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Two Current Gaps for Incorporation of NAMs into Toxicity Testing and Risk Assessment

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Conflict of Interest Statement

The speaker is a stockholder in 3M Company, the company whose efforts are described in this presentation. Any opinions or recommendations stated herein are those of the author, and should not be understood as representing the opinions or recommendations of 3M Company.

Since 1902

- Subsidiaries in 71 countries
- Sales in nearly every country
- >90,000 employees
- 200+ factories
- Sales: >$33B
- R&D investment: $~2B
- 55,000+ products
- 100,000+ patents
- One of 30 companies on the Dow Jones Industrial Index

Four Business Groups

Corporate Toxicology and Environmental Science at 3M

Group resides in the Research and Development organization

Approximately 40 individuals

- Includes division support toxicologists, environmental scientists and the Strategic Toxicology Laboratory (STL)

Centralized resource for toxicology and environmental science

- Coordinates all global toxicity testing and human health and environmental risk assessments

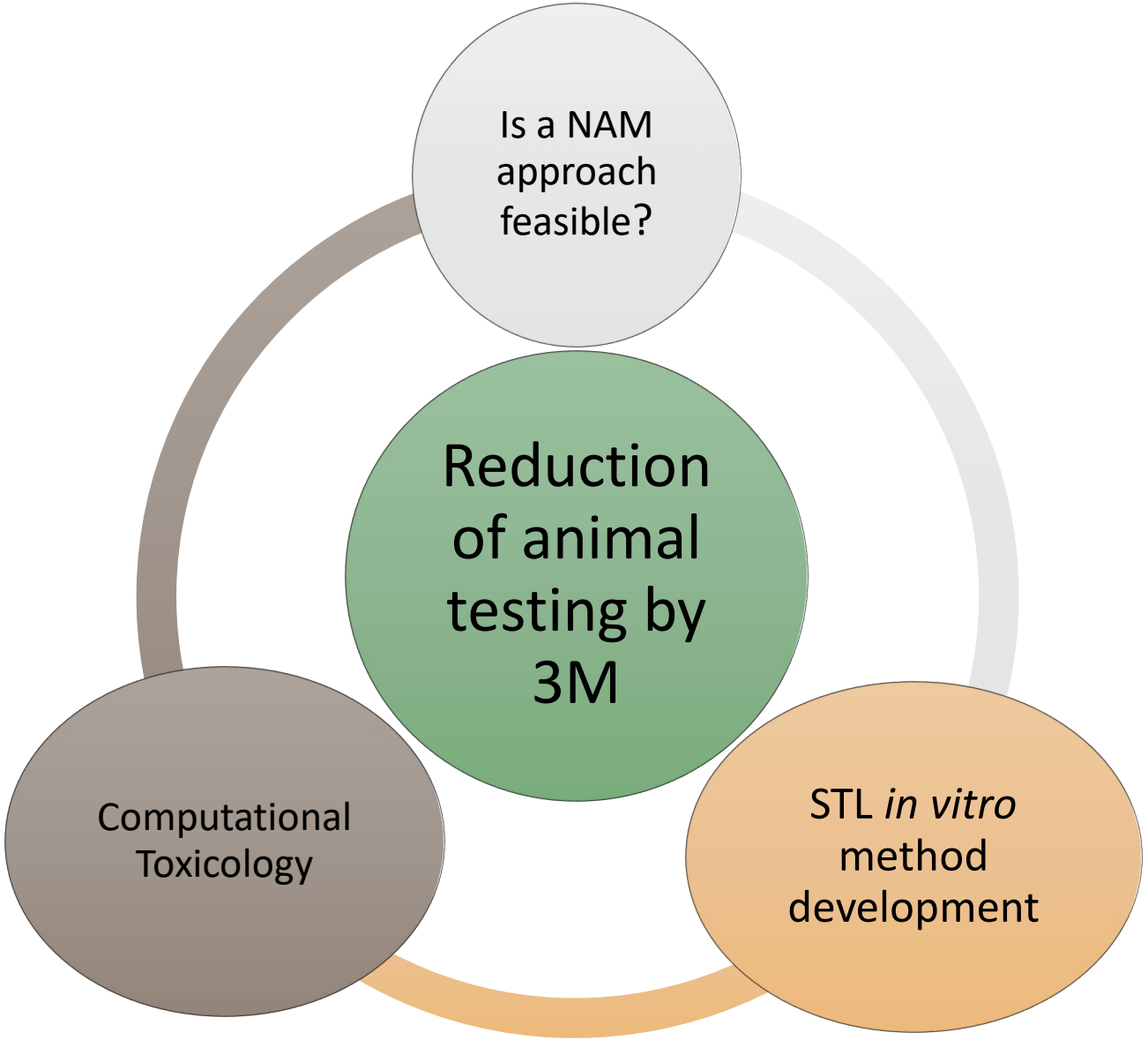
Animal Use Reduction at 3M

3M has long been committed to reduction of animal use

Over the last 10 years, significant progress has been made in the routine incorporation of New Approach Methodologies (NAMs) that don't involve animals

Diversity of 3M product categories adds complexity

- Global requirements
- Multiple regulatory categories
- Unique chemistries



3M Strategic Toxicology Laboratory (STL)

Provides high quality and cost effective toxicity testing and bio-analytical support to 3M business units and research labs for product development and health hazard investigation.

- *In vitro* testing is GLP compliant

- Both 2D and 3D culture systems

Computational Toxicology Program

Estimates used for a variety of endpoints and purposes

Acute toxicity

Dermal sensitization

Mutagenicity

Irritation potential

ADME

Environmental

GHS and other hazard classifications

REACH and other global chemical registrations

Regulatory submittals, including ICH M7 assessments

New chemistry screening

Environmental responses

Opportunities for Improvements

Two examples of gaps with NAM incorporation:

- Models that allow estimates for polymers and chemistries typically outside of the applicability domain for most approaches

- A dermal sensitization model that would allow testing for mixtures, final products and chemicals

Example One – Low toxicity but …

