Eli Lilly's Approach to Early Phase Chemical Reactivity Hazard Assesments

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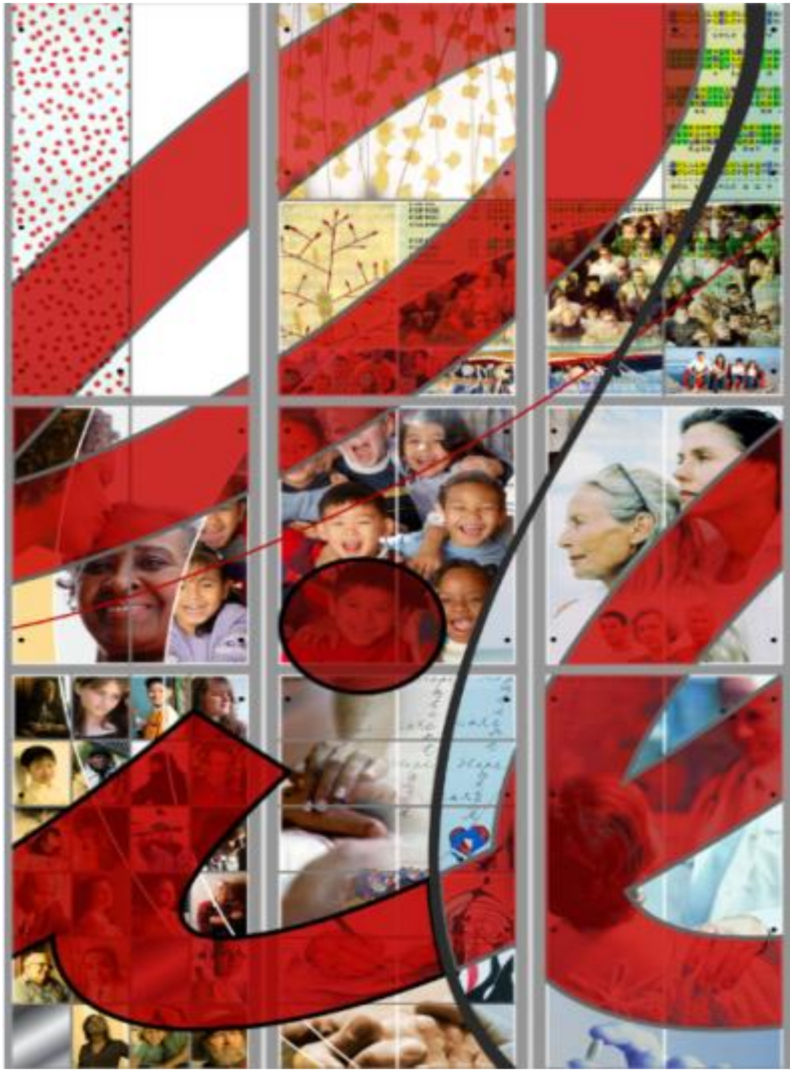
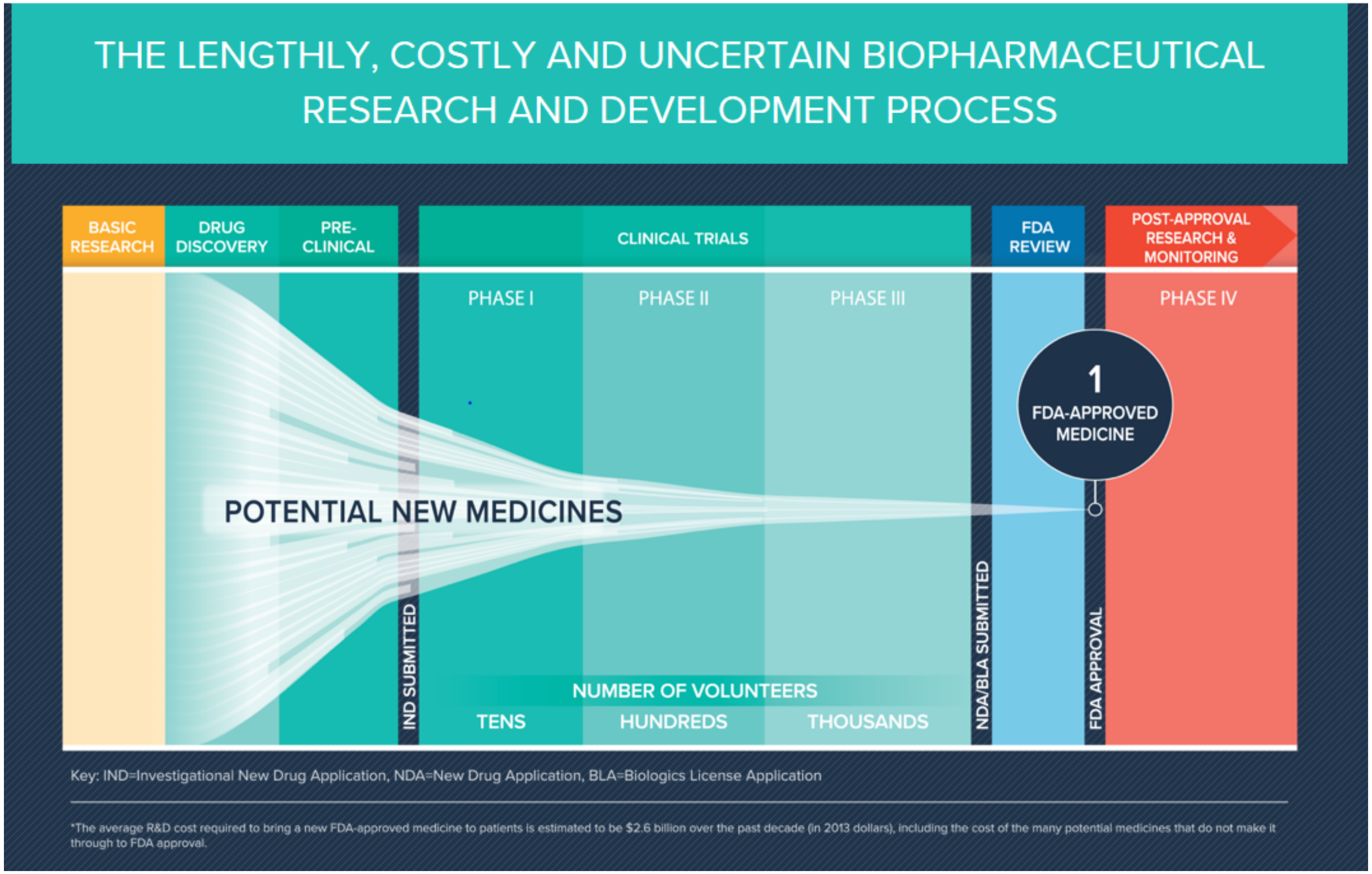
Our Fundamentals

