

The Crossroads of Chemistry and Toxicology: Advancing Greener, Safer Ingredients and Products

Pamela J. Spencer, Ph.D., D.A.B.T.
Senior Director of Regulatory Affairs & Product Stewardship
ANGUS Chemical Company



C
h
e
m
Toxicology
s
t
r
y



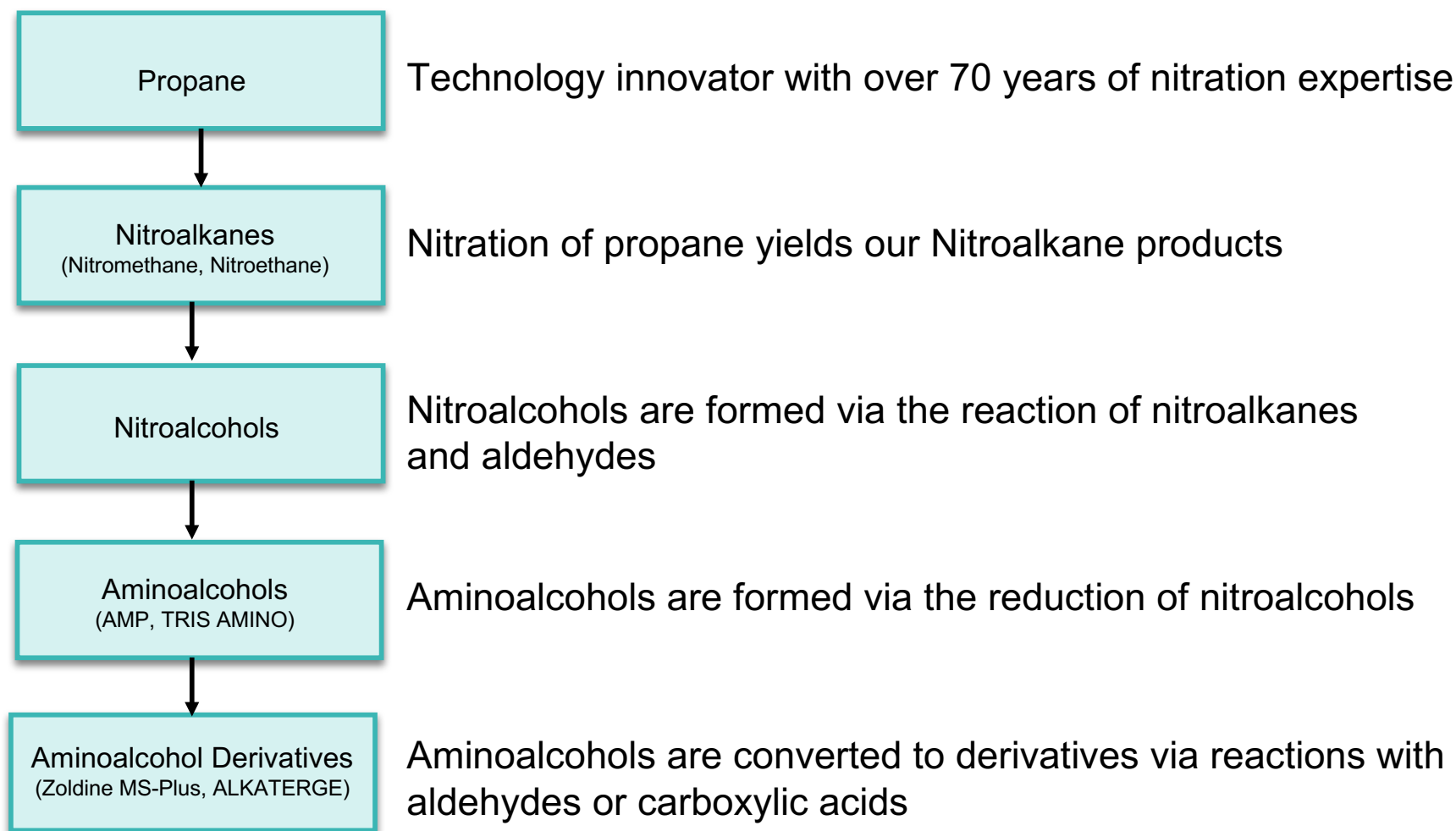
Overview

- Our Products
- Market Challenges
- New Product Introduction
- Early safety screening strategies
- Next steps
- Q&A

OUR PRODUCTS

Chemistry

ANGUS is the only manufacturer in the world that uses propane nitration technology to create a unique set of products.