- Routinely faced with lack of hazard data, especially acute toxicity (oral LD_{50}, etc.) for chemistries that are anticipated to be relatively non-toxic

- Types of chemistries:

  - Often polymers with variable molecular weights, typically with very limited water solubility

  - Halogens, metals other non-organic functional groups

Example One – Low toxicity but …

- Today, there is not a generally accepted non-animal approach that would be useful in this scenario

  - (Q)SAR programs don't run polymers and are limited for non-organics for oral LD_{50} estimates

  - There is not an *in vitro* approach to provide an estimate of acute toxicity (oral LD_{50}). OECD guidance document 129 has limited utility

Improved computational tools or in vitro models are needed to fill these gaps

Example Two – Dermal Sensitization Gaps

- Great progress has been made with NAM development for the dermal sensitization endpoint, especially with the OECD 442 series of test guidelines
- There are limitations to the current *in vitro* testing options though
  - Depending on the method chosen, there are physicochemical requirements for the test articles
  - The current OECD approved *in vitro* tests are two-dimensional cell culture assays, so the test article must be capable of being solubilized in cell culture media.
  - Also limited metabolizing capability

Example Two – Dermal Sensitization Gaps

These methods do not allow evaluation of insoluble chemicals or final products

- Compared to dermal irritation/corrosion assays using a three dimensional tissue culture model, which allow testing of multiple physical forms, solids, liquids, waxes, etc.

A model to allow evaluation of more forms of test articles (3D human tissue?)

- ***Eliminating solubility issues and physical limitations***
- ***Help inform risk assessment, i.e. trace level sensitizers in final formulations***
- ***Needs to be OECD approved***

Summary

The implementation of New Approach Methodologies (NAMs) has been very successful at 3M by focusing on building internal capabilities in computational toxicology and *in vitro* approaches.

Two examples of opportunities for improvements have been identified:

- Challenging test articles (polymers, non-organic functional groups, insolubilities) for *in silico* modeling and *in vitro* acute toxicity testing
- A model for dermal sensitization testing to allow evaluation of more test article forms and also help inform risk assessment for trace level sensitizers

Thank you!

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