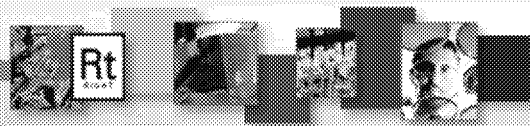
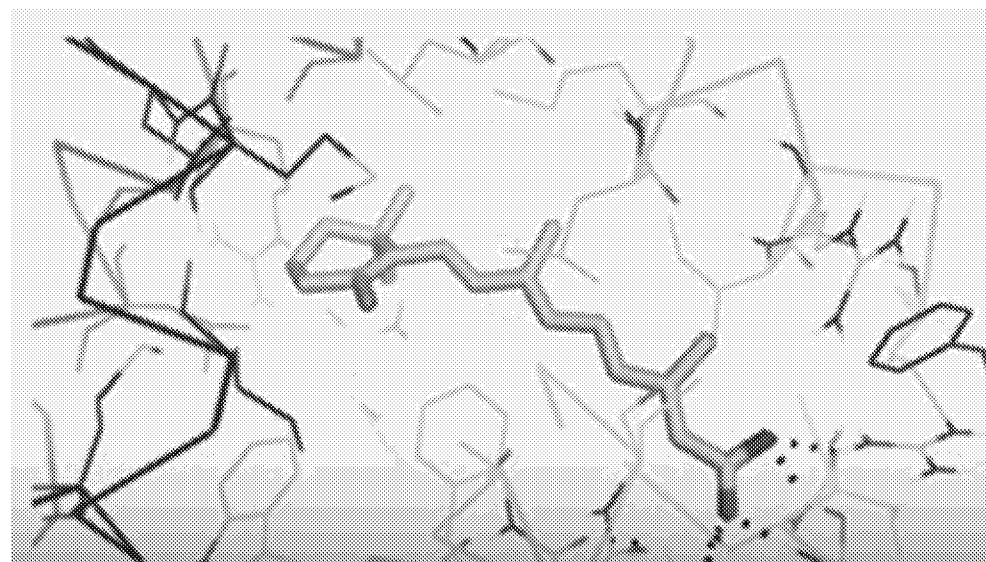


Dow's Predictive Toxicology Program and the LCSA

Sue Marty, PhD, DABT
TERC Science Director
August 16, 2017



The **Rt** Formula

Agenda

- An Introduction to TERC
 - Why does Dow need a Predictive Toxicology Program?
- Dow's Predictive Tox Program
 - Five Science Pillars
- TSCA/LCSA
 - An Integrated Approach
 - Opportunities to Partner?



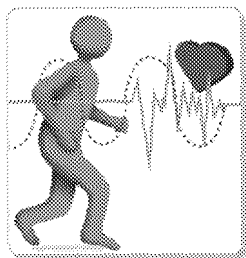
The  Formula

TERC- Toxicology and Environmental Research and Consulting

A Toxicology testing and consulting expertise center within Dow

An industry leader in applying the best science and technology to:

- Support sustainable product development (guide decision making)
- Support product registrations to speed time to market
- Address complex product safety questions



Protecting human health and the environment

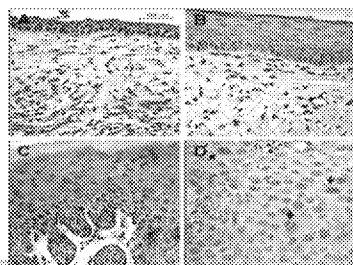
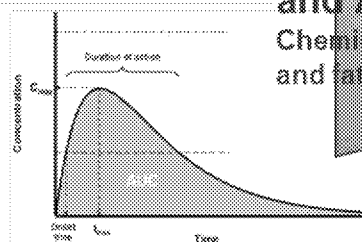
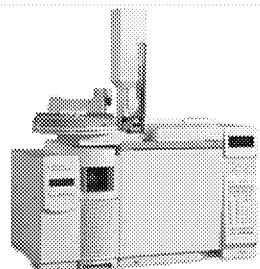
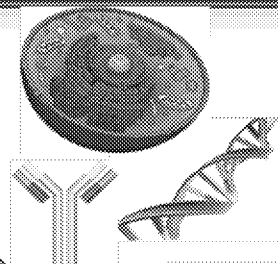
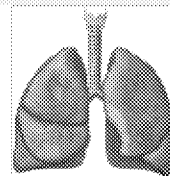


- ~200 people globally
 - Full-service Toxicology Lab in Midland Michigan
 - Expert Internal Toxicology Consultants- Globally
- > 70 advanced degrees in Toxicology or related disciplines (Ph.D, M.Sc., DVM, DABT)
- World Class Expertise in Traditional and 21st Century Toxicology testing approaches



The **Rt** Formula 3 3

TERC: Complete Toxicology Support for Product Safety Assessment



Developmental & Reproductive Toxicology

Respiratory Toxicology
Inhalation exposures

Genetic and Molecular Toxicology
Mechanistic research

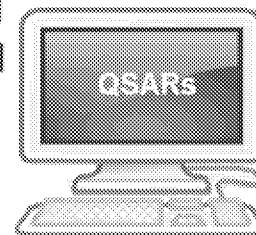
Toxicokinetics and Analytical
Chemical metabolism and rate

Toxicology Expertise

- supporting sustainable product development
- addressing complex product safety questions