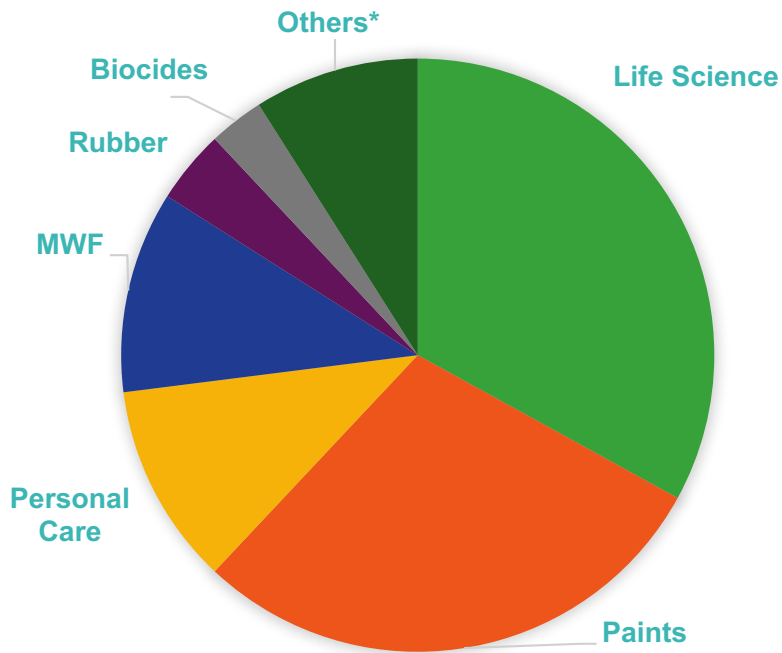
Performance Attributes

- Improves the quality and performance of a variety of formulations
- Extremely versatile and can be tailored to solve multiple challenges
- Multifunctional attributes may include several of the following:
 - Neutralization
 - Corrosion Control
 - Surfactancy
 - pH buffering
 - Moisture Scavenging
 - Oxygen Scavenging
 - Alkaline pH development
 - Emulsification (oil/water; water/oil)
 - Moisture Displacement
 - Dispersancy
 - Chemical scavenging
 - Free-radical scavenging
- Many of our products are known for their mildness and are suitable for sensitive applications such as personal care, pharmaceuticals and other life science utilities

Market Overview

Global specialty platform serving a diversified set of industries

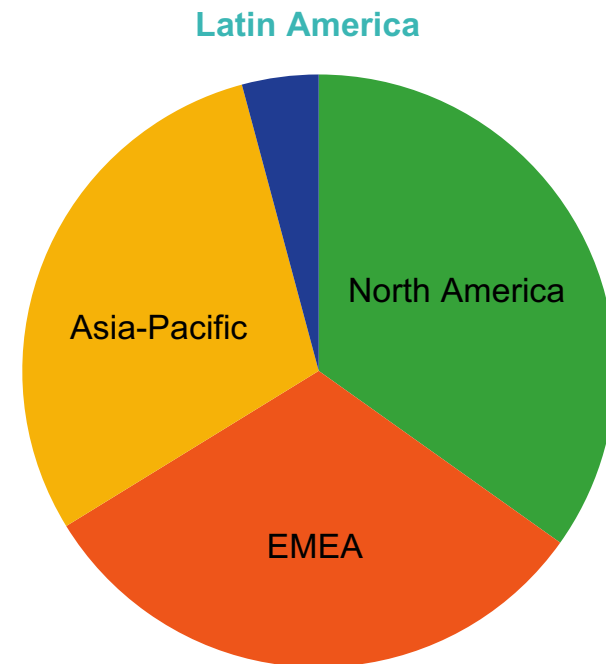
Revenue Split by Industry



Others*:

- Gas Treating
- Mineral Slurries
- Leather
- Adhesives
- Industrial Water

Revenue Split by Geography



Strong, balanced portfolio:

