Effective Process Safety Evaluations for CDMO API Operations

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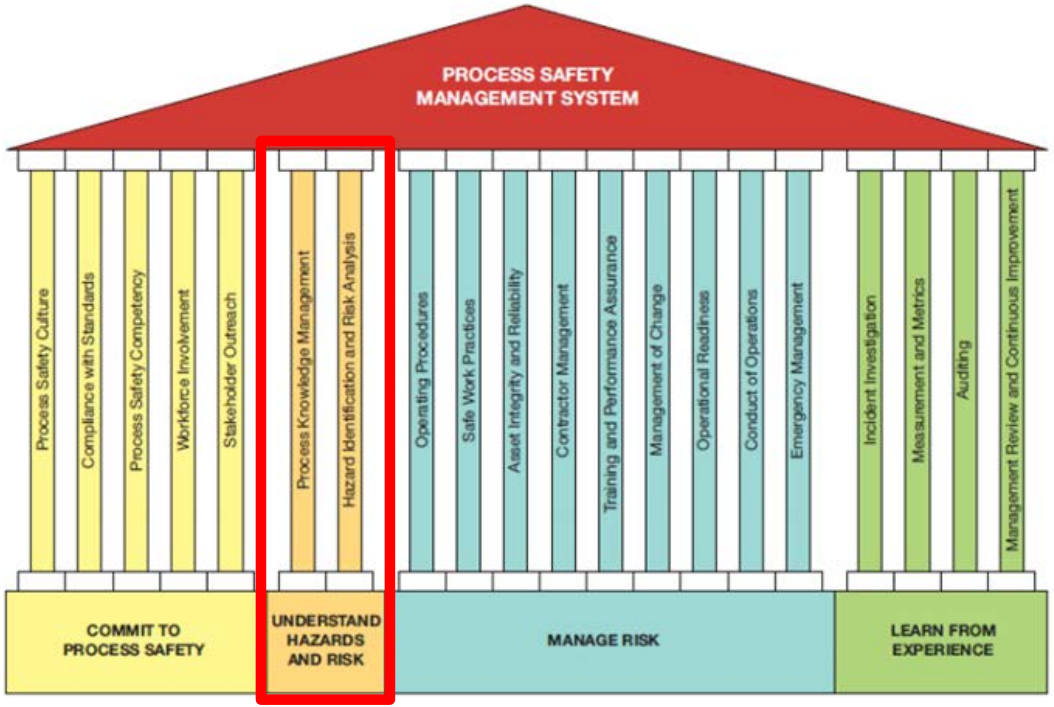
Biography

- Senior Process Safety Engineer, Ash Stevens LLC, a division of Piramal Pharma Solutions, located in Riverview, Michigan.
- 20+ years industry experience in process safety and process development including kinetic modeling of chemical reactions, utilizing laboratory PAT for data rich experiments, development of spray-dried amorphous dispersions, and crystallization trouble-shooting.
- B.A. Chemistry from Kalamazoo College, and B.S. Chemical Engineering from Michigan State University (3-2 Program).
- Industry Chair – Center for Chemical Process Safety (CCPS) Pharmaceutical, Food, and Fine Chemicals Subgroup.

Aspects of Process Safety



There are many elements to a robust process safety management system.

This presentation will review how to complete thorough reactive hazard reviews.

Photo credit: Guidelines for Risk Based Process Safety, AIChE Center for Chemical Process Safety. Wiley-AIChE, New York (2007)

Importance of Reactive Hazard Process Safety Understanding

In 2003, the US Chemical Safety Board released data on a comprehensive review of chemical reactive incidents that occurred between 1980-2001.

- 167 serious incidents were identified (due to data limitations, most likely an underestimate)
- 48 of these incidents resulted in 108 fatalities
- Two incidents resulted in public fatalities
- Nearly 50 affected the public (injury/fatality, offsite evacuation, or shelter-in-place)
- Hundreds of millions of dollars in property damage

Importance of Reactive Hazard Process Safety Understanding

Process safety incidents in the pharmaceutical industry not only have the potential to impact the business and surrounding community, they can also impact patients' access to critical drugs.

- "One US Pharmaceutical company had three different APIs affected by three runaways/explosions at different factories in 2005, when key raw materials and intermediates suddenly became unavailable."