A History of Scientific Excellence

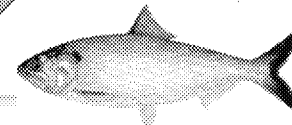
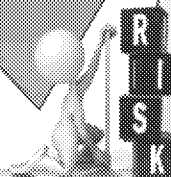
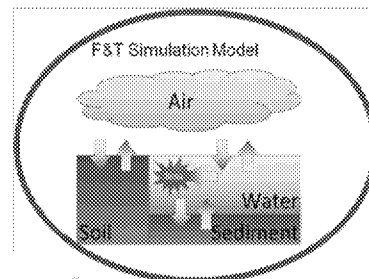
Predictive and Computational Toxicology
Non-animal approaches



Pathology
Board Certified Pathologists

Exposure and Risk Assessment

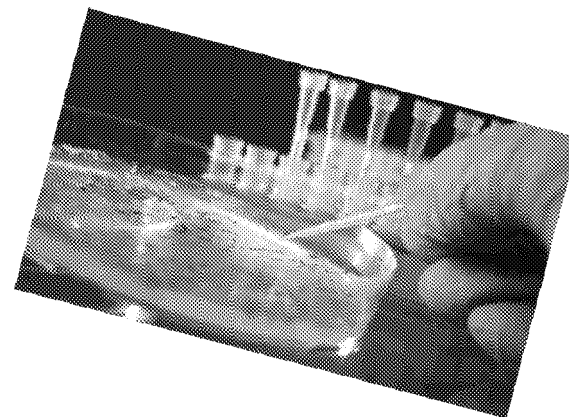
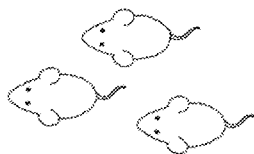
Environmental Fate and Ecotoxicology



The **Rt** Formula

Why Does Dow Need a Predictive Tox Program?

- PT applications in modern chemical product safety assessment
 - Design and select more sustainable products
 - Tailor regulatory testing based on alerts
 - Save time, money and animals



- Increase confidence in chemical technology (2025)
 - More attention to front end = less effort defending commercialized molecules
- Integrated testing strategy
 - Predictive approaches + conventional animal testing



Dow's Predictive Toxicology Program

Cheminformatics

Bioprofiling

Toxicokinetics

Environ Chem/Tox

Exposure

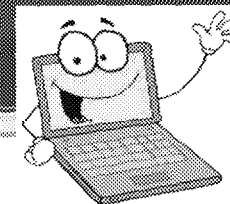
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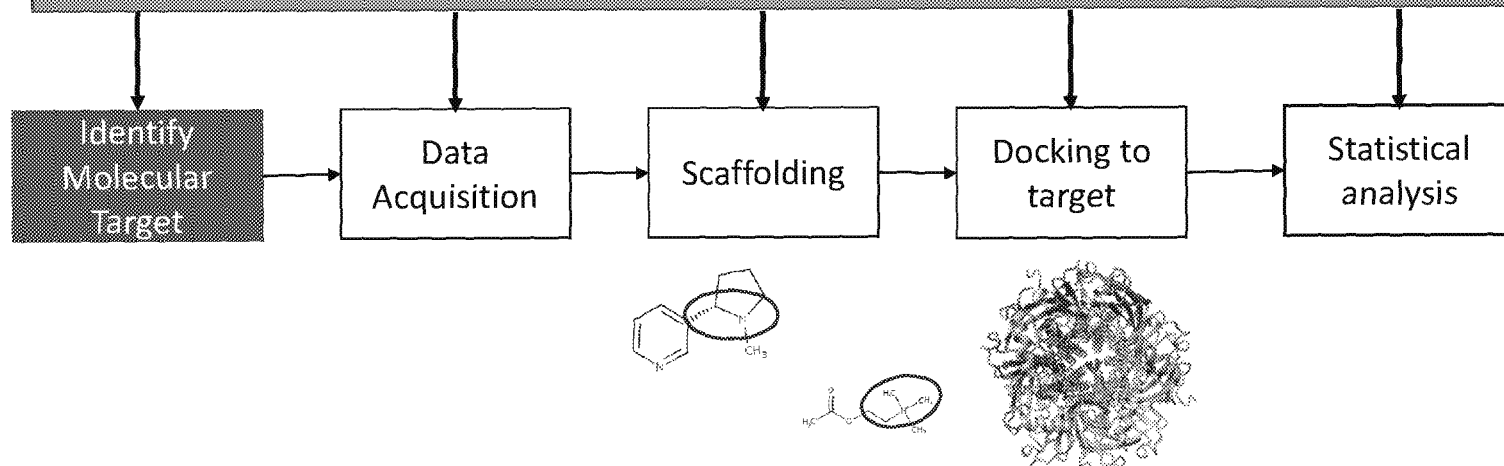
The
Rt
Formula

Formula

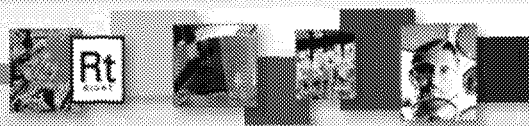
Cheminformatics: Identifying Cholinergics



The Human Element (SME in Area of Interest)



	<u>Nicotinic ACh Receptor</u>	<u>Muscarinic ACh Receptor</u>	<u>Acetylcholinest erase</u>
Sensitivity	96.44%	99.33%	98.91%
Specificity	82.35%	50.49%	23.94%
Predictive Negative Value	98.12%	98.93%	96.57%
Accuracy	86.68%	72.49%	56.78%



