Product Safety Assessment Screening Tools: A Method to Integrate Principles of Toxicology into Chemistry Curriculum

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Toxicology for Chemistry Workshop
GC&E Conference Workshop
June 20, 2017

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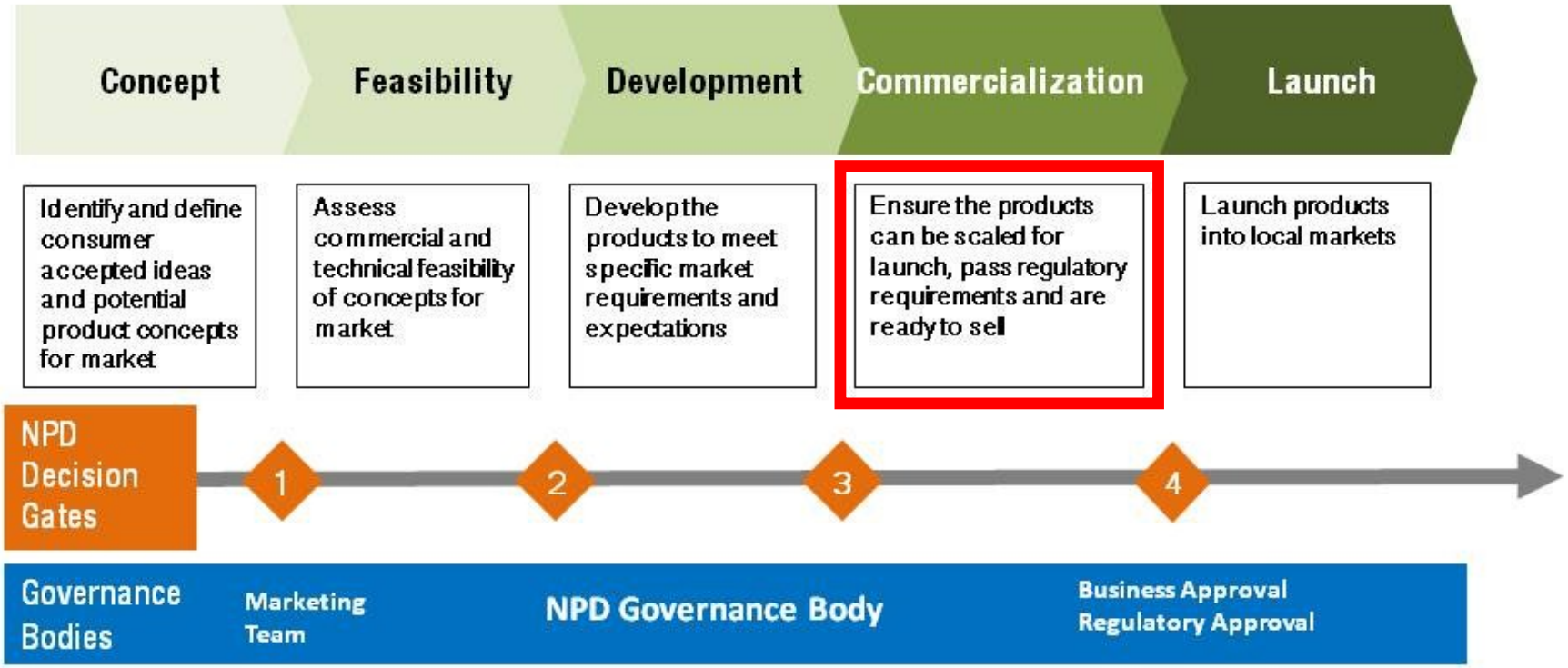
Overview

- Toxicology & New Product Development
- Early safety screening strategies
- Linking concepts of toxicology to chemistry
- Tools easily integrated into chemistry curriculum & course work
- Q&A