Ref: Laird, T. Process Research and Development in the Pharmaceutical Industry: Origins, Evolution, and Progress. In *Pharmaceutical Process Development: Current Chemical and Engineering Challenges*; Blacker, A. J., Williams, M. T. Eds.; RSC Drug Discovery Series No. 9; Royal Society of Chemistry: Cambridge, 2011; p 27

Scale-Based Approach to Process Safety

- Leverage resources to focus on higher risk activities
- Larger scale or higher hazard

Bench Scale | Walk-in Hood Scale | Kilo Lab Scale | Plant Scale

Increasing Process Hazards and Process Risk

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Reactive Hazard Considerations During Scale-up

Thermal Potentials

Gas Generation Potentials

– Desired reactions

– Undesired Reactions/Decompositions

– Inadvertent Mixtures

- Generate Heat
- Temperature Rise
- Accelerate Reaction / Initiate New Reaction
- Pressure Generation (Vapor pressure)

- Direct Gas Evolution
- Pressure Generation

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Process Safety Paper Assessment

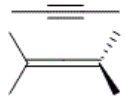
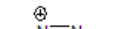
- A preliminary paper assessment should be performed upon receiving the request for proposal package.
  - Ensure the process does not present hazards outside the manufacturing core capabilities.
- Once the project moves forward, a more thorough paper assessment is completed to identify gaps and develop a process safety test plan.

Process Safety Paper Assessment

- Hazards to look for:
  - High energy functional groups
  - Gas generating reagents/reactions
  - Reactions known to be highly exothermic
  - Chemicals with special hazards: lachrymator, high toxicity, pyrophoricity, etc.

Process Safety Paper Assessment

- **Examples of high energy groups**

Bond Grouping	Functionality	Bond Grouping	Functionality
	acetylenic, metal acetylides, haloacetylene derivatives, allenes		high nitrogen containing compounds like triazoles, triazenes, tetrazoles, etc.
	terminal epoxides	—O—O—	O-O bonds, i.e. peroxides, peroxyacids and their salts, hydroperoxides, etc.
	Hydrazines and other bonded nitrogens (ring or chain)	—N—X	halogen azides, N-halogen compounds, N-haloimides
—N=N— 	N-N double or triple bonds, i.e. azos, azides, diazirines, triazoles, tetrazoles, etc.	—O—X	perchlorates, chlorite salts, halogen oxides, hypohalites, etc.
—N=O —N—O	N-O bonds, i.e. nitroso, hydroxylamines, oximes, etc.	—N—M	metal nitrides, amides, hydrazides, imides, cyanamide
—NO_2 —ONO_2	N-O bonds, i.e. nitro, nitrite, nitrate, etc.	Ar—M—X X—Ar—M	halo-arylmetals, haloarene metal complexes

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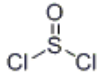
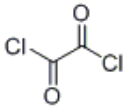
Process Safety Paper Assessment

- **Examples of gas generating reagents/reactions**

Reagent	Functionality	Gas of Concern
$XHCO_3$ X_2CO_3	Bicarbonates, carbonates	CO_2
$LiAlH_4$ $NaBH_4$ NaH	Lithium aluminum hydride, Sodium borohydride, sodium hydride	H_2
	n-Butyl lithium	Butane
	Thionyl chloride	SO_2, HCl
	Oxalyl chloride	CO_2, CO, HCl

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Process Safety Paper Assessment

- **If the paper assessment does not raise any concerns extensive safety testing may be deferred until later in process development/ scale-up.**
  - **Testing will better reflect the process as it will be scaled- up.**

Reactive Hazard Tools – Thermal Stability Testing

Differential Scanning Calorimetry (DSC)

- Advantages: Small sample (1-10 mg), accurate integration of energy
- Disadvantages: no pressure tracking, lack of kinetic extrapolation to scale

Thermal Screening Unit (TSu)

- Advantages: Pressure tracking
- Disadvantages: Inability to integrate energy, no scalable kinetic data
- Other similar instruments – RSD, RADEX, RSST

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Photo credits: TA Instruments (www.tainstruments.com), HEL Group (www.helgroup.com)

Reactive Hazard Tools – Thermal Stability Testing

Accelerating Rate Calorimetry (ARC)

- Advantages: Provides pressure and temperature data. Kinetic data that can be extrapolated for scale-up.
- Disadvantages: Test results must be corrected for “phi factor”, large footprint and expensive.

$$\Phi = \frac{M_s \cdot C_{p,s} + M_{cell} \cdot C_{p,cell}}{M_s \cdot C_{p,s}}$$

$$T_f = T_0 + \Phi \cdot \Delta T_{ad}$$

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Photo credits: Thermal Hazard Technology (www.thermalhazardtechnology.com), Fauske & Associates, LLC (www.fauske.com)

Reactive Hazard Tools – Thermal Stability Testing

Vent Sizing Package 2™ (VSP2™)

- Advantages: Temperature and pressure rise rates are directly scalable due to low thermal inertias (phi-factor) by larger sample, thinner & lighter test cell.

$$\Phi = \frac{M_s \cdot C_{p,s} + M_{cell} \cdot C_{p,cell}}{M_s \cdot C_{p,s}} \cong 1$$

- Disadvantages: 4-L high pressure containment vessel is heavy, requires high pressure N2 cylinder, experimental setup and execution not very intuitive.