- Product
- End Market
- Geography

MARKET CHALLENGES

Ingredient Safety – Ingredient Bans

The Campaign for Safe Cosmetics

RED LIST

SHAMPOO

- ✓ Ethanolamines (cocamide DEA and others)
- ✓ Parabens (e.g., butylparaben)
- ✓ UV filters (Octinoxate, Oxybenzone)
- ✓ Formaldehyde releasing preservatives (diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin)
- ✓ Sodium Laureth Sulfate and other -eth compounds, which can be contaminated with 1,4-dioxane and ethylene oxide

CAMPAIN FOR SAFE COSMETICS

Toxic Chemicals in Shampoo

Fragrance can be made of dozens of different secret ingredients

Parabens linked to breast cancer

Sodium Laureth Sulfate contaminated with the carcinogen 1,4-dioxane

DMDM Hydantoin releases the carcinogen formaldehyde

Look for the **MADE SAFE** seal.

www.madesafe.org



3 APPS FOR CHECKING PRODUCT INGREDIENTS
IN FOOD, BEAUTY, AND CLEANING PRODUCTS

DISSECTING IN-N-OUT[®] BURGER & FRIES

- Meat from large **Factory Farms** where beef is raised with **Routine Antibiotics** which is putting us at risk for contracting dangerous antibiotic-resistant infections that can no longer be treated with antibiotics.
- Meat that is raised with **Growth Hormones** that are linked to increased cancer risk.
- **French Fries** are submerged and fried in **GMO Cottonseed Oil** - one of the worst inflammation promoting oils grown with toxic pesticides not approved for food.
- Sandwiched between buns made with **Fully Hydrogenated Soybean Oil** and **Sugar Beets** likely from GMO crops heavily treated with **Monsanto's Roundup Herbicide**, a probable carcinogen according to the World Health Organization.
- Slathered with sauce made with **High Fructose Corn Syrup** shown to contribute to Type II Diabetes, especially in children.
- Sauce artificially colored with **Yellow #5** derived from petroleum and linked to childhood behavioral problems requiring a warning label in Europe.
- The complete Ingredient list is **TOP SECRET...** and until In-N-Out releases it you'll never know exactly what you're eating!

FoodBabe.com **FOOD BABE** #FoodBabeArmy

ARE BATH BOMBS SAFE?

