3M Science. Applied to Life.™

Alternative Method Program Development for Inhalation Toxicity at 3M

Lawrence Milchak, Ph.D., DABT
Senior Manager, Corporate Toxicology and Environmental Science
3M Sustainability and Product Stewardship

Since 1902

- Subsidiaries in 71 countries
- Sales in nearly 200 countries
- >90,000 employees
- 200+ factories
- Sales: >$30B
- R&D investment: $~2B
- 55,000+ products
- 100,000+ patents

Science improving lives for more than a century

- Wetordry™ Sandpaper
- Scotch® Masking Tape
- Scotch® Cello Tape
- Scotchlite™ Reflective Signage
- 3M™ Flat Fold Disposable Respirator with Valve
- Scotch-Brite™ Sponge
- Micropore™ Medical Tape
- Command™ Adhesive Strips
- Post-it® Notes
- 3M™ Aluminum Conductor Composite Reinforced (ACCR)
- Cubitron™ Abrasives
- 3M™ 360 Encompass™ System
- Scotch® Magnetic Tape

Corporate Toxicology and Environmental Science at 3M

Toxicology group resides in the Sustainability and Product Stewardship Department

- Corporate staff group reporting through Research and Development

Approximately 35 individuals

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

Centralized resource for toxicology

- Coordinates all global toxicity testing and human health risk assessments

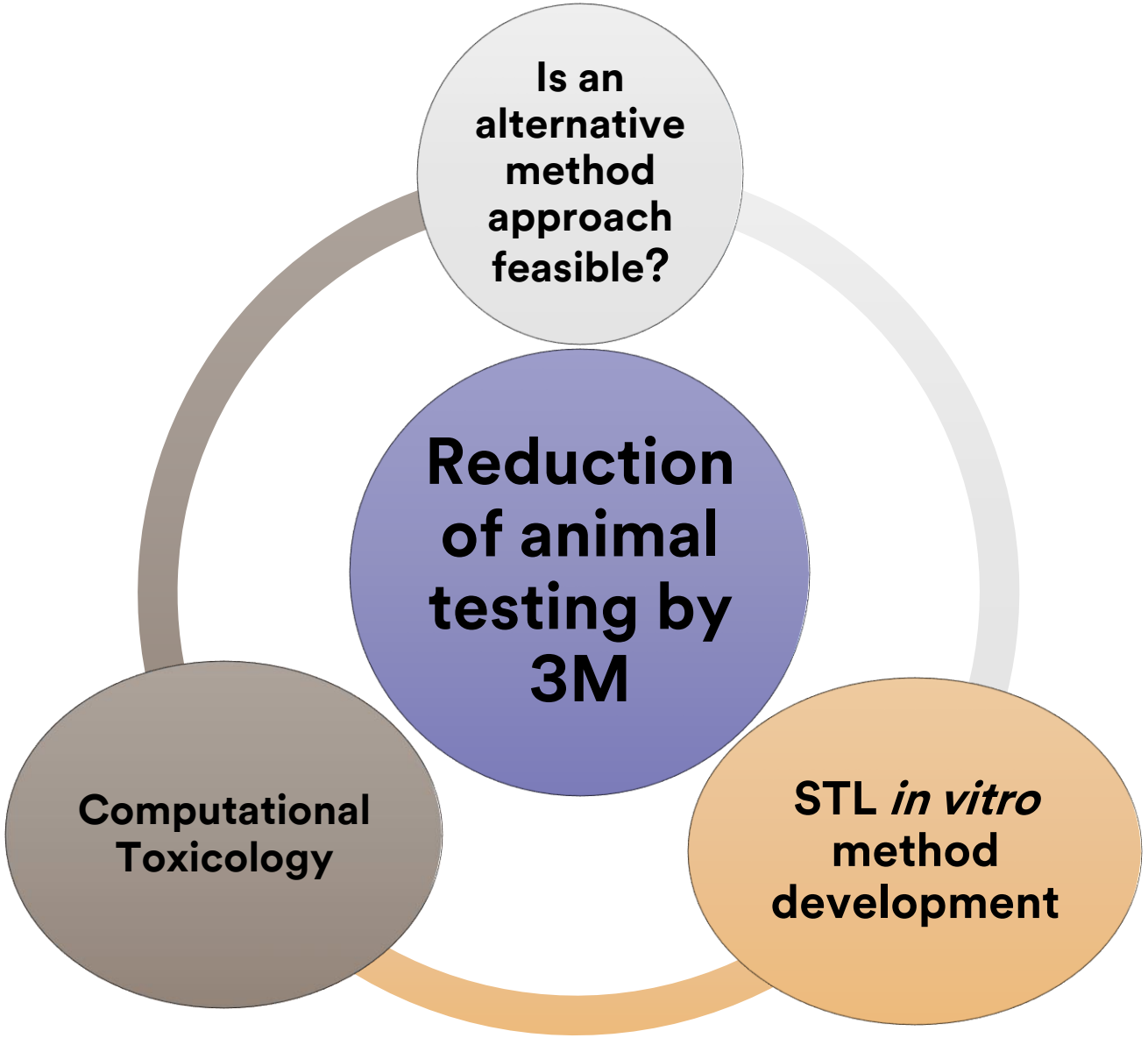
Animal use reduction at 3M

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 non-animal evaluation methods

Diversity of 3M product categories adds complexity

- Global requirements
- Multiple regulatory categories
- Unique chemistries



Computational Toxicology Program Development

Build Internal Capabilities – Acute Toxicity Estimates

- Estimates of acute toxicity for GHS classifications
- Built software approaches for data collection, (Q)SAR, structural alerts and read-across
- Public and commercial software
- Greatly eased testing burden for acute toxicity studies