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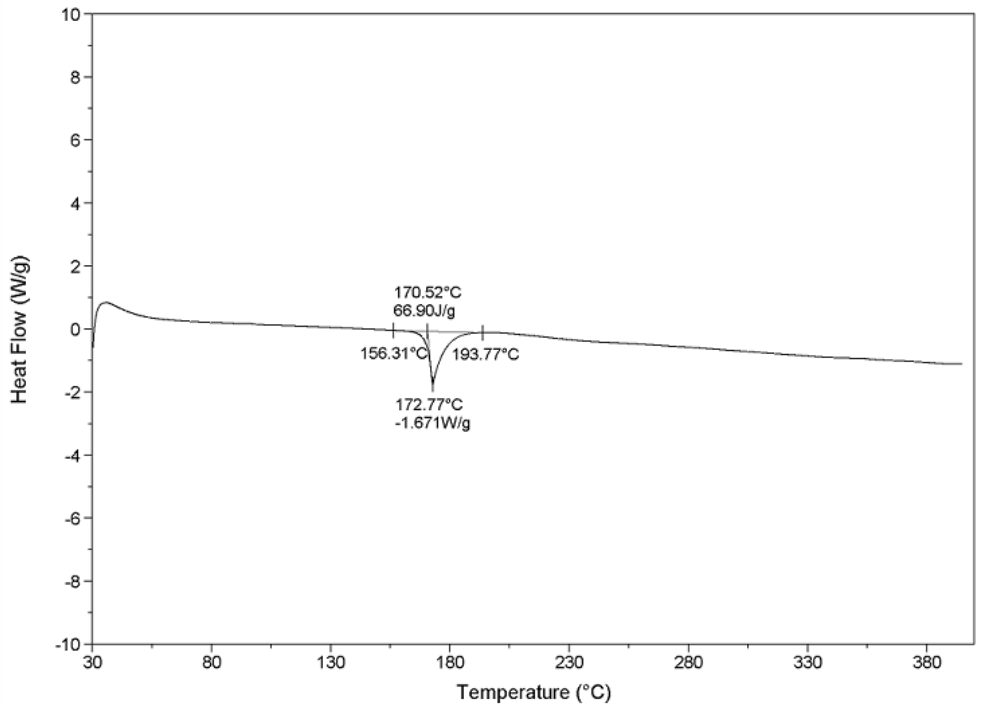
Photo credits: Fauske & Associates, LLC (www.fauske.com)

Thermal Stability Testing – DSC Examples



This test of a solid reveals the material melts with no additional activity.
Thermal stability risk is low.

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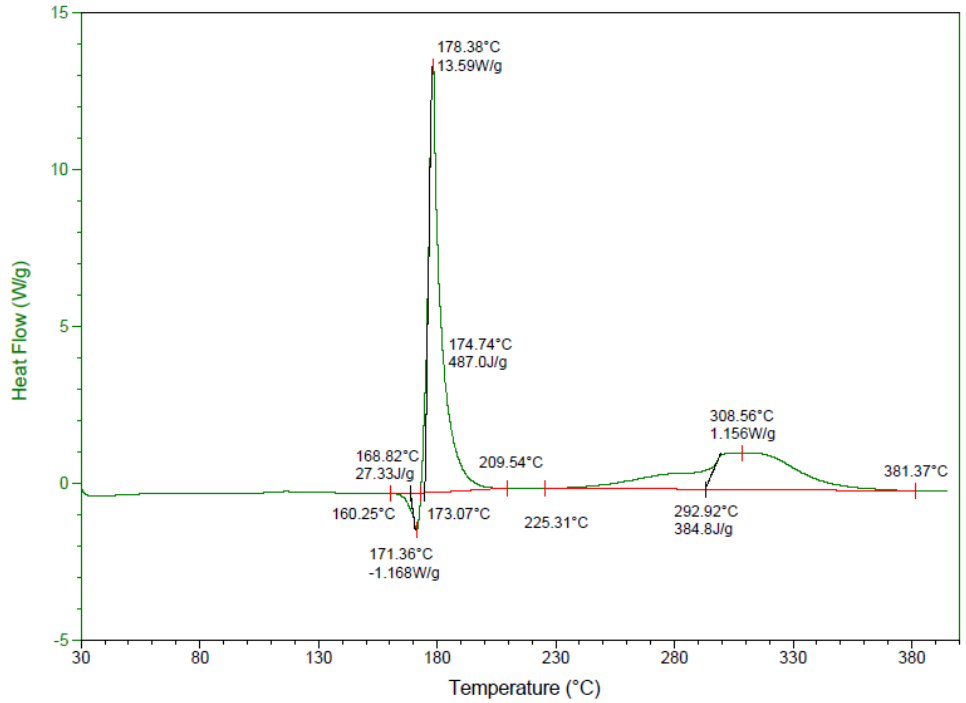
Thermal Stability Testing – DSC Examples