The **Rt** Formula

TERC Cheminformatics: Mechanisms of Acute Toxicity

■ Reactivity

- Acids/bases – protein denaturation
- Non-specific protein-binding via reactivity
- Metabolism to reactive protein-binder
- Alkylation
- Radiation poisoning – DNA/tissue destruction
- PhysChem properties subject to precipitation

■ Non-specific lipid membrane disruption

■ Chelation

■ Mitotic spindle poison by binding tubulin

■ Energy

- Mitochondria inhibition
- Phosphorylation of glucose inhibition
- Hexokinase (glycolysis) inhibition
- Transketolase (glycolysis) inhibition
- Inhibit pyruvate dehydrogenase (glycolysis)
- Bcr-Ablytysine kinase inhibition
- Inhibit aconitase (TCA cycle)

■ Vitamin interference

- Vit B6: Pyridoxine phosphokinase
- Ubiquinone analogs
- Folate analogs

■ Protein synthesis inhibit

■ Nucleotide synthesis inhibit

- GMP synthetase inhibit – purine biosyn
- G6PD inhibition
- IMP dehydrogenase inhibit – purine biosyn
- Adenylsuccinate synthetase inhibit – purine biosyn
- Adenylsuccinase inhibit – purine biosyn

■ Blood

- Anticoagulation
- Heme biosynthesis inhibit

■ Vasoactive/blood pressure

- Histamine activation – inhibit ligand-gated Cl⁻ channel

■ G-Protein coupled receptors

- 5-Hydroxytryptamine) receptor
- α - β Adrenergic receptor agonist
- GABA receptor
- Dopamine receptor
- Adenosine receptor
- CNS μ -, d-, K-opioid receptors

■ Cys-loop ligand gaited ion channels

- Nicotinic acetylcholine receptor
- GABA receptor
- Glycine receptor
- 5-HT₃ (5-Hydroxytryptamine) receptor

■ Neuro/Ion Channel Signaling

- Acetylcholinesterase inhibit
- Voltage-gaited channels
- Sodium/potassium ATPase
- Block synthesis of neurotransmitter glutamate
- Norepinephrine reuptake inhibitor
- NMDA receptors
- Ether-a-go-go (ERG) voltage-gated K⁺ channel

■ Aryl hydrocarbon receptor

■ Beta2-macroglobulin binding kidney

■ Nuclear receptors; Transcription factors



Bioprofiling: Current *in vitro* Capabilities

Dermal corrosion & irritation

- Corrositex
- EpiDerm corrosion
- EpiDerm irritation

Ocular corrosion & irritation

- BCOP
- NRR
- EpiOcular

Skin sensitization

- KeratinoSens
- DPRA
- SENS-IS (2017)

Phototoxicity

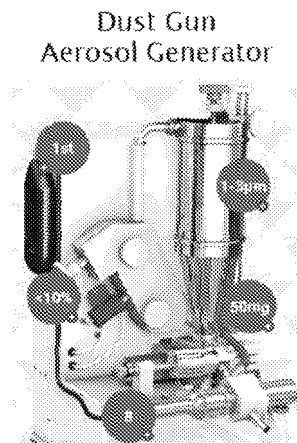
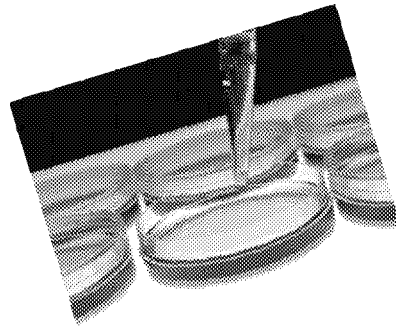
- 3T3 NRU

Respiratory irritation

- EpiAirway
- MucilAirway

Cancer MOA

- NR expression in hepatocytes
- Genomics



Acute oral/dermal/inhalation

- No good *in vitro* assays
- Basal cytotoxicity
- Calculation method for formulations