Dr. Axe

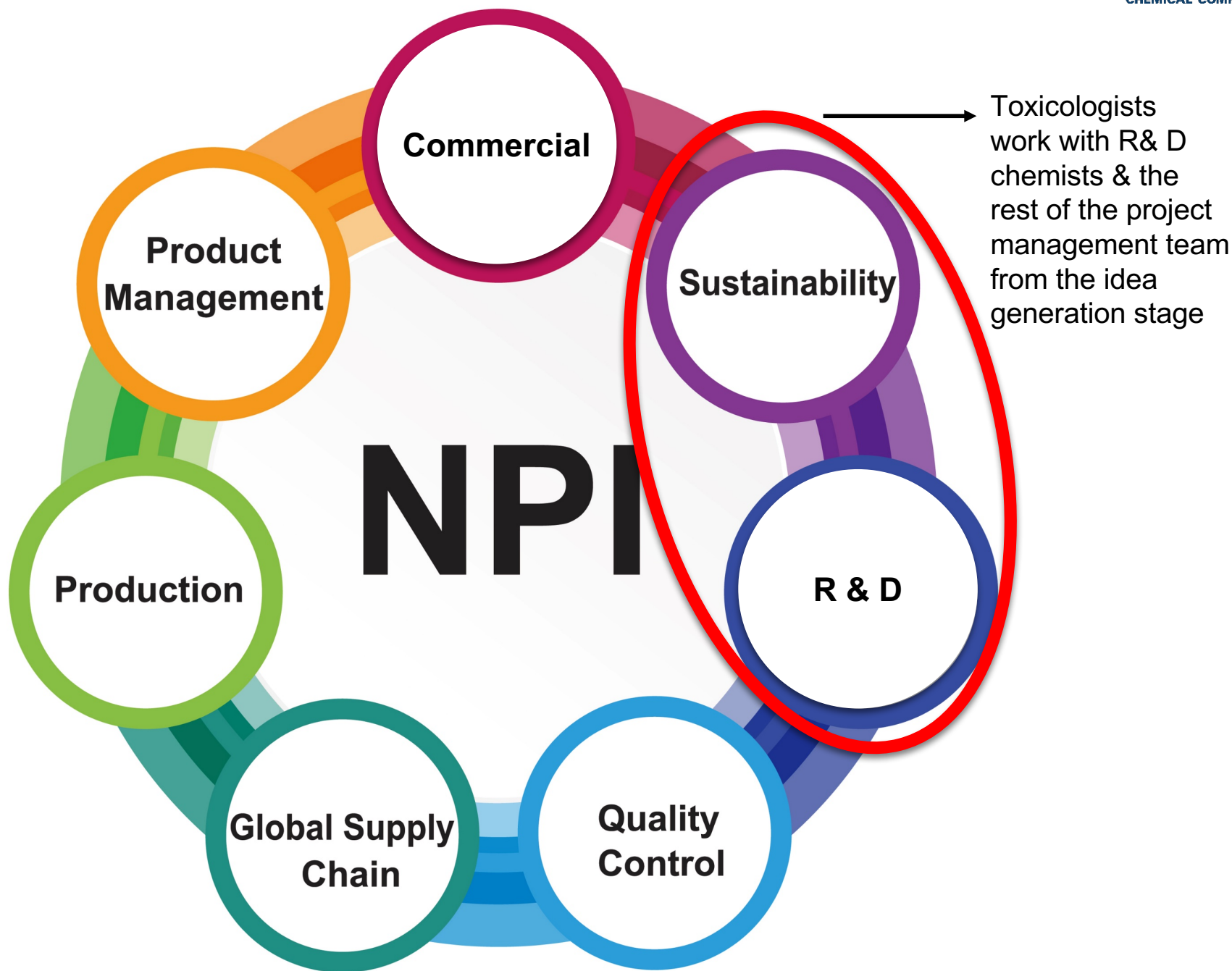
Titanium Dioxide Applications

- Food Industries:** Confectionaries, Sweets
- Cosmetic Industries:** Toothpaste, Sunscreen
- Bakery Industries:** Bread