This test of a solid reagent reveals the material melts at ~160 °C, followed by immediate exothermic decomposition. In solution, the absence of melt may allow decomposition at lower temp. Additional testing of reaction mixture warranted.

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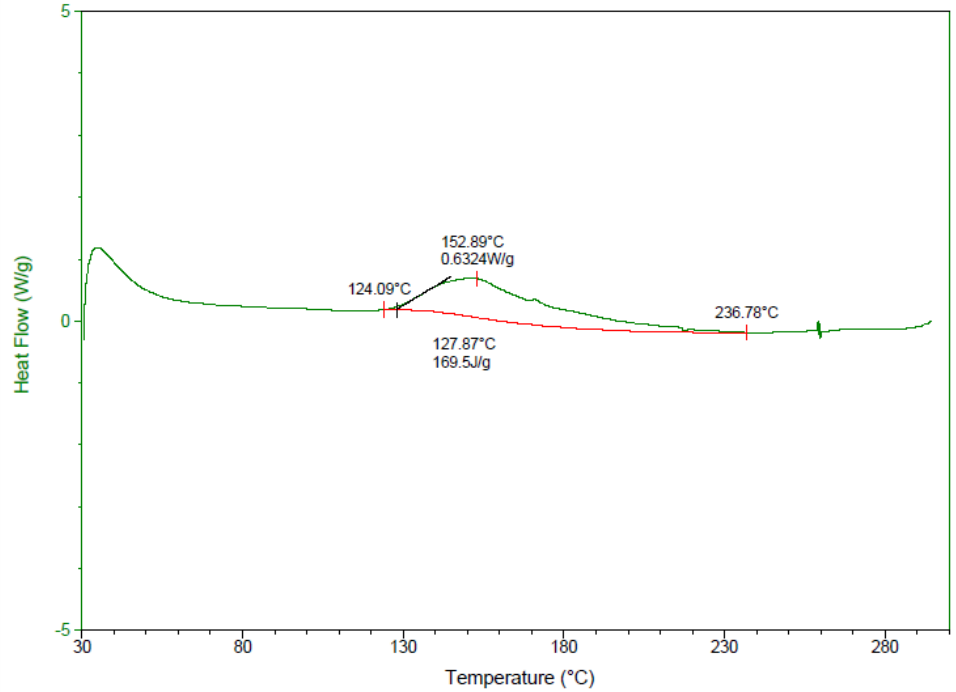
Thermal Stability Testing – DSC Examples



This is a test of the previous reagent as an 18 wt% solution in acetonitrile. The DSC now detects exothermic activity at 124 °C. In addition, the exothermic energy is all released in a single event.

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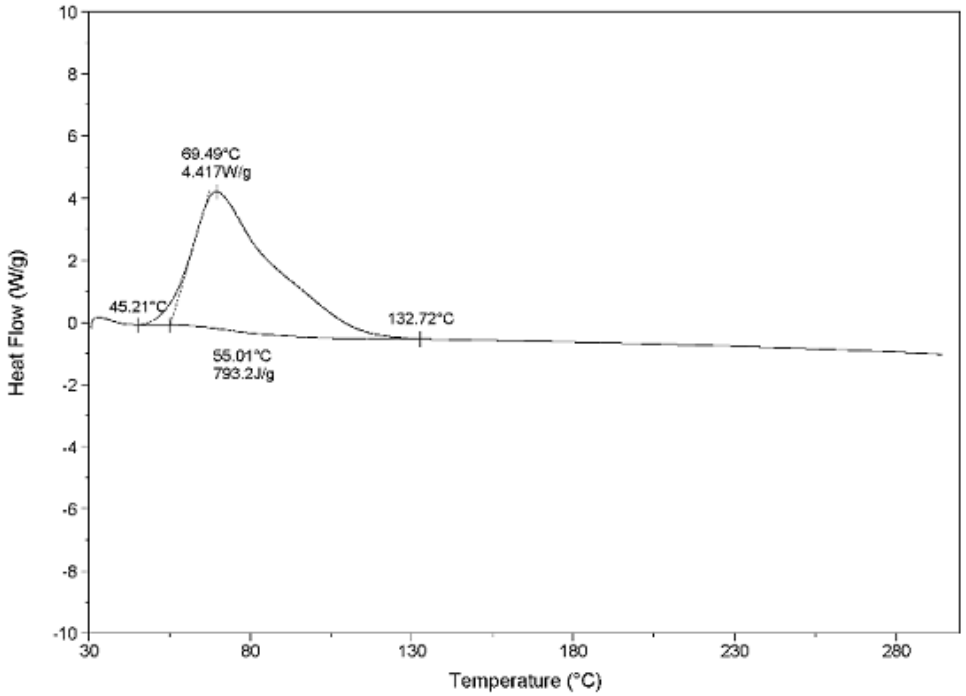
Thermal Stability Testing – DSC Examples