Endocrine

- ER/AR binding
- ER/AR transactivation
- Aromatase
- Steroidogenesis

DART

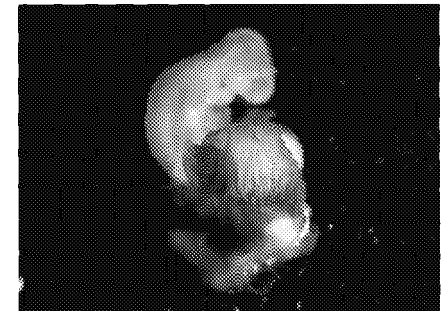
- WEC
- Zebrafish embryo
- Genomics

Genetic Toxicity

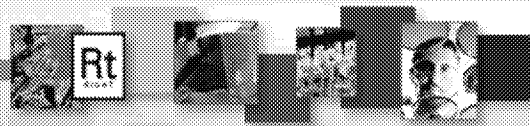
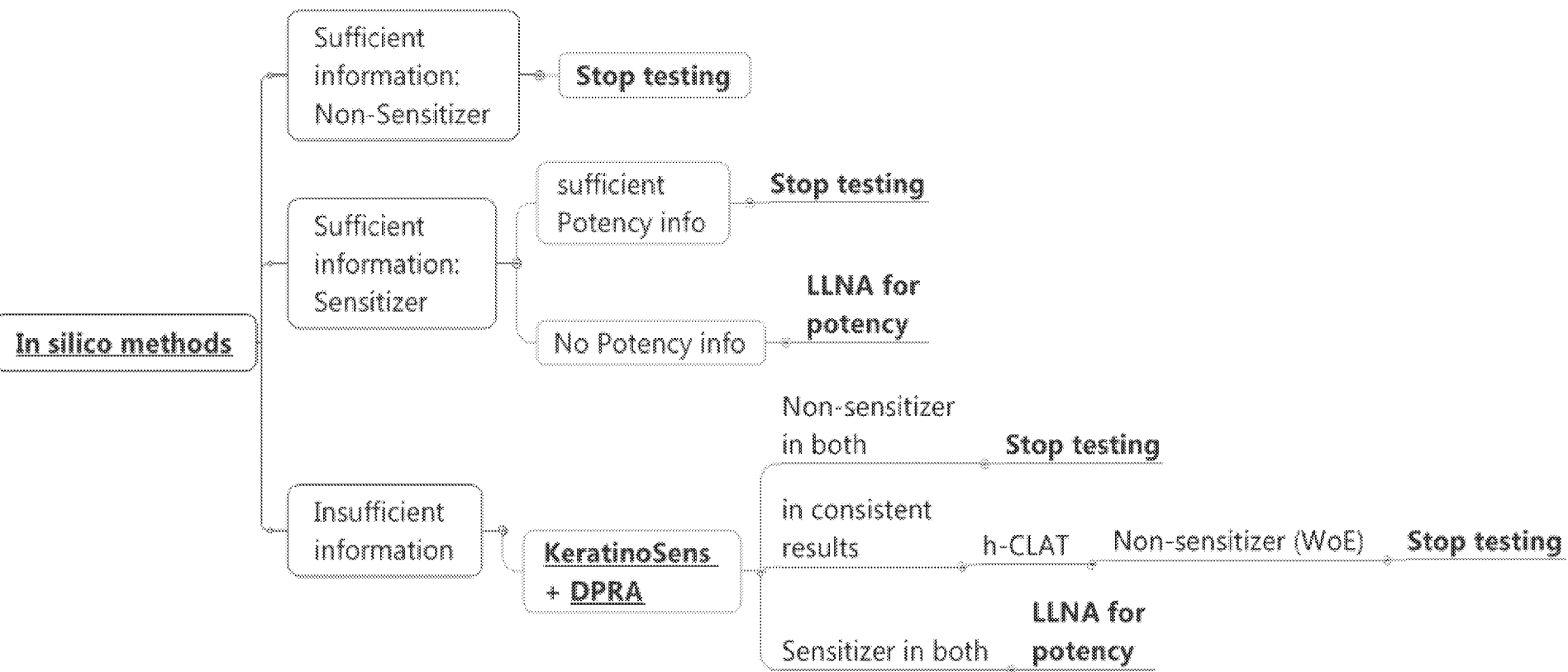
- RLCAT
- In vitro MNT
- Hgprt

Oxidative stress

- ROS, Mt activity, cytotoxicity



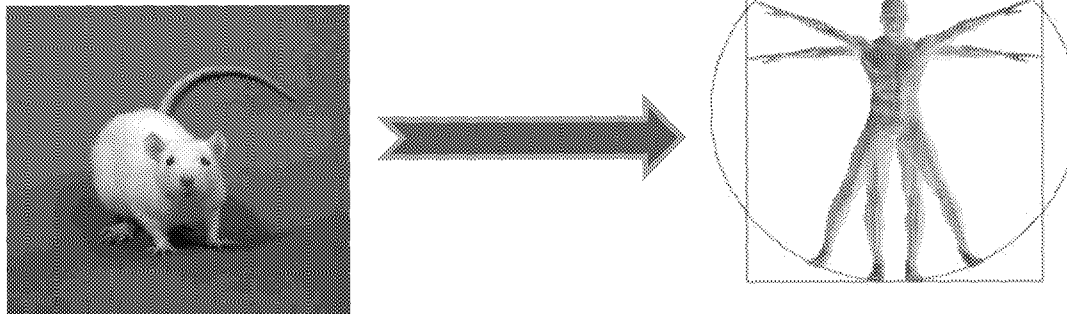
Integrated Approaches to Testing and Assessment: Sensitization