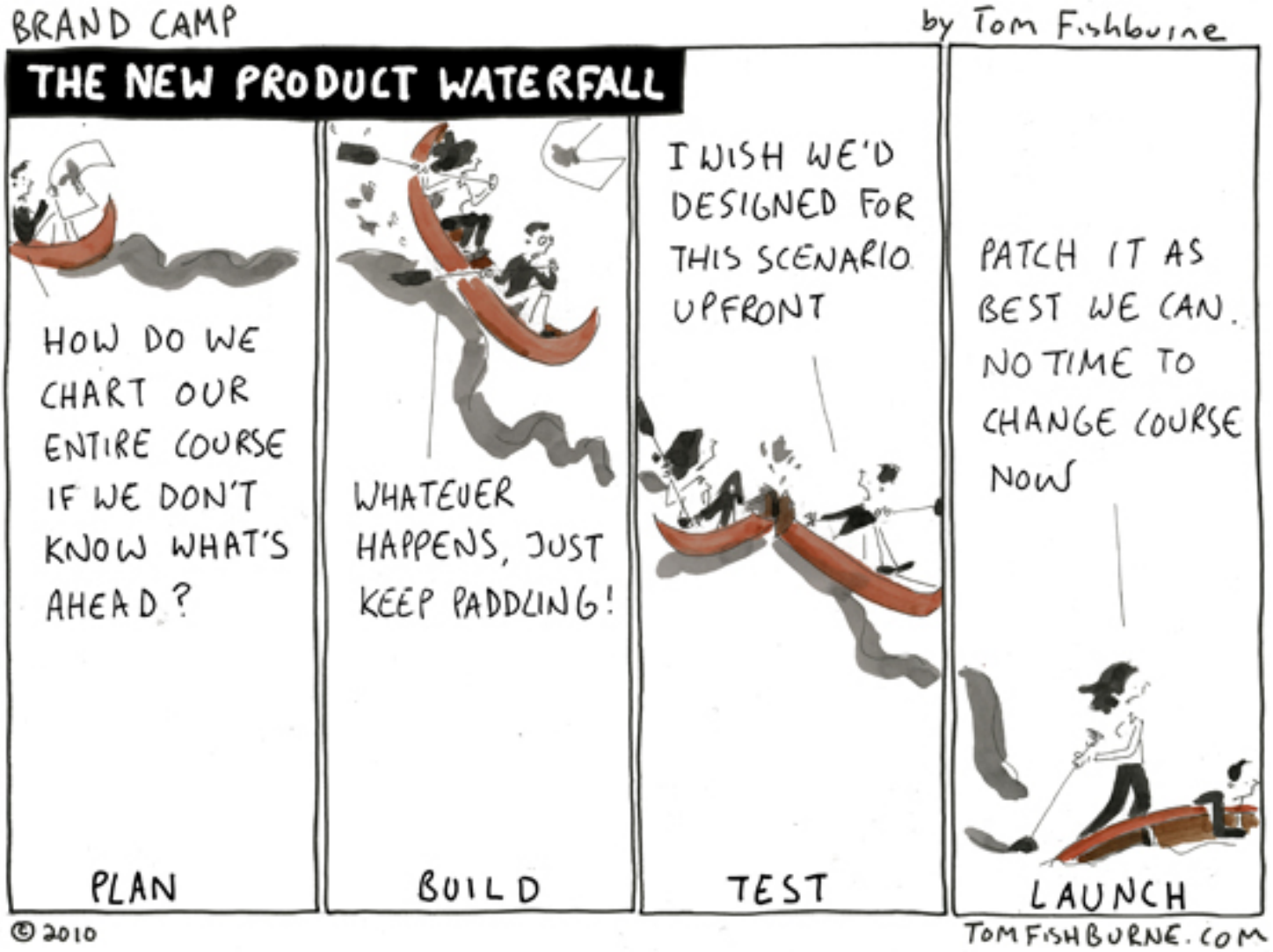
Product Development Process

Stage Gate – process to increase probability of success but -



Safety assessments occur late in the process!

Time, Money and Finite Resources Lost if Tox Issues Identified Late!