This test of 30% H_2O_2 reveals the material decomposes with high energy at low temperatures. Additional testing including ARC should be completed.

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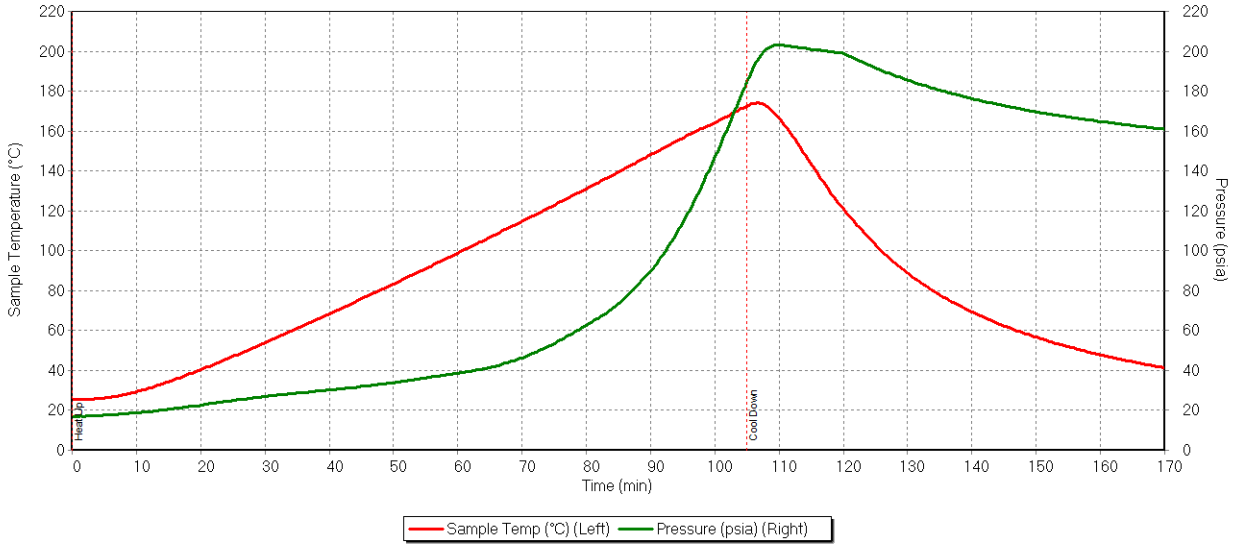
Thermal Stability Testing – TSu Example



This test reveals non-condensable gas generation in the pressure profile (green), while the sample temperature (red) shows no exotherm or endotherm.

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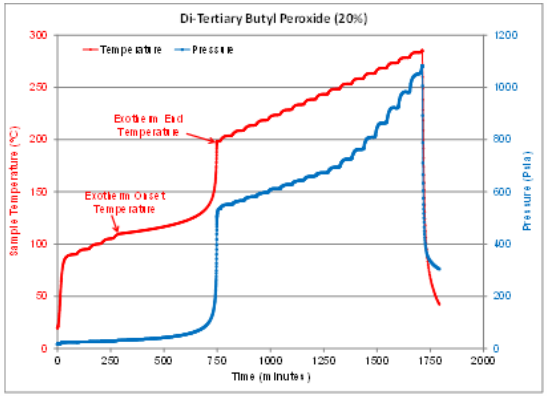
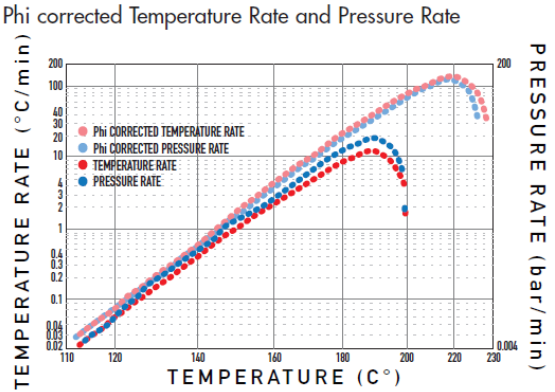
Thermal Stability Testing – ARC Example