In Silico Toxicokinetics: GastroPlus Modeling

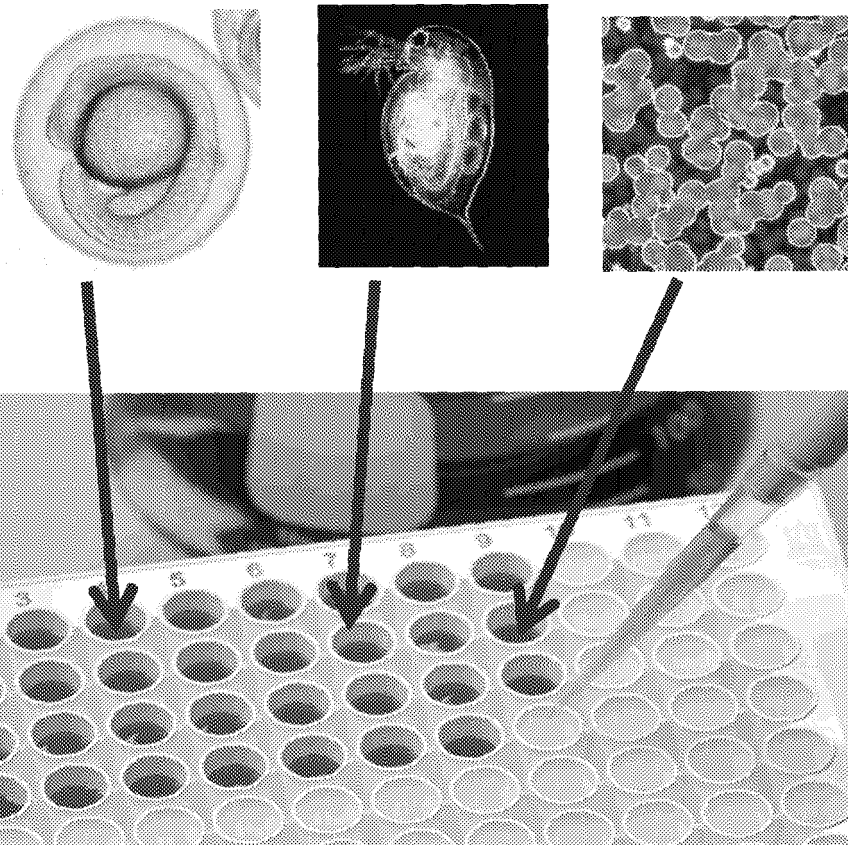
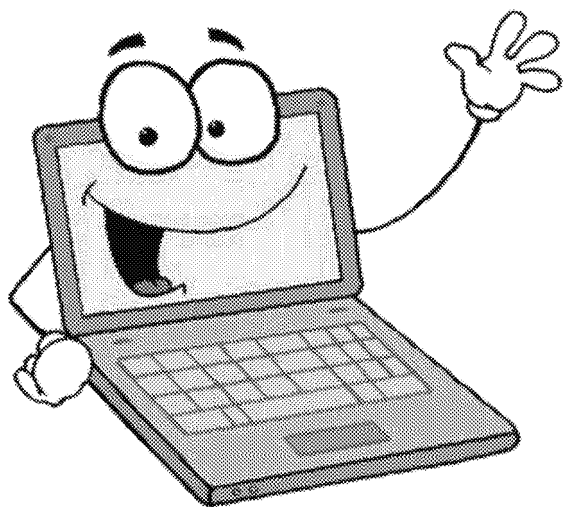
GastroPlus to predict:

- Systemic exposure/Bioavailability
- Absorption rates, Metabolic clearance, Plasma protein binding and Tissue distribution
- Parent compound and metabolite(s)
- In vitro-to-in vivo extrapolations (IVIVE)
- Support for multiple exposure routes (oral, inhalation, dermal)
- Supports various species (human, rat) and life stages

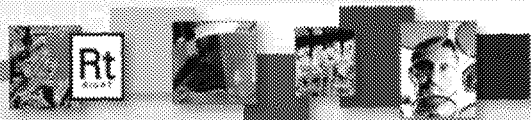


Environmental Chemistry and Toxicology

Predictions of the persistence and environmental fate of chemicals in the environment as well as their effects on taxa in the environment

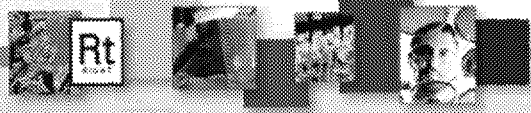
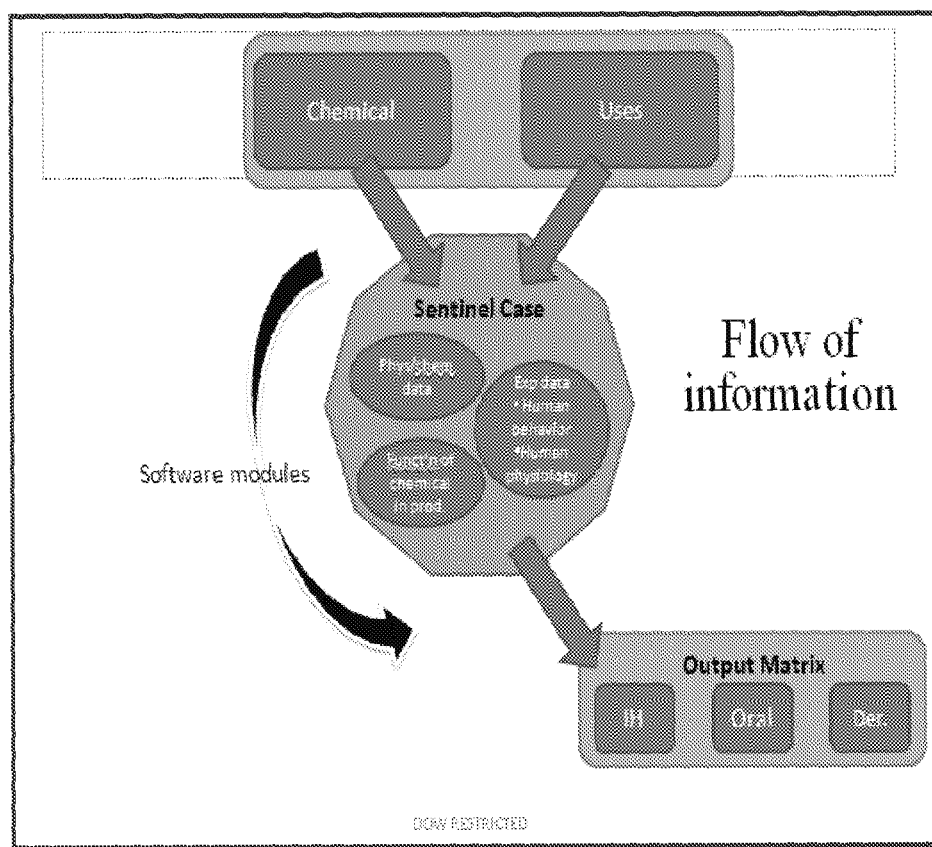


(e.g., Biodegradation, persistence, fate, bioconcentration factor, acute/aquatic toxicity)



Exposure: HEAT Model

Using *in silico* models as a high-throughput approach to predict human exposures to environmental chemicals, particularly consumer products.