- Our Mission: We make medicines that help people live longer, healthier, more active lives.
- Our Vision: We will make a significant contribution to humanity by improving global health in the 21st century.
- Our Values: Integrity, excellence, respect for people



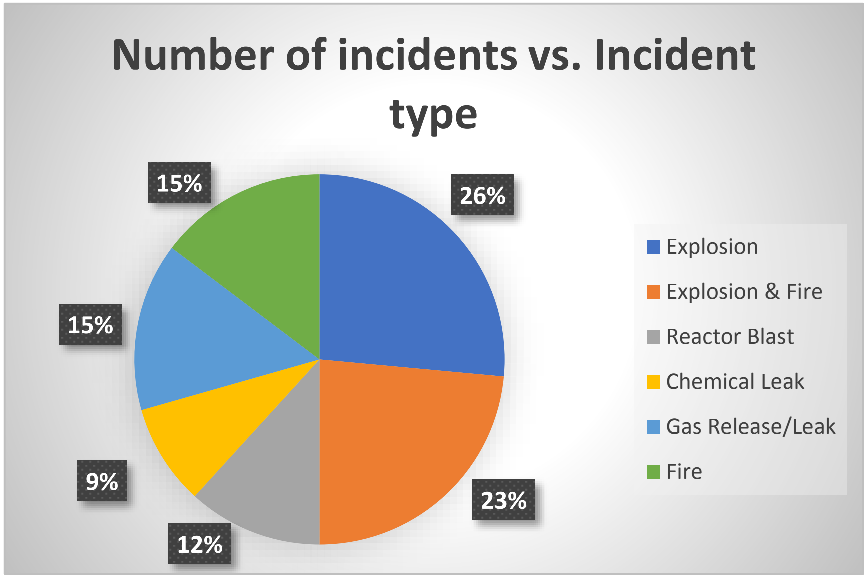
The Biopharmaceutical Research & Development Process