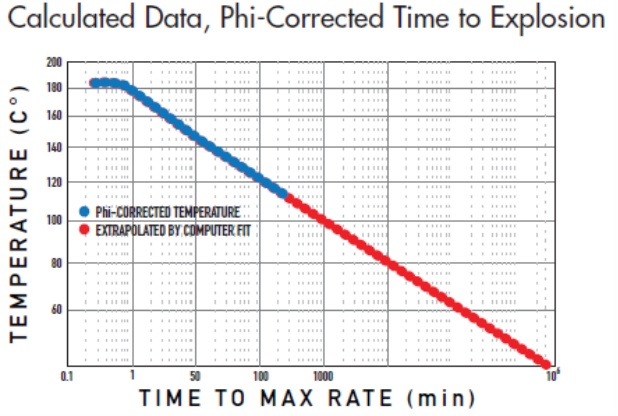


Photo credit: Thermal Hazard Technology (www.thermalhazardtechnology.com)

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Reactive Hazard Tools – Heats of Reaction Testing

Estimation Techniques

- Advantages: Consumes no materials
- Disadvantages: No kinetic info, need quality heat of formation data, may miss heats of mixing, side reactions, etc.

Micro-reaction Calorimetry (μRC)

- Advantages: Consumes negligible material (2-mL vial), accurate heat integration
- Disadvantages: Extracting kinetic information not straightforward.

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Photo credit: Thermal Hazard Technology (www.thermalhazardtechnology.com)

Reactive Hazard Tools – Heats of Reaction Testing

Reaction Calorimetry (RC1)

- Advantages: Robust automated instrument – controlled dosing and temperatures, pH, etc. Pressure vessels available. Can provide full mass and energy balance under plant conditions.
- Disadvantages: Can consume relatively large amount of material (≥500 mL vessel sizes). Good design and execution of experiment requires expertise. Cost prohibitive for smaller firms.
- Similar calorimeters – SIMULAR, Atlas, Chemisens

Photo credit: Mettler Toledo (www.mt.com)

Heats of Reaction Testing – Typical Results

Values obtained for the *desired* chemistry:

- Normalized Enthalpy of Reaction (ΔH_{rxn} in kJ/mole or kcal/mole)
- Adiabatic Temperature Rise of the reaction system

ΔT_{ad} = Total Rxn Heat / (Total Rxn Mass x Cp)