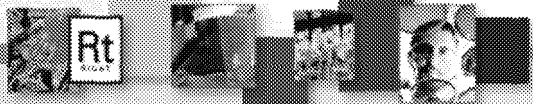
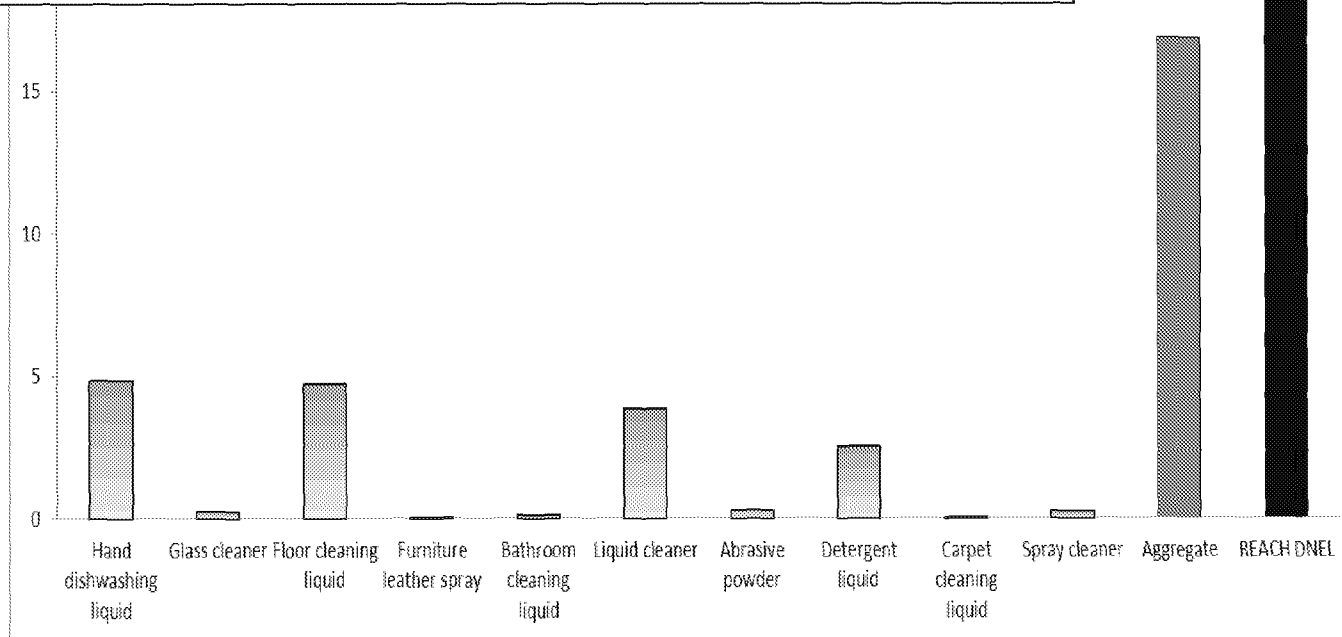
The **Rt** Formula

Application: HEAT Case Study with Cleaning Solvent

35

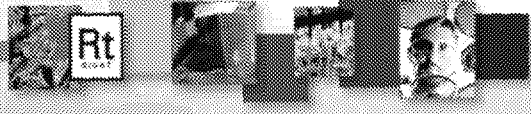
Aggregate exposure to one chemical

- Solvent use in household cleaners; 3 exposure routes
- Ten most frequently used groups of cleaners
- One from each group with average percentage of chemical in formulation
- “Spring cleaning” scenario



The **Rt** Formula

TSCA/LCSA APPLICATIONS



The **Rt** Formula

Current EPA PMN Assessment Process

With insufficient tox data, the New Chemicals Program may:

- Run the ‘Sustainable Futures’ tools
- Use read-across, possibly based on CBI (PMN) information
- Issue consent orders and SNURs

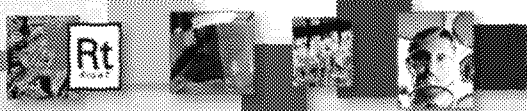
Health or environmental hazard concerns

- Often leads directly to in vivo testing
- Extensive hazard characterization – limited consideration of exposure