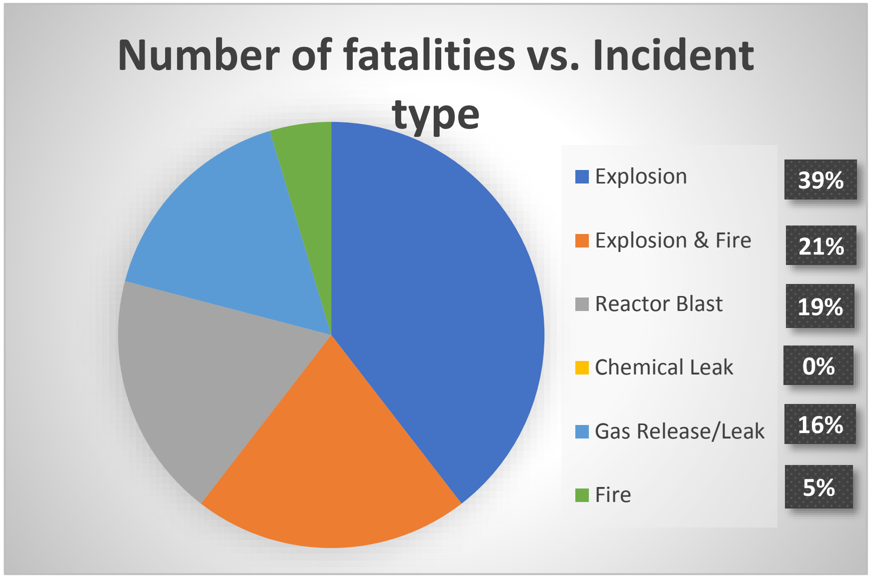


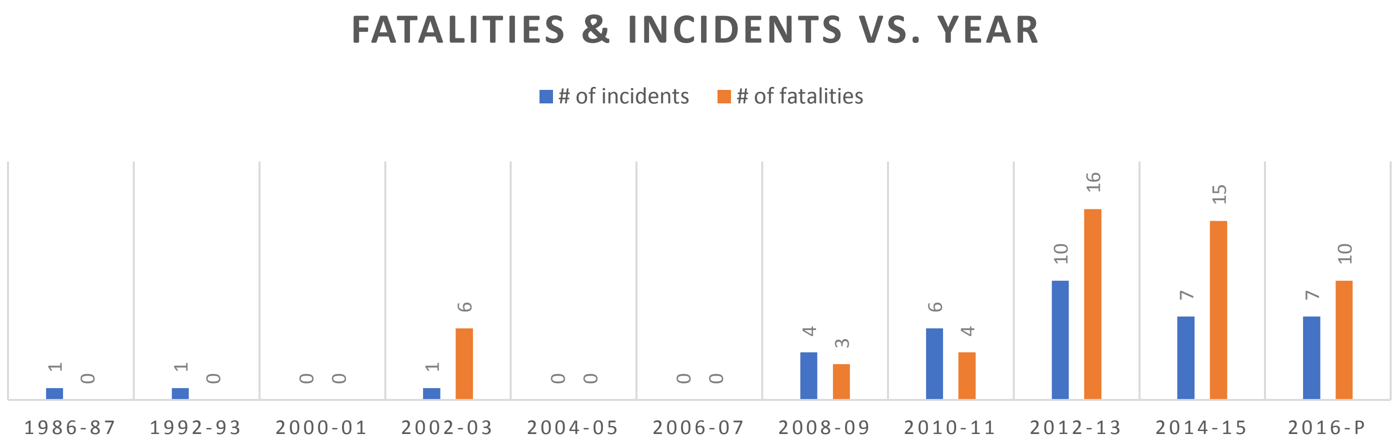
On average it takes 10 to 15 years for a medicine to make its way through the entire R&D process to approval by the U.S. Food and Drug Administration (FDA).