Toxicology is Front & Center in Product Safety Debate

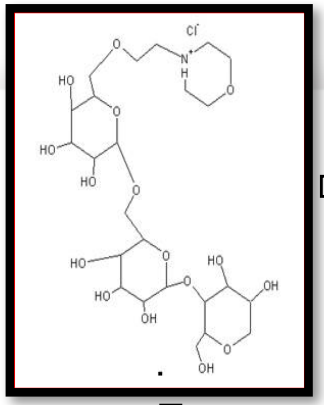
- Can determine the market success or failure of a product
- Awareness of toxicology can:
  - prepare you to respond to customer questions/concerns about a product/chemicals safety
  - provide background to speak to the way products are assessed for safety
  - identify opportunities to improve hazard profiles of materials & products

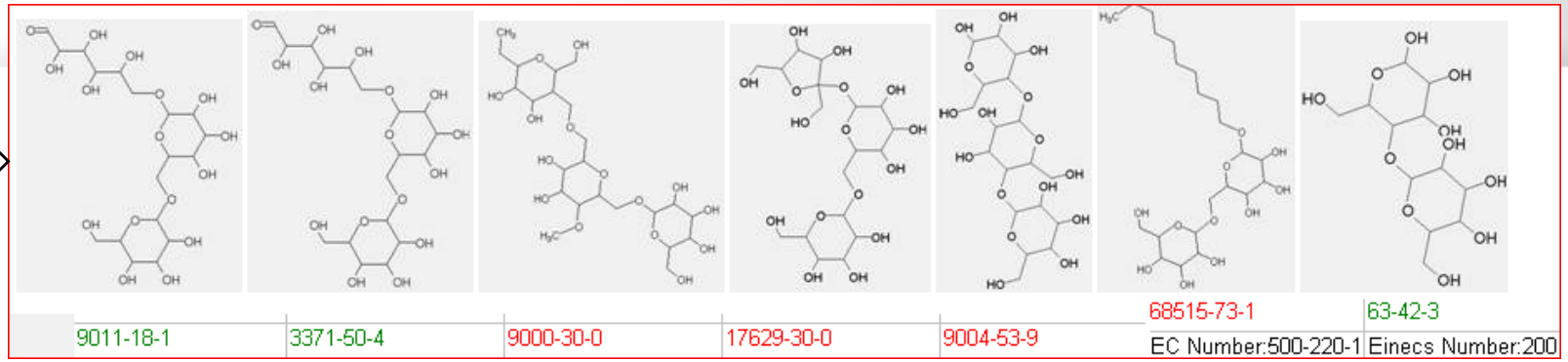
Early Screens: Toxicology “Red Flags”

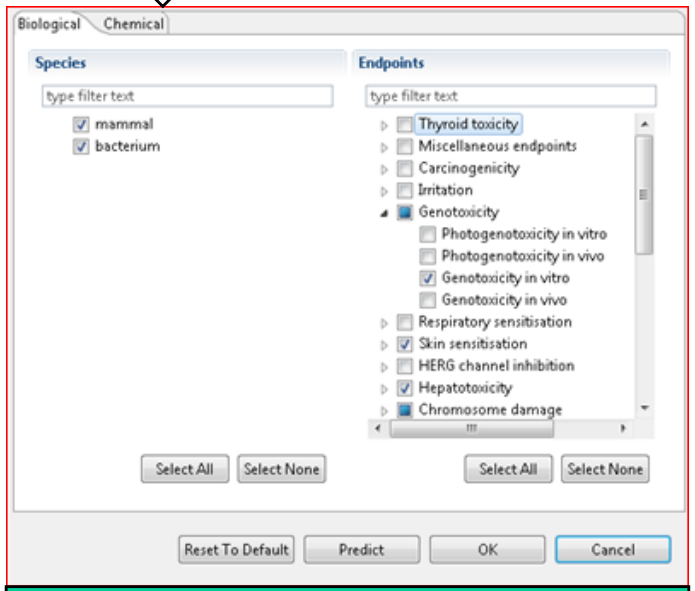
- CMRs
  - **C**arcinogen
  - **M**utagen
  - **R**eproductive/Developmental Toxicant
- PBTs
  - **P**ersistent
  - **B**ioaccumulative
  - **T**oxic to the Environment

Cheminformatics as a teaching tool

Example: Cheminformatics for RSSDS*







- **QSAR endpoints**
  - **Mutagenicity**
  - **Skin sensitization**
  - **Estrogen receptor binding, etc.**