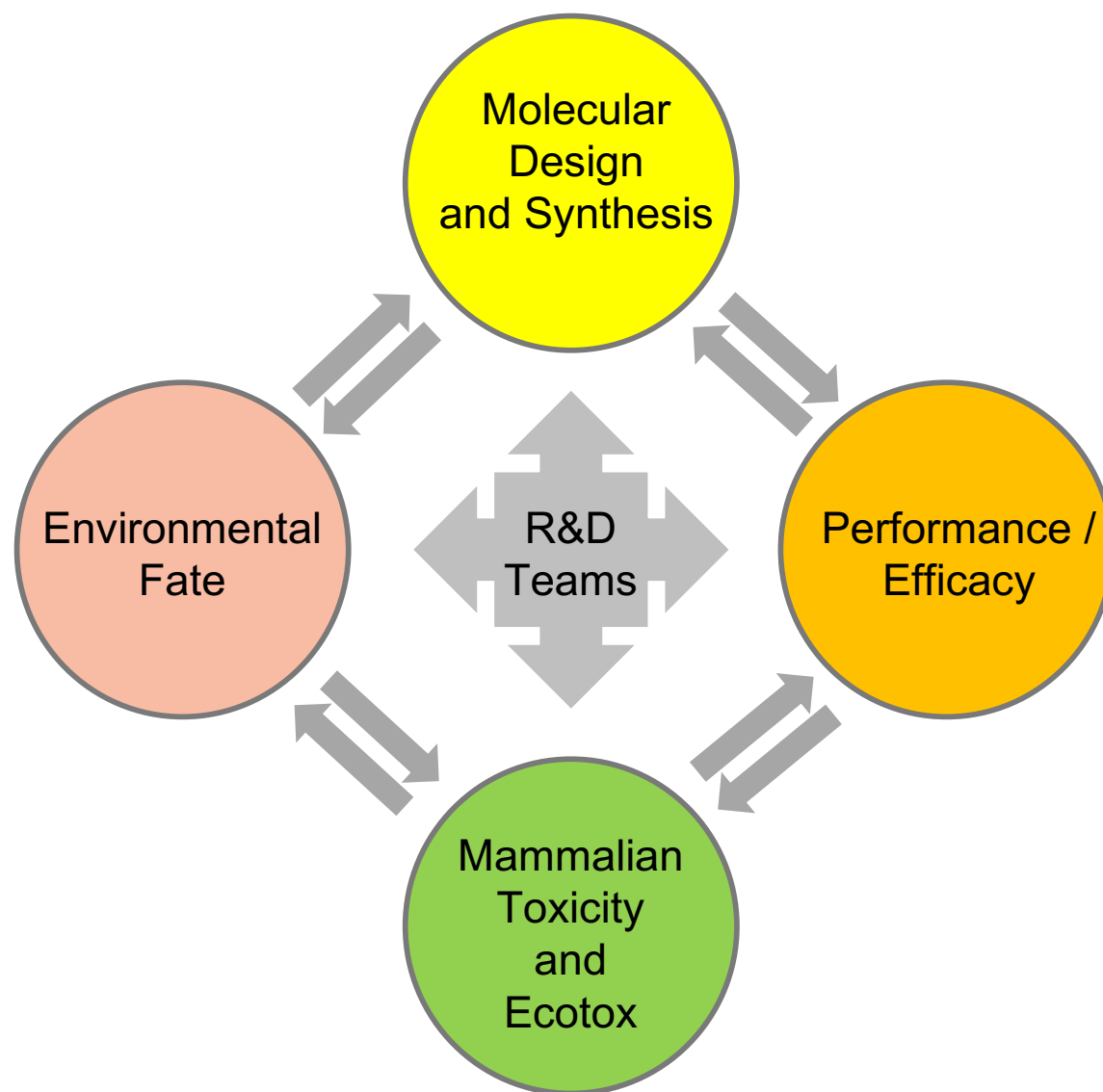
Debra.com

NEW PRODUCT INTRODUCTION

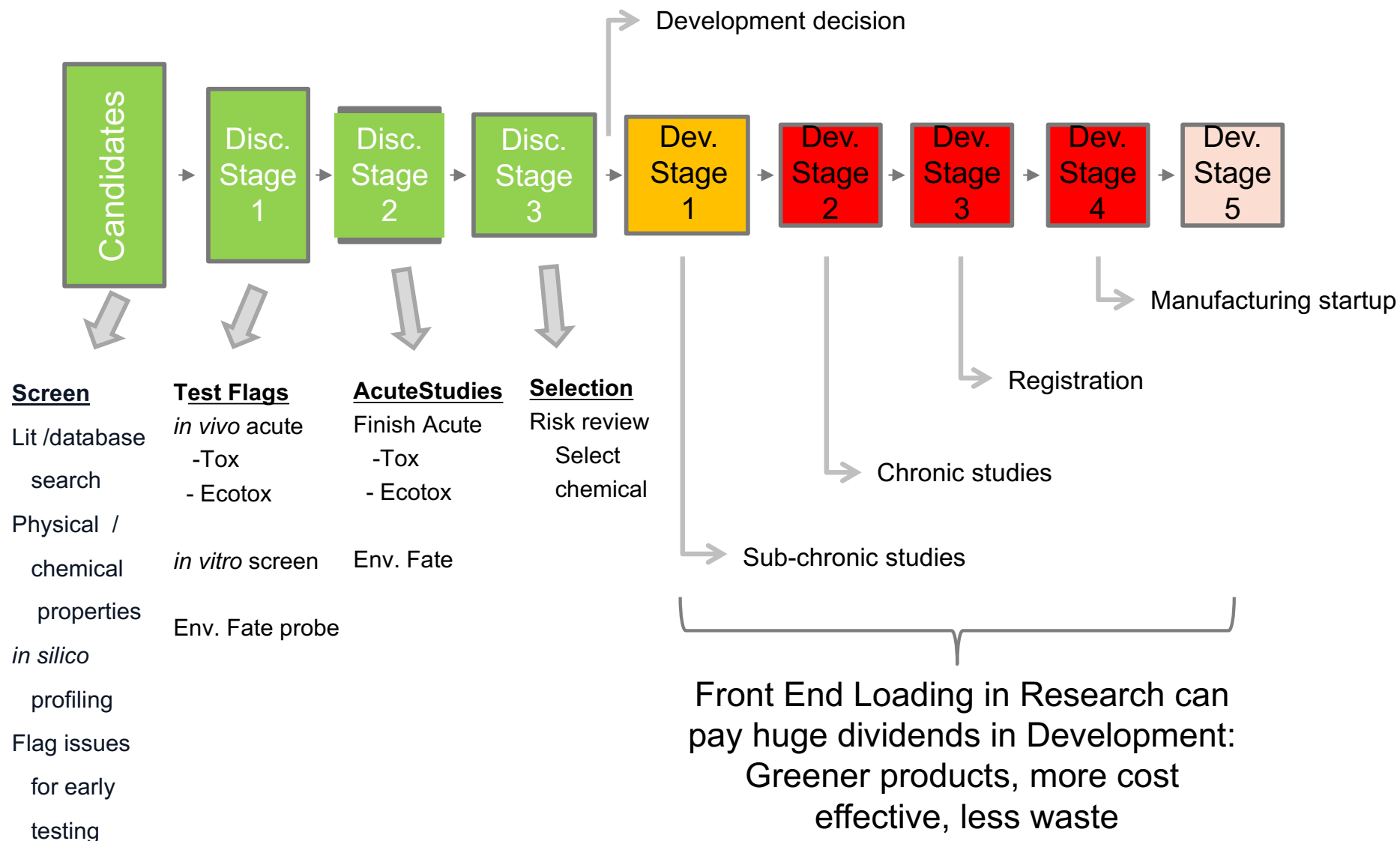
New product Introduction (NPI)