Source: PhRMA

Process Safety Incidents in the Pharma Industry







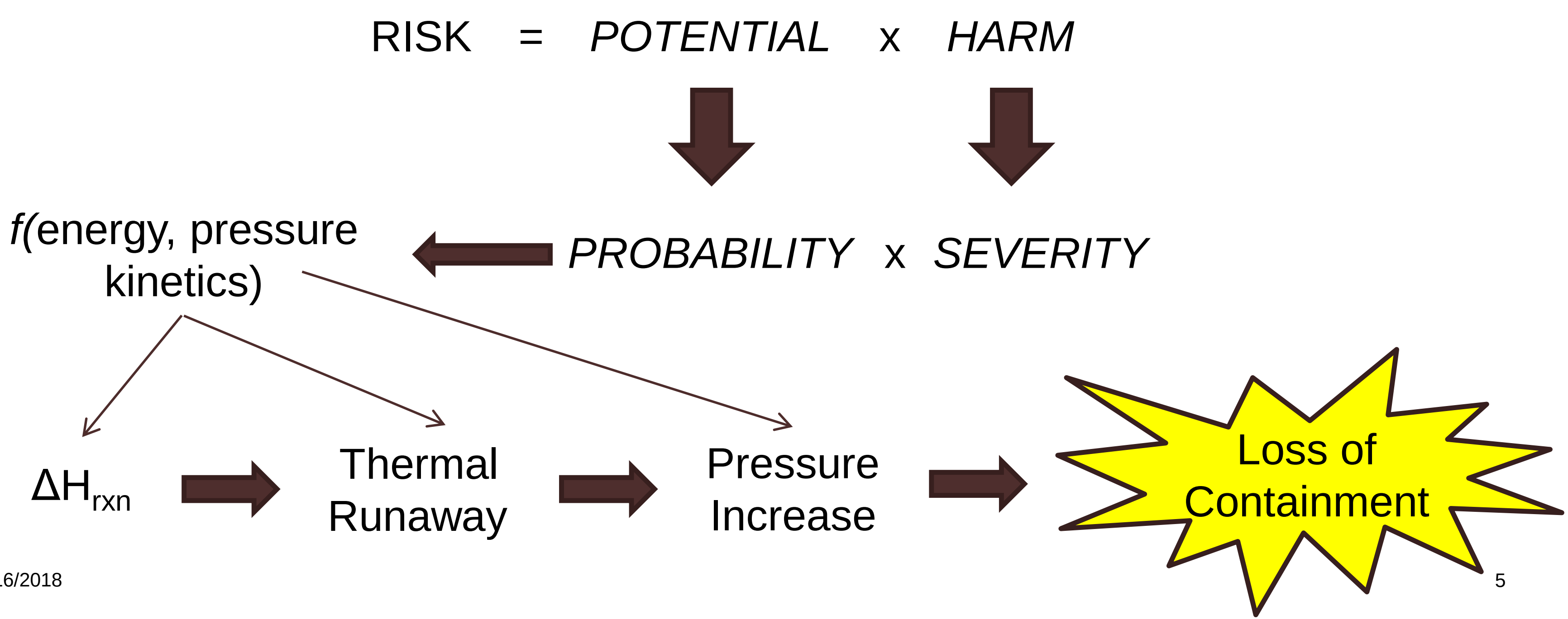
Professor Ray Mentzer, Purdue Process Safety and Assurance Center (P2SAC)

Risks

- *"A situation that has the <u>potential</u> to cause <u>harm</u> to human, environment, and property"*

-*European Federation of Chemical Engineering*

-Stoessel, F. (2008). <u>Thermal Safety of Chemical Processes</u>.



The concept of Reaction Scale as a Surrogate for Risk Likelihood

Heat Balance for a Batch Reactor

Exponential — Linear

$$\overbrace{k_0 e^{-E/RT} \cdot C_{A0}^{n} (1 - X)^n \cdot V \cdot (-\Delta H_r)}^{q_r} \leq \overbrace{U \cdot A \cdot (T_c - T_r)}^{q_{ex}}$$

Both are functions of geometry

Scale	Reactor Volume (m^3)	Exchange Area (m^2)	Specific Cooling Capacity (W/kg·K)	Typical Cooling Capacity (W/kg)
Research Lab	0.0001	0.01	30	1500
Bench Scale	0.001	0.03	9	450
Pilot Plant	0.1	1	3	150
Production	1	3	0.9	45
Production	10	13.5	0.4	20

Assesment of Reactivity Hazards – High Hazard Reactions

- Check against internal pick list of known high hazard transformations:

