
<td>h</td>
<td>l</td>
<td>h</td>
</tr>
<tr>
<td>215</td>
<td>m</td>
<td>m</td>
<td>h</td>
</tr>
<tr>
<td>218</td>
<td>h</td>
<td>l</td>
<td>l-m</td>
</tr>
</tbody>
</table>
**Step 1. Read Across to a Chemically Similar Analog***

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>New chemical candidate</th>
<th>Read across analog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Oral</td>
<td>LD50 688 mg/kg Rats</td>
<td></td>
</tr>
<tr>
<td>Acute Dermal</td>
<td>LD50 ~2000 mg/kg Rats</td>
<td></td>
</tr>
<tr>
<td>Skin Irritation/Corrosion</td>
<td>Corrosive</td>
<td></td>
</tr>
<tr>
<td>Eye Irritation/Corrosion</td>
<td>Corrosive</td>
<td></td>
</tr>
<tr>
<td>Skin Sensitization</td>
<td>Sensitizer LLNA</td>
<td></td>
</tr>
<tr>
<td>Repeated Dose</td>
<td>Mild Liver effects at 1000 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Reproduction</td>
<td>NOAEL 1000 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Genotox</td>
<td>Negative in all in vitro and in vivo studies</td>
<td></td>
</tr>
<tr>
<td>Biodegradation</td>
<td>57% degradation in 56 days in OECD 301F</td>
<td></td>
</tr>
<tr>
<td>Acute Aquatic Toxicity</td>
<td>EC/LC50 &gt;10-100</td>
<td></td>
</tr>
</tbody>
</table>

*The chemical structures and following data are meant to serve as an illustrative example and do not represent an actual pre-screening assessment.*
Step 2. OECD Toolbox Modeling for Candidate Chemical

New chemical candidate

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Model(s)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Oral</td>
<td>Cramer Original/Extension</td>
<td>Low Toxicity</td>
</tr>
<tr>
<td>Skin Irritation/Corrosion</td>
<td>Inclusion/Exclusion rules by BfR</td>
<td>Inclusion Rules Not Met</td>
</tr>
<tr>
<td>Eye Irritation/Corrosion</td>
<td>Inclusion/Exclusion rules by BfR</td>
<td>Inclusion Rules Not Met</td>
</tr>
<tr>
<td>Skin Sensitization</td>
<td>OASIS v.1.4</td>
<td>No Alerts</td>
</tr>
<tr>
<td>Genotox</td>
<td>alerts by ISS</td>
<td>No Alerts</td>
</tr>
<tr>
<td>Repeated Dose</td>
<td>HESS</td>
<td>Not Categorized</td>
</tr>
<tr>
<td>Developmental/Reproduction</td>
<td>DART Scheme v.1.0.</td>
<td>No Alerts</td>
</tr>
<tr>
<td>Primary Biodegradation</td>
<td>Biowin 4</td>
<td>Degradation in weeks to months</td>
</tr>
<tr>
<td>Ecotoxicity</td>
<td>Verharr (Modified)</td>
<td>Determination Not Possible</td>
</tr>
</tbody>
</table>
Step 3. **REACHAcross™** Modeling* for Candidate Chemical

**New chemical candidate**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Read Across</th>
<th>QSAR Modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Oral</td>
<td>LD50 688 mg/kg Rats</td>
<td>Low Toxicity (OECD) Oral Hazard (REACH Across)</td>
</tr>
<tr>
<td>Acute Dermal</td>
<td>LD50 ~2000 mg/kg Rats</td>
<td>Low Toxicity (OECD) Not a Dermal Hazard (REACH Across)</td>
</tr>
<tr>
<td>Skin Irritation/Corrosion</td>
<td>Corrosive</td>
<td>Out of Domain (OECD) Severe Skin Irritant (REACH Across)</td>
</tr>
<tr>
<td>Eye Irritation/Corrosion</td>
<td>Corrosive</td>
<td>Out of Domain (OECD) Severe Eye Irritant (REACH Across)</td>
</tr>
</tbody>
</table>

* Results indicate whether chemical will require GHS classification or not for that endpoint.
**Step 3. REACHAcross™ Modeling* for Candidate Chemical (cont.)**

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<thead>
<tr>
<th>Endpoint</th>
<th>Read Across</th>
<th>QSAR Modeling</th>
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<tbody>
<tr>
<td>Skin Sensitization</td>
<td>Sensitizer LLNA</td>
<td>No Alerts (OECD) Skin Sensitizer (REACH Across)</td>
</tr>
<tr>
<td>Repeated Dose</td>
<td>Mild Liver effects at 1000 mg/kg</td>
<td>Not categorized (OECD)</td>
</tr>
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<td>NOAEL 1000 mg/kg</td>
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<td>Negative in all in vitro and in vivo studies</td>
<td>No Alerts (OECD) Possible Mutagen (REACH Across)</td>
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<td>Determination Not Possible (OECD) Not an Acute Aquatic Hazard (REACH Across)</td>
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In Vitro Test Results Inform Disparate QSAR results

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<tr>
<td>Skin Irritation/Corrosion</td>
<td>Corrosive</td>
<td>Out of Domain (OECD)</td>
<td>Irritating GHS Cat 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe Skin Irritant (REACH Across)</td>
<td></td>
</tr>
<tr>
<td>Eye Irritation/Corrosion</td>
<td>Corrosive</td>
<td>Out of Domain (OECD)</td>
<td>Corrosive GHS Cat 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe Eye Irritant (REACH Across)</td>
<td></td>
</tr>
<tr>
<td>Skin Sensitization</td>
<td>Sensitizer LLNA</td>
<td>No Alerts (OECD)</td>
<td>Not sensitizing</td>
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Safety Screening in Product Introduction Stage Gate

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Training & Education Activities

- Forming collaborations with tool developers to encourage tools that will improve early product safety screening
  - UL cheminformatics suite
  - NICEATM’s Integrated Chemical Environment (ICE)

- Road shows to promote concept of Green Toxicology
  - ACS National Meeting
  - Green Chemistry & Engineering Conference
  - Biennial Conference on Chemical Education
  - Product Stewardship Annual Meeting
Take Home Messages for Next Gen Toxicologists

Develop knowledge of chemistry associated toxicity - becoming increasingly important!

Build internal & external collaborations

Start with highest confidence platforms and build out

Take advantage of publicly-available high throughput data (e.g., ICE) and data bases (e.g., OECD Tool Box)

Continually build knowledge bases & us to inform in vivo data needed to meet registration requirements

Do not sacrifice current levels of confidence during transition period

- Recognize and address limitations of new methods
- Defining the level on uncertainty in the predictive approaches will assist us in how we use the information (some decisions and some endpoint can tolerate a higher level of uncertainty than others!)- often there are no bright lines.
“Green Toxicology” is a feasible approach but will require:

- Education & training for toxicologists to think differently
- Collaboration to develop and successfully launch sustainable products to market

Green toxicology/application of evolving 21st century methods benefits:

- Design and selection of more sustainable products
- Evaluate safety more efficiently and accurately
- Less effort and expense defending commercialized molecules

Good for society and good for business!

Looking to the Future of Safer Products/Processes