Look for analogues with toxicity data

↘

QSAR, Read-across

↘

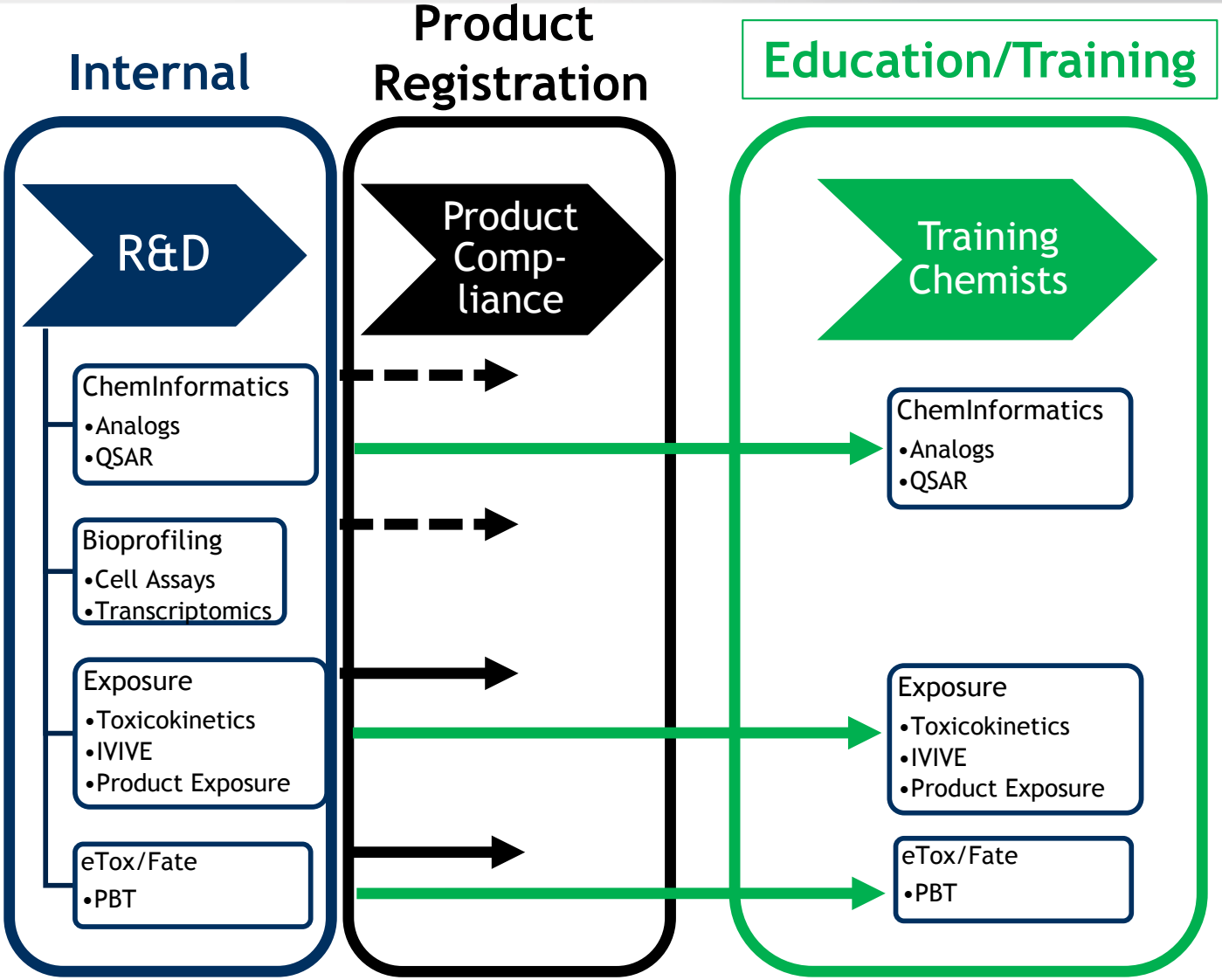
Toxicologist interprets findings

*Research Sample Safety Data Sheet

Why use cheminformatics?