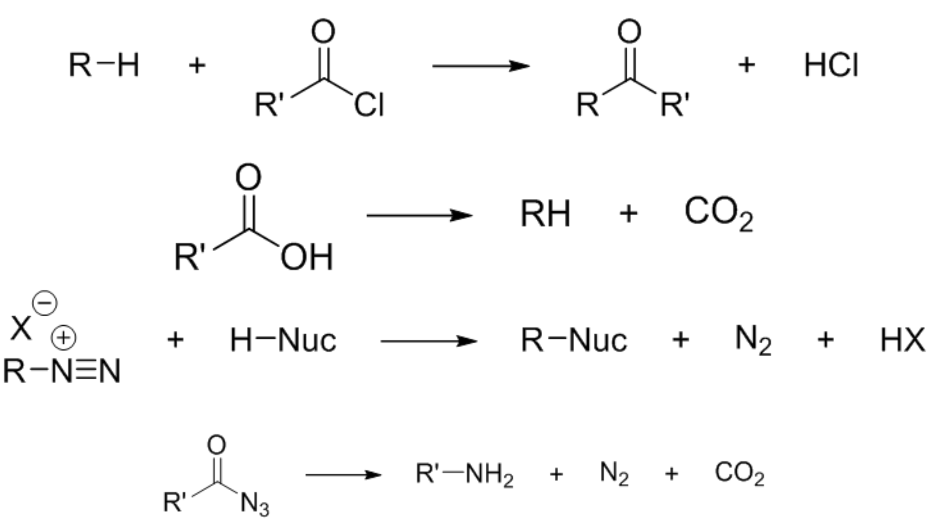
Water Reactives

$$RX + Mg(0) \longrightarrow R{-}MgX$$

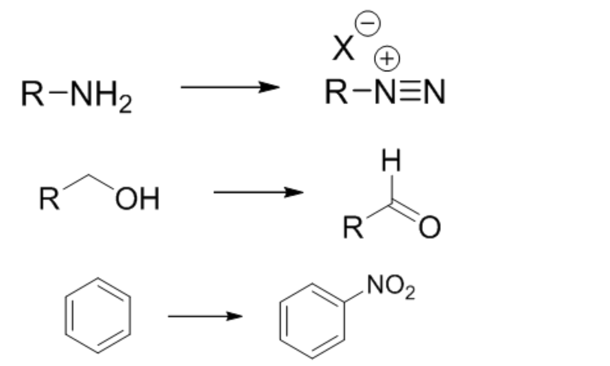
$$RX + R'MgX \longrightarrow R{-}MgX + R'X$$

$$R{-}X + {}^{n}BuLi \longrightarrow R{-}Li + {}^{n}BuX$$

Gas Generating Reactions

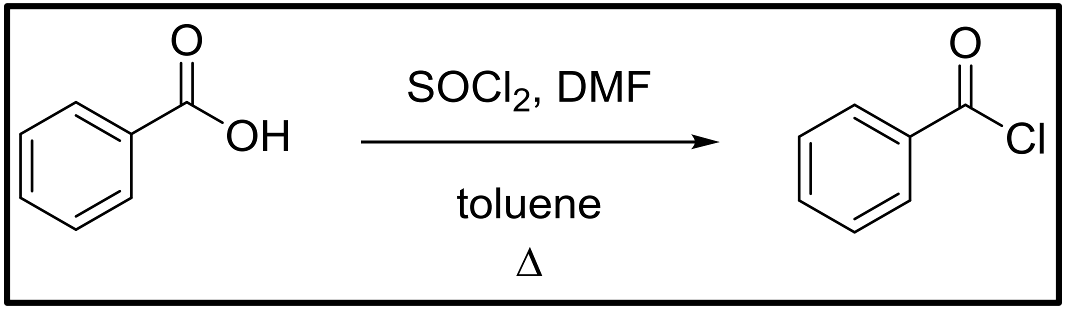


Known High Energy Transformations

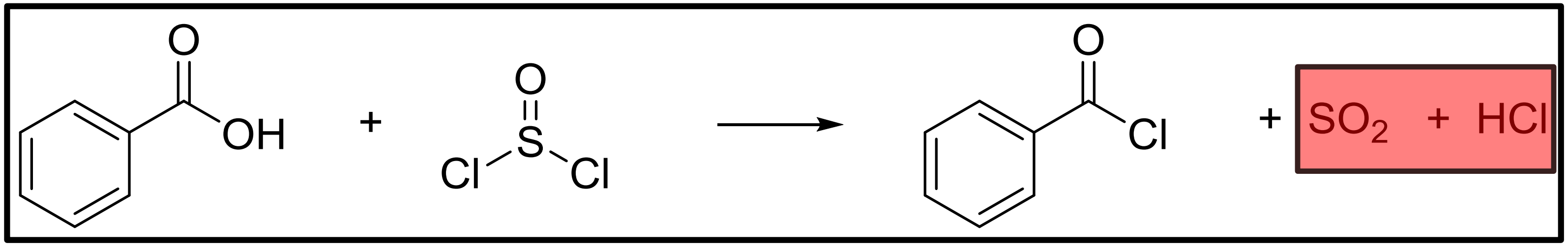


The Importance of a Balanced Chemical Equation

- Oftentimes, when chemistry comes from the lab, the reaction scheme only focuses on what we ‘want’ to make:

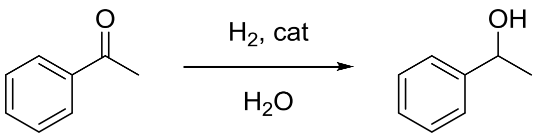


- Unbalanced chemical equation can mask certain hazards:



Assessment of Reactivity Hazards with limited Data

"A ketone is to be hydrogenated to the corresponding alcohol in an aqueous solution at a concentration of 0.1 M and a pressure of 2 bar in a reactor protected against overpressure by a safety valve with a set pressure of 3.2 bar."



- No thermal data are available
- Assess the severity that thermal risks pose for this reaction.
- What now?