Build Database for Computational Tox Results

- Stores all results and structures
- Searchable by structural similarity, substructure, etc.
- Greatly improved consistency and speed of estimates
- Database today contains nearly 1000 compounds that been assessed

Expand Capabilities for Endpoint Estimates

- Internal guidance process for other endpoints
- Defines use of computational estimates for classification purposes
- Further refinement of tools for (Q)SAR, structural alerts and read-across

Build Internal (Q)SAR Models

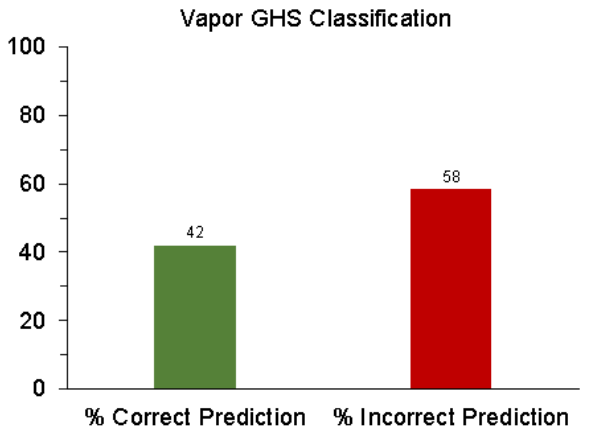
- Build (Q)SAR models using historical, internal data
- Difficulty in model building due to differences in test methods
- Acute toxicity - inhalation model
- New test results are constantly being added to the model

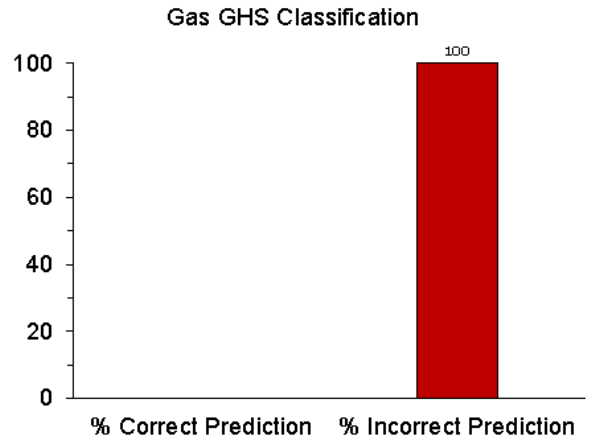
Computational Approaches for Inhalation Toxicity

- Acute inhalation toxicity is a key endpoint for evaluation
- Historically, few commercially available models for LC50 estimation
- Evaluation of available model did not show good estimation potential when compared to internal, historical LC50 data[1]

GHS Classification Criteria for 4-Hr Acute Inhalation Toxicity[4]

GHS Hazard Category	Vapor	Gas
Category 1	≤0.5 mg/L	≤100 ppm
Category 2	>0.5 mg/L to ≤2 mg/L	>100 ppm to ≤500 ppm
Category 3	>2 mg/L to ≤10 mg/L	>500 ppm to ≤2,500 ppm
Category 4	>10 mg/L to ≤20 mg/L	>2,500 ppm to ≤20,000 ppm
Category 5	>20 mg/L	>20,000 ppm





[1] All animal testing performed under IACUC-approved studies and laboratories are under IACUC/Ethics Committee oversight

Computational Approaches for Inhalation Toxicity

- Chemicals of interest from historical dataset were not represented well in the commercially available model
  - Vapor LC50s - model more commonly predicted a higher LC50 than actual data
  - Gas LC50s - model predicted a lower LC50 than actual data
- Next step – improve model by supplementing and building with internal data
- Adding data to the model improved prediction capability
  - Vapor LC50 estimates improved by 34%
  - Gas LC50 estimates improved by 25%
- Identification of key structural features and physical properties that impact overall toxicity

3M

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.

- Emphasis on alternative method utilization
- Heavy use of 3D human tissue models

Strategic Toxicology Laboratory (STL)

Inhalation Toxicology Testing

- Need an *in vitro* model to screen new chemistries
- Initial focus on vapors and gases
- Three dimensional tissues offer promise
- Correlate with *in vivo* LC50 vs local effects

3M

Strategic Toxicology Laboratory (STL)

Vitrocell® System

- 12/12 system with dilution system and climatic chamber
- Vapor exposures (vaporized liquids) and also gases
- Can expose at three different concentrations
- Micro-GC to measure concentrations

3M

Strategic Toxicology Laboratory (STL)

Key Learnings and Challenges

- 3D tissues are representing a target area
  - Acute inhalation toxicity can involve many systemic targets and mechanisms
- Metabolic capabilities of tissue types
- Dosimetry – direct liquid applications vs vapor exposures
- Lack of validated model – Must define the goal of experimental approaches

3M

Summary

The implementation of alternative methods has been very successful at 3M by focusing on building internal capabilities in computational toxicology and *in vitro* approaches.

Acute inhalation toxicity is particularly challenging, can involve many exposure differences, target systems and mechanisms

Commercially available computational models may not represent chemical classes of interest

- More success building internal models

Work with exposure systems for *in vitro* evaluations requires significant development time to gain a thorough understanding of many critical aspects, such as exposure concentration, dosimetry and viability measurements – a defined goal is critical

3M will continue to invest heavily in the development of animal alternative methods

Thank you