Iterative Nature of Early R&D



Integration of New Tools into NPI



Early Screens: Toxicology “Red Flags”

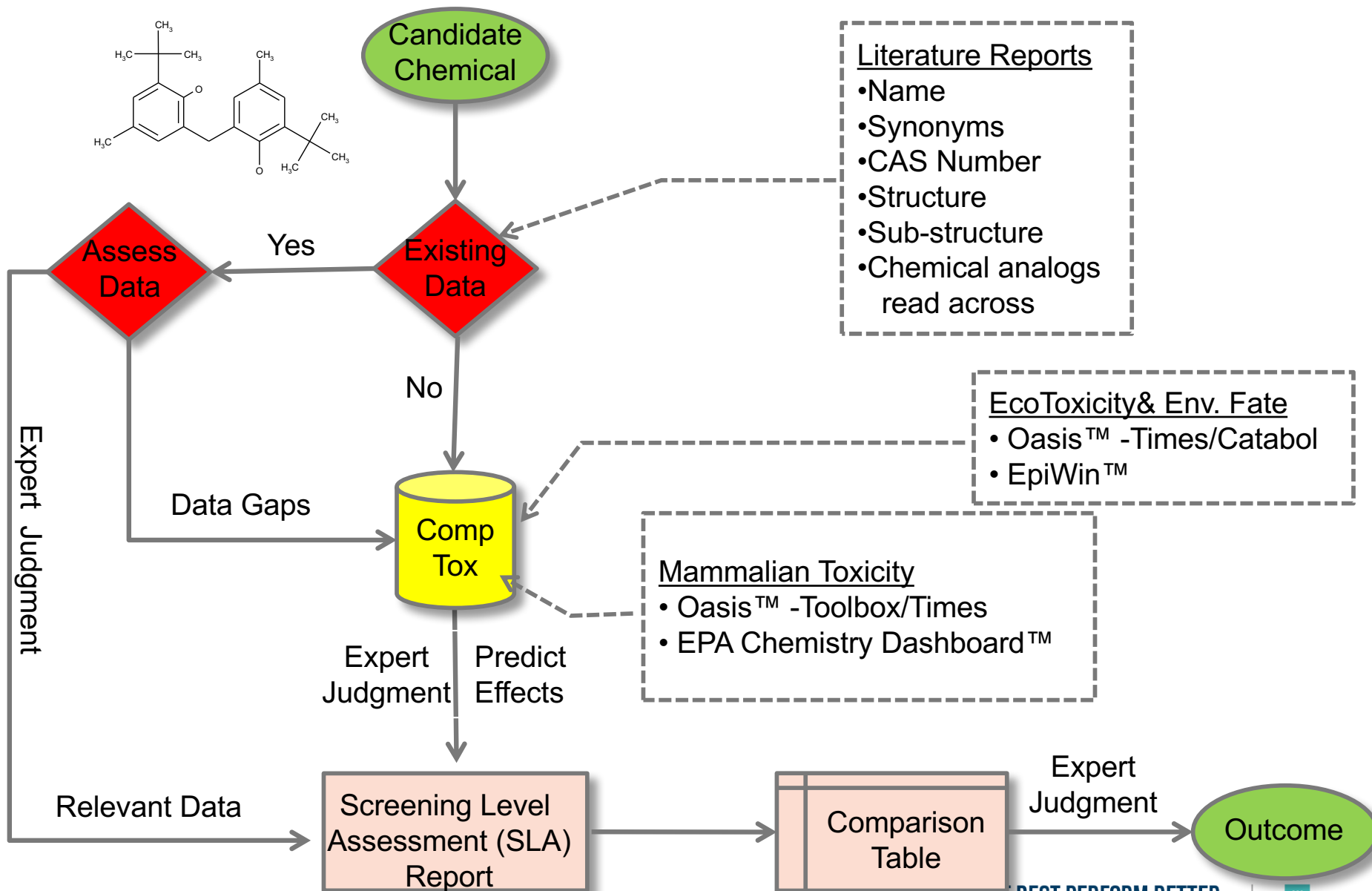
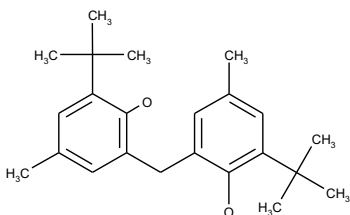
- CMRs
 - Carcinogen
 - Mutagen
 - Reproductive/Developmental Toxicant
- PBTs
 - Persistent
 - Bioaccumulative
 - Toxic to the Environment