Use of tabulated Data Provides a Good, Quick entry

$$Q_r' = \frac{C \cdot (-\Delta H_r)}{\rho}$$

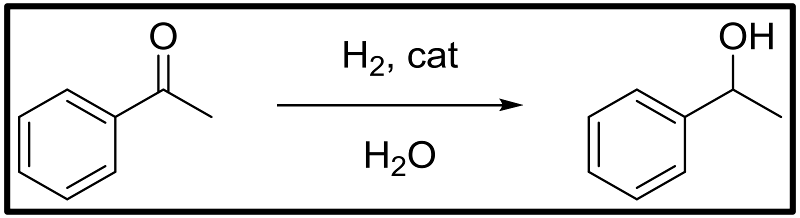
Given (0.1 M)

ρ=1 for H_2O

- 10-fold change in concentration leads to increase of heat release by an order of magnitude!
- If switching to nitro group hydrogenation:
  - 0.1 M sol'n => 56 kJ/kg
  - 1.0 M sol'n => 560 kJ/kg

Reaction	ΔH_{rxn} (kJ/mol)
Neutralization (HCl)	-55
Neutralization (H_2SO_4)	-105
Sulfonation	-150
Hydrogenation (alkene)	-200
Hydrogenation (nitro)	-560
Hydrogenation (ketone)	-200
Nitration	-130

More ‘Sophisticated’ Modeling Approaches



Group Additivity Calcs

$$\Delta H_r = -56\,\frac{kJ}{mol}$$

$$Q_r' = \frac{0.1\,\frac{mol}{L}\cdot\left(-\left(-56\,\frac{kJ}{mol}\right)\right)}{1.00\,\frac{kg}{L}} = 5.6\,\frac{kJ}{kg}$$

- Benson Group Increment Theory
- *Approximations* account for atomic, bond and group contributions to ΔH°

Quantum Calcs

$$\Delta H_r = -67\,\frac{kJ}{mol}$$

$$Q_r' = \frac{0.1\,\frac{mol}{L}\cdot\left(-\left(-67\,\frac{kJ}{mol}\right)\right)}{1.00\,\frac{kg}{L}} = 6.7\,\frac{kJ}{kg}$$

- Fundamental electronics calculations.
- Doesn’t rely on group energies

Assessment Criteria for Severity of a Runaway

- The severity of a runaway can be evaluated using the temperature levels attained if:
  - the desired reaction and the undesired reaction proceed under adiabatic conditions.

$$\Delta T_{ad} = \frac{(-\Delta H_{rxn}) \times CA_0}{\rho \times c'_p} = \frac{Q'_{rxn}}{c'_p}$$

Assessment Criteria for Runaway Reaction Severity

Severity	ΔT_{ad} (K)	Q' (kJ/kg)
High	>200	>400
Medium	50-100	100-400
Low	<50*	<100

* and no pressure increase

Method	Q'_r (kJ/kg)	ΔT_{ad} (K)
Tabular	20	~6
Group Additivity	5.6	~2
Quantum	6.7	~2

CONCENTRATION DEPENDENCE!!
1.0 M => 200 kJ/kg
$\Delta T_{ad} \sim 60\ K$

Differential Scanning Calorimetry (DSC)