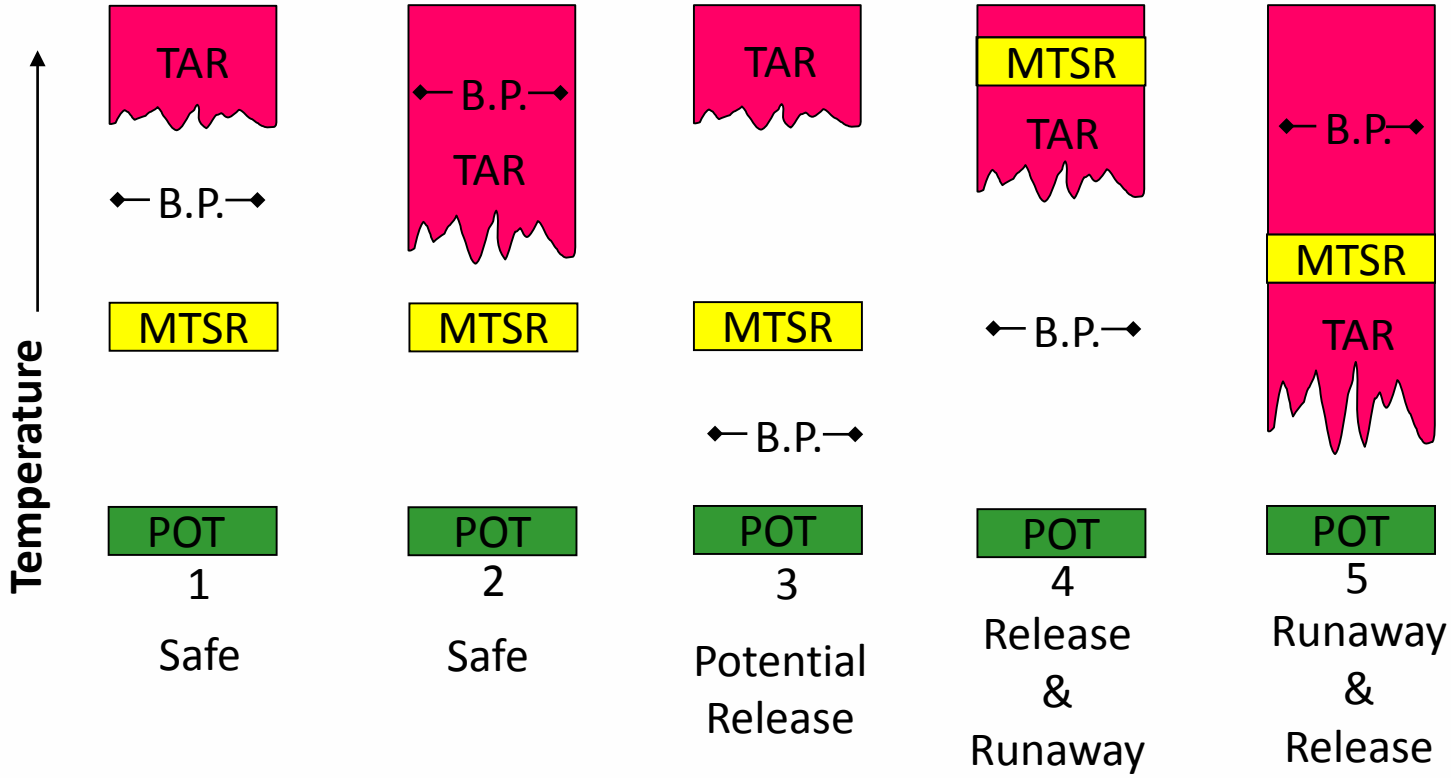
➢ This calculation gives us an indication of where the energy of the unchecked desired reaction can take us temperature / pressure-wise.

Process Safety Assessment for Scale-up

For exothermic reactions, we consider the relative position of the following:

- Process Operating Temperature – POT
- Maximum Temperature of Synthetic Reaction – MTSR
  ($POT + \Delta T_{ad}$)
- Temperature of Acceptable Risk – TAR
  (Defined by the thermal stability testing)
- Boiling point of the Solvent or Reaction Mass – B.P.

Process Safety Criticality Classes



Ref: Stoessel, F. What is your thermal risk?. *Chem. Eng. Prog.* **1993**, 10, 68-75.

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Process Safety Assessment for Scale-up

Scenarios to Consider for Thermal Runaway:

- Loss of Cooling
- Loss of Agitation (restart)
- Too much reagent/catalyst (wrong recipe)
- Too much reagent/catalyst at once (fast flow)
- Too much heat (i.e. equipment malfunction or operator error)
- Water/Air exposure

Heat Transfer on Scale-up

The heat removal capacity of a vessel decreases dramatically with increasing scale.

- An exothermic add that can be completed in minutes at research scale may require hours in the plant.