Confirm Relevant QSAR Models for Target Chemistry

QSAR Validation Project

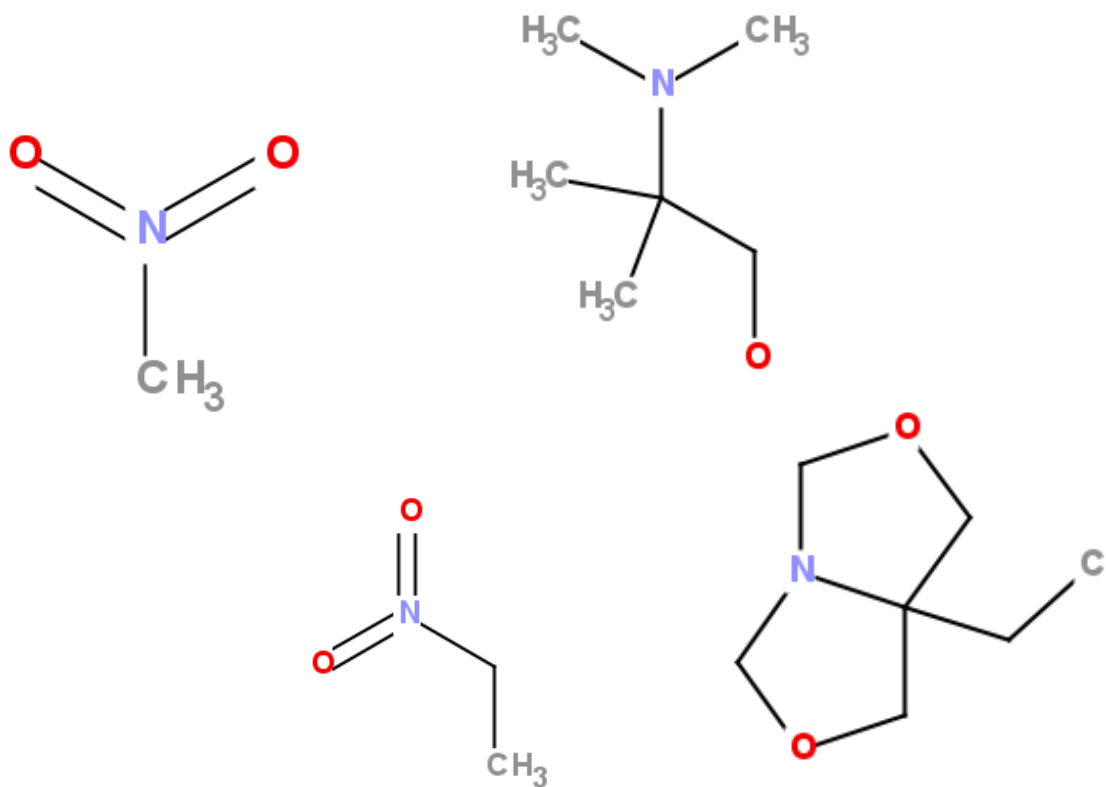
- A number of QSAR models and assessed their applicability for the ANGUS nitroparaffin and derivative chemicals with reference to sensitization, mutagenicity, and ready biodegradability
- TopKat QSAR model not recommended for future use for Angus molecules
- *In silico* models were improved by acquiring additional data to enhance the training sets
- For mutagenicity the QSAR tools appear to have some degree of reliability
- In the case of skin sensitization, it is evident that providing a predictive set of *in vitro* and QSAR models is complex and needs further research
 - conflicting results from *in vitro* assays compared with *in vivo* assay may be the result of the potential for *in vivo* skin metabolism, corrosive properties of these compounds
 - different vehicles used in performing the tests
- For biodegradability when multiple models were used some reliability was also found.