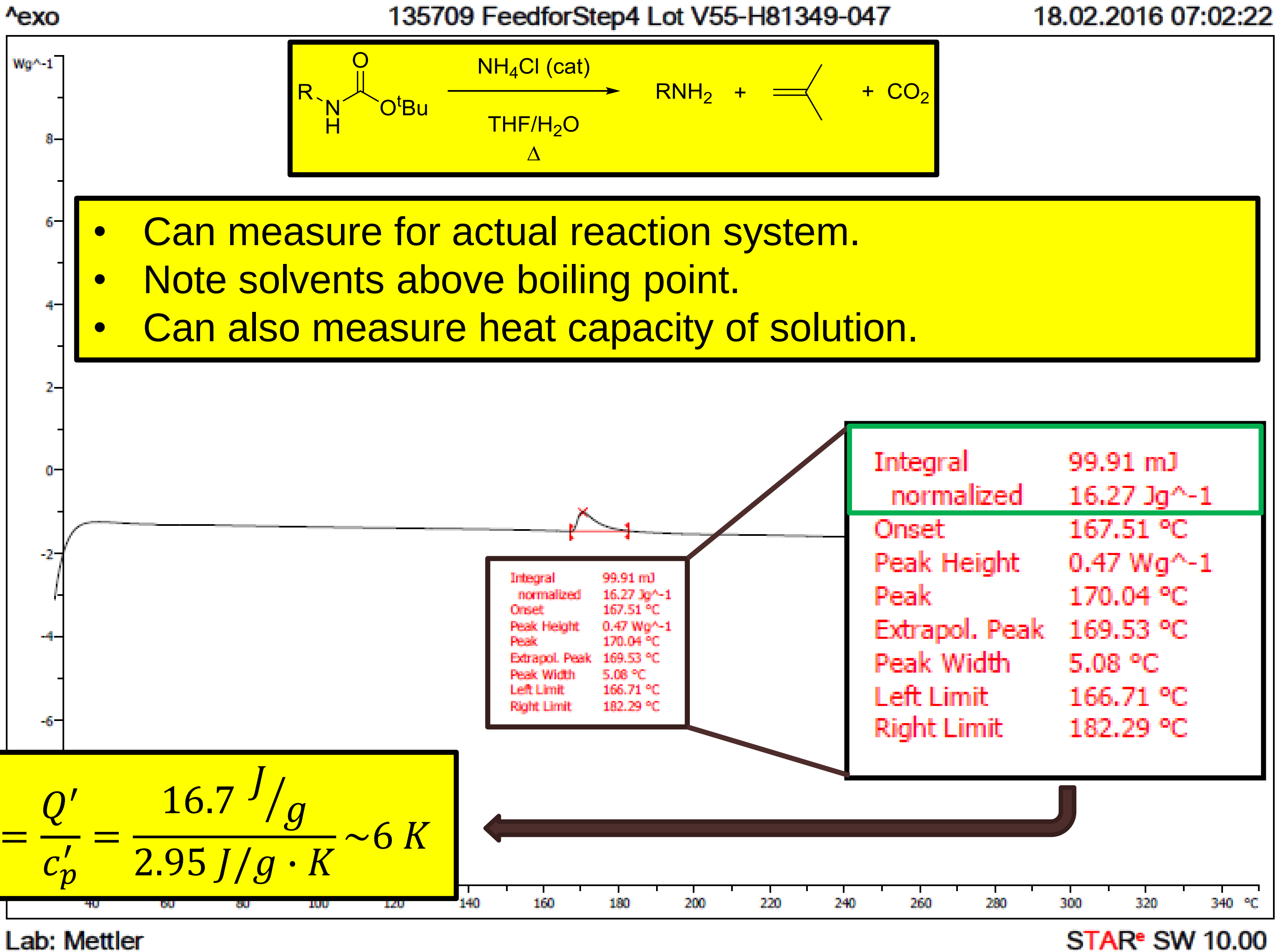
Thermal events are visualized as

$T_{sample} \neq T_{ref}$

Exotherm: $T_{sample} > T_{ref}$
Endotherm: $T_{sample} < T_{ref}$

- Good screening tool – sample 5-20mg
- No pressure measurement
- Correlation calculations allow prediction of shock sensitivity and explosion propagation (Yoshida Correlation).
- Program extensions allow easy accurate calculation of Cp and kinetics

ΔT_{ad} Estimation for Continuous Flow Thermal Deprotection



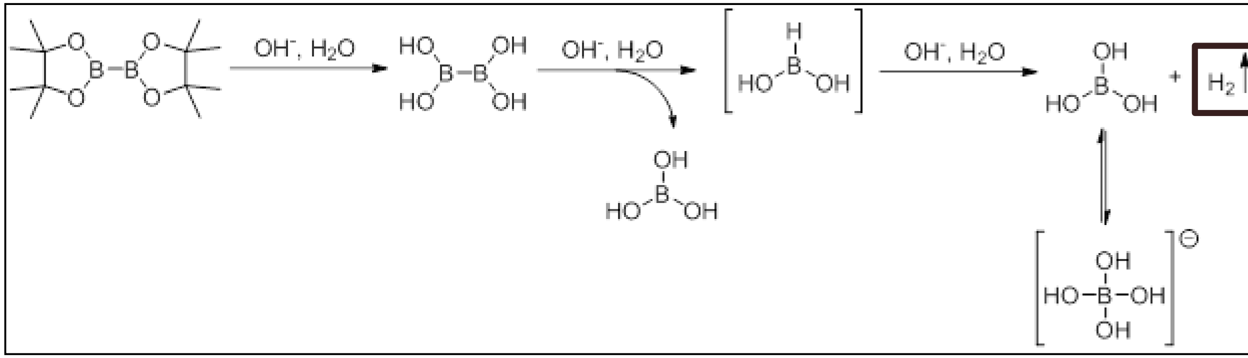
- Can measure for actual reaction system.
- Note solvents above boiling point.
- Can also measure heat capacity of solution.

$$\Delta T_{ad} = \frac{Q'}{c_p'} = \frac{16.7\ {}^{J}/_{g}}{2.95\ J/g \cdot K} \sim 6\ K$$