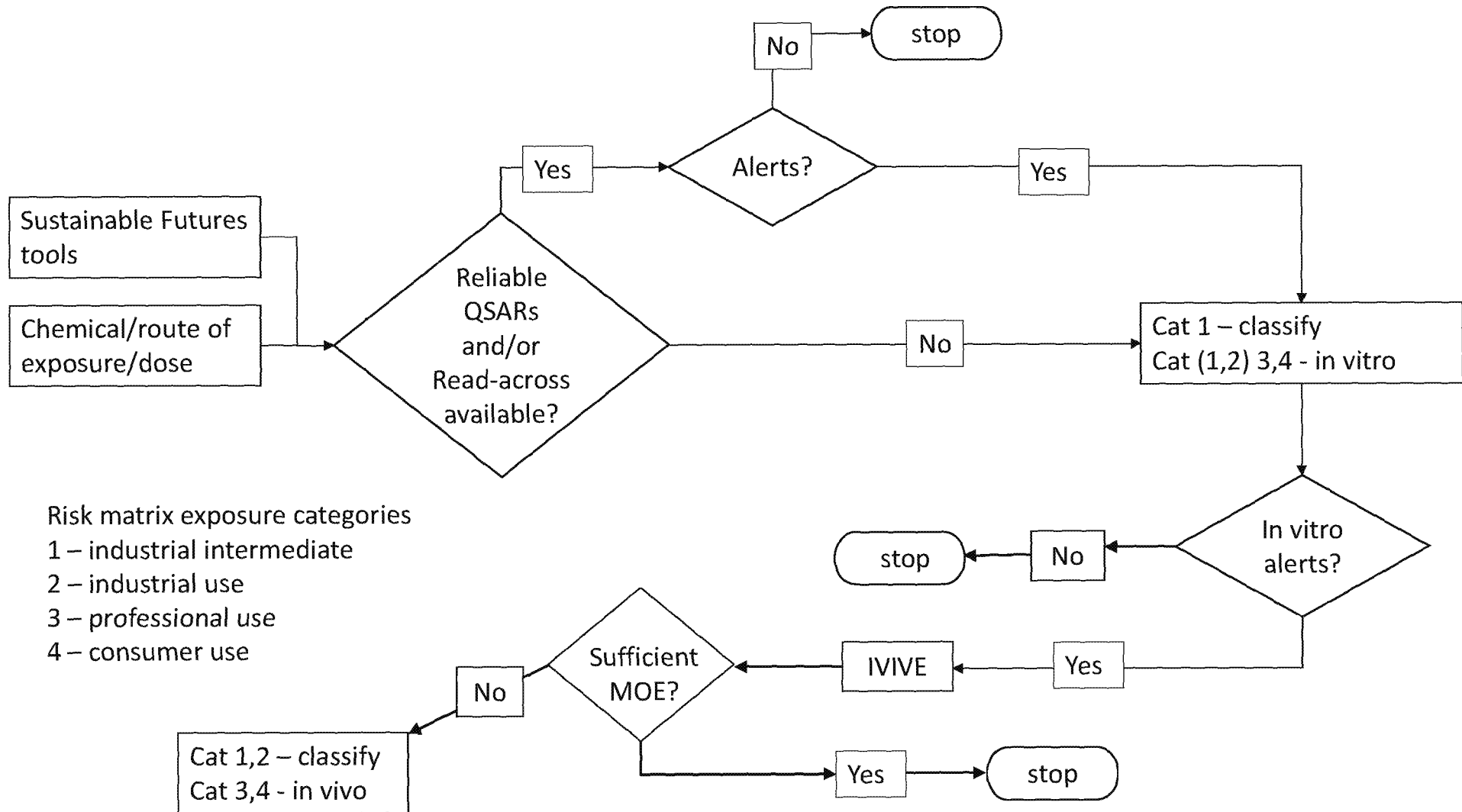


A Proposed Approach to PMNs

- Exposure-driven and Risk-based for reasonably foreseen uses
- Greater use of non-animal methods for hazard screening
 - EPA guidance: Incorporate alternative approaches in risk assessment
- Integrated approach to evaluate ‘Sustainable Futures’ endpoints
 - Take into account existing data from other jurisdictions (ECHA, Canada, other programs)
 - Use *in silico* methods (i.e., read-across, categories, QSAR)
 - Use *in vitro* approaches
 - Margins of safety determine need for animal testing

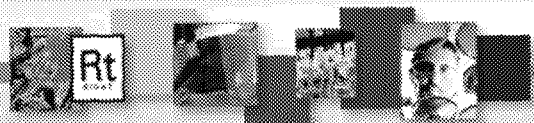


Hazard Identification with Exposure Consideration

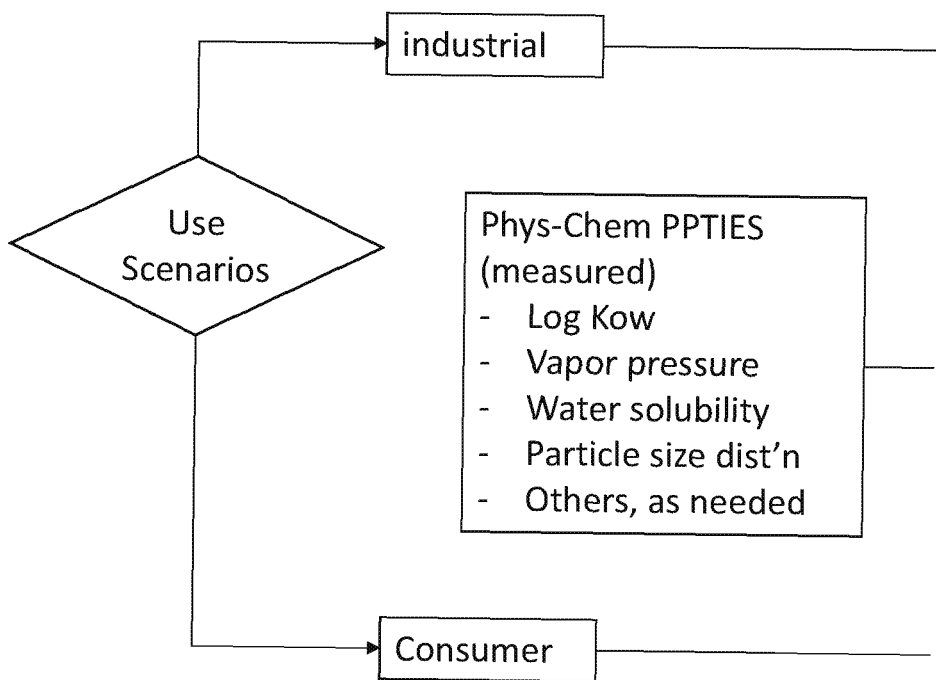


Dow Proposed Process

- Incorporate IATAs for Sustainable Futures endpoints
 - Mutagenicity
 - Sensitization
 - Irritation
 - Aquatic toxicity
 - Biodegradation
 - Bioaccumulation
 - Others as they become available