Flow Chart of Screening Level Assessment & Green Chemical Evaluation Process



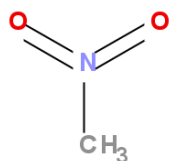
EARLY SAFETY SCREENING STRATEGIES IN PRACTICE

It all starts with a structure!

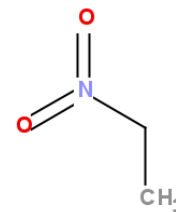


Which one is safer?

Step 1. Read Across to a Chemically Similar Analog*



New chemical candidate



Read across analog

Endpoint	Analog
Acute Oral	LD50 688 mg/kg Rats
Acute Dermal	LD50 ~2000 mg/kg Rats
Skin Irritation/Corrosion	Corrosive
Eye Irritation/Corrosion	Corrosive
Skin Sensitization	Sensitizer LLNA
Repeated Dose	Mild Liver effects at 1000 mg/kg
Reproduction	NOAEL 1000 mg/kg
Genotox	Negative in all in vitro and in vivo studies
Biodegradation	57% degradation in 56 days in OECD 301F
Acute Aquatic Toxicity	EC/LC50 >10-100

*The chemical structures and following data are meant to serve as an illustrative example and do not represent an actual data for the structures.

Step 2. OECD Toolbox Modeling for Candidate Chemical

Endpoint	Model(s)	Result
Acute Oral	Cramer Original/Extension	Low Toxicity
Skin Irritation/Corrosion	Inclusion/Exclusion rules by BfR	Inclusion Rules Not Met
Eye Irritation/Corrosion	Inclusion/Exclusion rules by BfR	Inclusion Rules Not Met
Skin Sensitization	OASIS v.1.4	No Alerts
Genotox	alerts by ISS	No Alerts
Repeated Dose	HESS	Not Categorized
Developmental/Reproduction	DART Scheme v.1.0.	No Alerts
Primary Biodegradation	Biowin 4	Degradation in weeks to months
Ecotoxicity	Verharr (Modified)	Determination Not Possible

Report Out Weight of Evidence Safety Assessment

- No significant alerts resulted from read across or modeling
- OECD Toolbox
 - Modeling results were supported by the testing for chemical analog, except for skin sensitization
 - Three endpoints (skin/eye irritation/corrosion and ecotoxicity) where the target molecule was out of scope for the models utilized

Recommendations/Next Steps

- Advanced candidate chemical to Step 3: in vitro testing to better characterize endpoints out of scope of modeling tools and/or did not align with chemical analog data
- Invitro Test Results:
 - Skin/eye irritation – non irritating
 - Skin sensitization – not a skin sensitizer
- Biodegradation/ecotoxicity screen may also be necessary
- Continue engagement with Project Management Team for NPI to plan for key studies need to ultimately register new product in target global regions

Future Work

- Collaborative project underway with UL to validate REACHAcross™ Tool for use with ANGUS Chemistry
- Project will be modeled will utilize data set from previous QSAR validation work
- Goal – determine if REACHAcross™ tool has improved domain coverage over other QSAR tools currently utilized

Summary

- Concerns over product safety can determine success or failure of product
- Companies can now apply quick and inexpensive tools for estimating EH&S issues early in product development (ID Red Flags)
- When a concern is highlighted via these tools a thoughtful approach to resolving the concern with toxicology data can be prepared in advance to avoid adverse findings in screening analysis
- Increases the ability to launch sustainable new products more cost effectively

Thank You