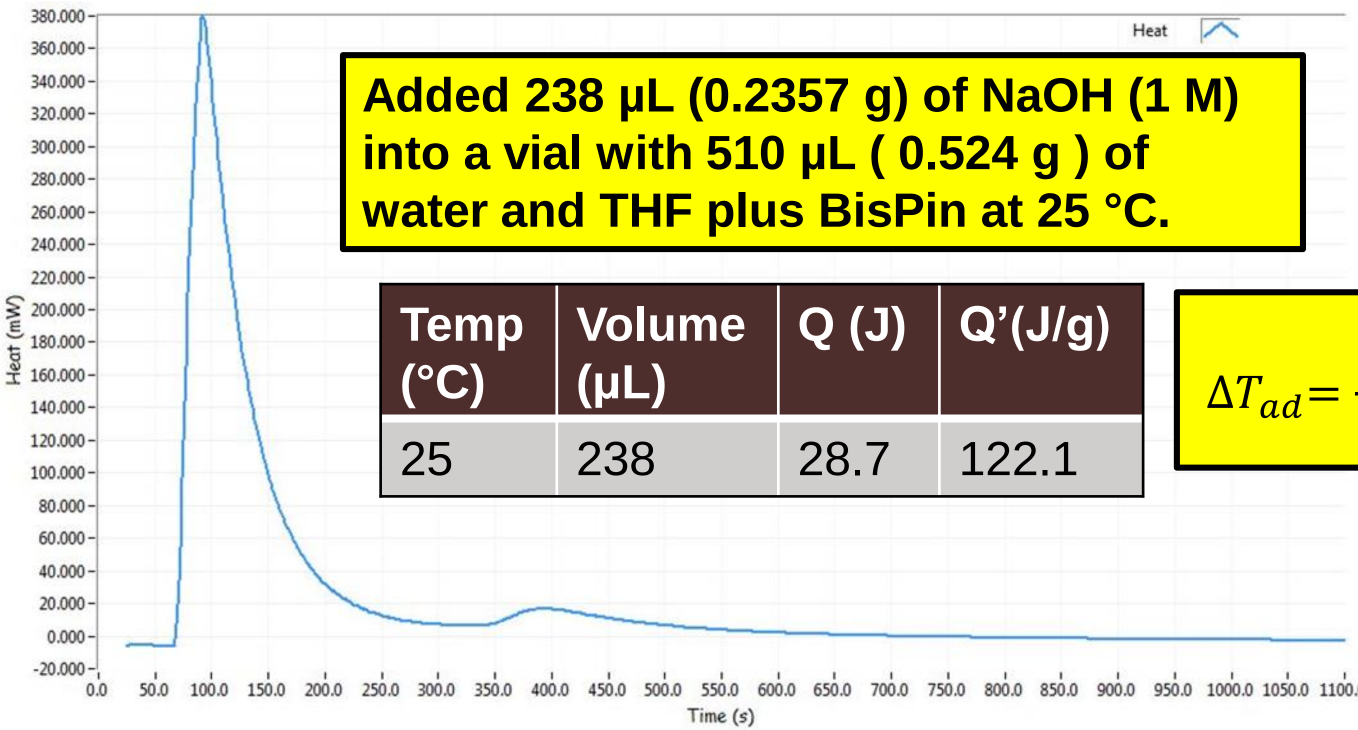
Micro Reaction Calorimeter

- Early Phase Screening Tool
- Variety of Data
  - Heat of Reaction/Mixing
  - Titration of reagents
  - Heat Capacity Determination
- Small sample size (3 mL total volume)
- Automated Dosing
- Solids addition

Use of microcalorimeter to estimate adiabatic temperature rise



$H_2 \uparrow$



Added 238 µL (0.2357 g) of NaOH (1 M) into a vial with 510 µL (0.524 g) of water and THF plus BisPin at 25 °C.

Temp (°C)	Volume (µL)	Q (J)	Q'(J/g)
25	238	28.7	122.1

$$\Delta T_{ad} = \frac{Q'}{c_p'} = \frac{122.1\ J/g}{2.95\ J/g \cdot K} \sim 41\ K$$

Jeremy Merritt
Odilon Campos

Reacting to Early Phase Risk Assessments

- Use scale as a measure of likelihood =>
    - Larger scale (volume) indicates increased risk
    - Policy to evaluate all reactions run in lab hood if >5L scale (>2 L scale if identified high hazard transformation).
- Leverage modeling data as much as possible early on; confirm with screening experimentation in medium/high severity situations.
- Don’t be afraid to call a safety timeout.

Lilly's Thermal Hazard Lab Vision
our 'Why'

Proactively identify and eliminate/mitigate Thermal Hazard Risks to Lilly's:

Process Safety is fundamentally 'Respect for People' in action.

Through 'inherently safer' intermediate and process design