Exposure Assessment



Industrial activities

- Existing IH data
- Process steps (unloading, mixing, method of application, disposal, ...)
- Locations of activities (# of sites)
- Emissions
- ...

Exposure Assessment

- Who
- What route
- How much
- How often
- For how long
-
- Environmental compartment
- Trophic level
- Frequency of emission
- ...

Use Scenario

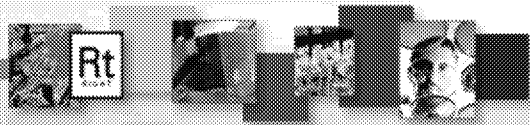
- Concentration of PMN substance in product
- Intended use
- Technical effect
-



Outcome of Dow Proposal

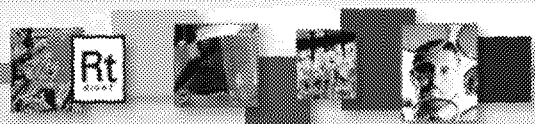
Evaluation of potential RISK for intended conditions of use

- Determine if additional refinement is needed (animal testing, measure exposures, etc...)
- Risk informs decisions, i.e., whether to support certain applications, require engineering controls or PPE, C&L, etc...



Next Steps:

- Desire to partner with EPA
 - With the program office to improve registration process
 - With ORD/research groups to incorporate alternative approaches for regulatory use
- Dow to submit a case study for PMN review
- Visit TERC Laboratory
 - Coincide with ACC LRI discussions
- EPA development of a strategic plan for incorporating alternative approaches



1																	18					
1 H Hydrogen 1.008																	2 He Helium 4.003					
3 Li Lithium 6.941	4 Be Beryllium 9.012	<table border="1" style="width: 100%; text-align: center;"> <tr> <td style="width: 20%;">90 Th Thorium</td> <td style="width: 20%;">124 A Adamantium</td> <td style="width: 20%;">7 N Nitrogen</td> <td style="width: 20%;">19 K Potassium</td> <td style="width: 20%;">16 S Sulphur</td> </tr> </table>										90 Th Thorium	124 A Adamantium	7 N Nitrogen	19 K Potassium	16 S Sulphur	5 B Boron 10.811	6 C Carbon 12.011	7 N Nitrogen 14.007	8 O Oxygen 15.999	9 F Fluorine 18.998	10 Ne Neon 20.180
90 Th Thorium	124 A Adamantium											7 N Nitrogen	19 K Potassium	16 S Sulphur								
11 Na Sodium 22.990	12 Mg Magnesium 24.305	13 Al Aluminum 26.982	14 Si Silicon 28.086	15 P Phosphorus 30.974	16 S Sulfur 32.066	17 Cl Chlorine 35.453	18 Ar Argon 39.948															
19 K Potassium 39.098	20 Ca Calcium 40.078	21 Sc Scandium 44.956	22 Ti Titanium 47.88	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.933	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546	30 Zn Zinc 65.39	31 Ga Gallium 69.723	32 Ge Germanium 72.64	33 As Arsenic 74.922	34 Se Selenium 78.97	35 Br Bromine 79.904	36 Kr Krypton 84.80					
37 Rb Rubidium 84.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224	41 Nb Niobium 92.906	42 Mo Molybdenum 95.94	43 Tc Technetium 98.907	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.906	46 Pd Palladium 106.42	47 Ag Silver 107.868	48 Cd Cadmium 112.411	49 In Indium 114.818	50 Sn Tin 118.71	51 Sb Antimony 121.760	52 Te Tellurium 127.6	53 I Iodine 126.904	54 Xe Xenon 131.29					
55 Cs Cesium 132.905	56 Ba Barium 137.327	57-71 Lanthanides	72 Hf Hafnium 178.49	73 Ta Tantalum 180.948	74 W Tungsten 183.85	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.22	78 Pt Platinum 195.08	79 Au Gold 196.967	80 Hg Mercury 200.59	81 Tl Thallium 204.383	82 Pb Lead 207.2	83 Bi Bismuth 208.980	84 Po Polonium [209]	85 At Astatine 209.987	86 Rn Radon 222.018					
87 Fr Francium 223.020	88 Ra Radium 226.025	89-103 Actinides	104 Rf Rutherfordium [261]	105 Db Dubnium [262]	106 Sg Seaborgium [266]	107 Bh Bohrium [264]	108 Hs Hassium [269]	109 Mt Meitnerium [268]	110 Ds Darmstadtium [269]	111 Rg Roentgenium [272]	112 Cn Copernicium [277]	113 Uut Ununtrium unknown	114 Fl Flerovium [289]	115 Uup Ununpentium unknown	116 Lv Livermorium [293]	117 Uus Ununseptium unknown	118 Uuo Ununoctium unknown					



The **Rt** Formula