- Approach connects principles of chemistry and toxicology
- Ability to predict safety information using just a chemical structure and/or surrogate molecules when no other information is available
- Hypothesize mechanism-of-action
- Train chemist who can help get sustainable products to market faster
  - Speed, solution-oriented and customer-focused
  - Assist in ranking R&D candidates, business decision-making
  - Support registration and environmental operations

Opportunities for New Chemical Technology Tools



New Tools in Application

LINKING TOXICOLOGY TO CHEMISTRY

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Transferable Concepts

- Connects green chemistry to “green” toxicology
  - There is a need for chemicals that can serve the same function while minimizing potential toxicity
- Computational approaches that can be easily integrated into Chemistry course objectives
  - Physical/Chemical Properties
  - Structural Alerts (SA)
  - Quantitative Structure Activity Relationship (QSAR)

Phys/Chem Properties & Aquatic Toxicity

- Molecular Size & Weight
- Octanol-water partition coefficient (logP)
- Water solubility

- MW increases, aquatic bioavailability/toxicity decrease
- Chemicals with logP<2 have a higher probability of having low acute/chronic aquatic toxicity
- Very poorly water-soluble chemicals (<1 ppb) generally have a low bioavailability, less toxic

NAS. 2014. NAS Framework to Guide Selection of Chemical Alternatives - Case Studies. https://www.nap.edu/read/18872/chapter/14

Structural Alerts

- Chemical structures that indicate or are associated with toxicity
- Can consist of one atom or several connected atoms
- Also called toxicophores/toxic fragments
- Ruled based:

IF (chemical_substructure) IS (present) THEN (skin_sensitizer IS certain)

Structural Attributes that Enhance Biodegradation

- Minimal number of **halogens** (especially F and Cl).
- Minimal chemical **branching** (especially quaternary C).
- Minimal number of **tertiary amine, nitro, nitroso, azo**, and **arylamino groups**.
- Minimal number of **polycyclic residues** (especially more than three fused rings).
- Presence of **esters** (including phosphonates).
- Presence of **oxygen atoms**.
- Presence of **short linear alkyl chain**s (< 4 C) or phenyl rings that can act as sites for oxygenase enzyme activity.

SOURCE: Meylan et al. 2007; Howard and Muir 2013.

Examples – Biodegradability

Negative Influence	Positive Influence
Aromatic sulfonate	Aliphatic sulfonate
Aromatic amine	Aliphatic amine
Aliphatic Ether	Aromatic ether
4+ aromatic rings	Phosphate ester
Azo group	Carboxylate ester
Pyridine ring	Carboxylate amide
Branched hydrocarbon chain	Unsaturated hydrocarbon chain $\geq$ 4 methylene carbon units
Aliphatic ring(s)	Unsubstituted aromatic ring(s)
Aromatic or aliphatic Nitro	Aliphatic nitrile/cyano group
Halogenation (F > I > Cl > Br)	

Quantitative Structure Activity Relationship (QSAR)

- More complex approach than structural alerts
- Model types
  - knowledge-based models
  - statistical models
  - 3-D receptor binding models
  - regression analysis in OECD Toolbox using regional analogs

Free Cheminformatics Tools

- **EPI Suite**
  - Phys/chem properties
  - bioconcentration factor (BCF)
  - https://www.epa.gov/tsca-screening-tools/download-epi-suitetm-estimation-program-interface-v411
- **ECOSAR**
  - Aquatic toxicity
  - https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model
- **OECD Toolbox**
  - Phys/chem properties
  - bioconcentration factor (BCF)
  - Aquatic toxicity
  - Mammalian toxicity (skin/eye irritation, skin sensitization, developmental, ER/AR Binding, genotoxicity
  - http://www.oecd.org/chemicalsafety/oecd-qsar-toolbox.htm

Summary

- Concerns over product safety can determine success or failure of product
- Companies increasingly need chemists who are trained to recognized product safety “red flags” early in the product development process
- Advances in the field of toxicology now make it feasible to easily integrate principles of toxicology into chemistry curriculum
- Cheminformatics, computational models are easily integrated into chemistry curriculum
  - Integrates training on early hazard identification in new product development

Thank You!

Any questions?