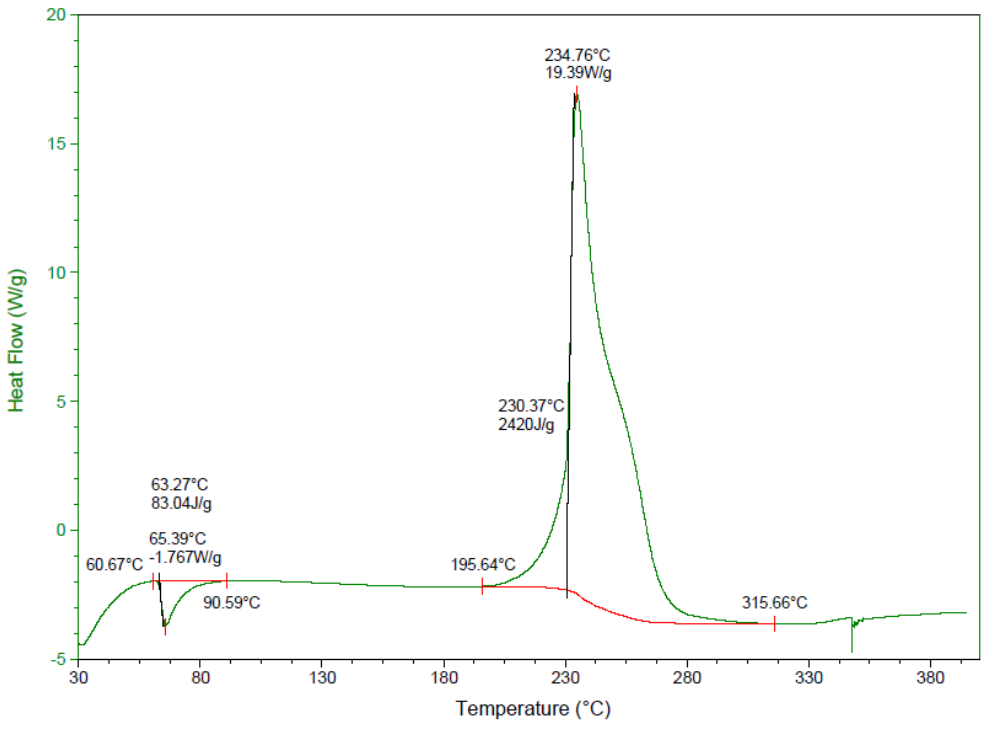
Scale	Reactor Volume (m^3)	Surface Heat Exchange Area (m^2)	Surface Area to Volume Ratio (m^{-1})	Typical Cooling Capacity (W/kg)
Research	0.0001 (100 mL)	0.01	100	1500
Research	0.001 (1 L)	0.03	30	450
Pilot Plant	0.1 (100 L)	1	10	150
Production	1 (1000 L)	3	3	45
Production	10 (10,000 L)	13.5	1.35	20

Ref: Stoessel, F. *Thermal Safety of Chemical Processes*; Wiley-VCH: Weinheim, 2008.

Case Study – The Problem Of "Distance Rules" to Set Temperature Limits

- A common practice is to set safe temperature limits based on the "onset temperature" from a single DSC test, (i.e. the "100 °C Rule").
- However, there is no scientific basis for an "onset" or starting temperature of a reaction. Reaction rates increase exponentially with temperature according to the Arrhenius Law.
- As such, the safe temperature limit is strongly influenced by the activation energy of the decomposition reaction.
- Therefore it is advisable to set safe temperature limits based on time to maximum rate (TMR) analysis.

Case Study – The Problem Of "Distance Rules" to Set Temperature Limits



- Compound exhibits very high energy decomposition
- Per ASTM E537
  - "Onset" = 195 °C
  - "Extrapolated Onset" = 230 °C

  (Both values commonly used to apply 100 °C rule)
- Practitioners using 100 °C rule could set limits at:
  - 95 °C
  - 130 °C

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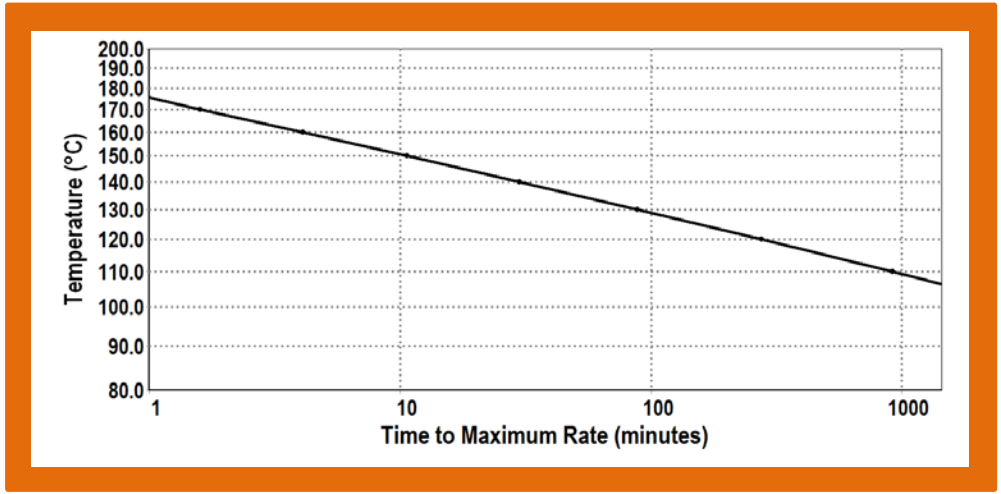
Case Study – The Problem Of "Distance Rules" to Set Temperature Limits



- A TMR analysis using more advanced Phi-TEC I test data provides the following results:
  - TMR_{ad} = 24 hrs @ 106 °C
  - This is a commonly accepted safe temperature limit.
- At 130 °C, the TMR is only ~90 minutes. This is an unsafe limit.
- At 95 °C, the TMR is > 2 days. This would be a safe limit, ***for this particular case***.

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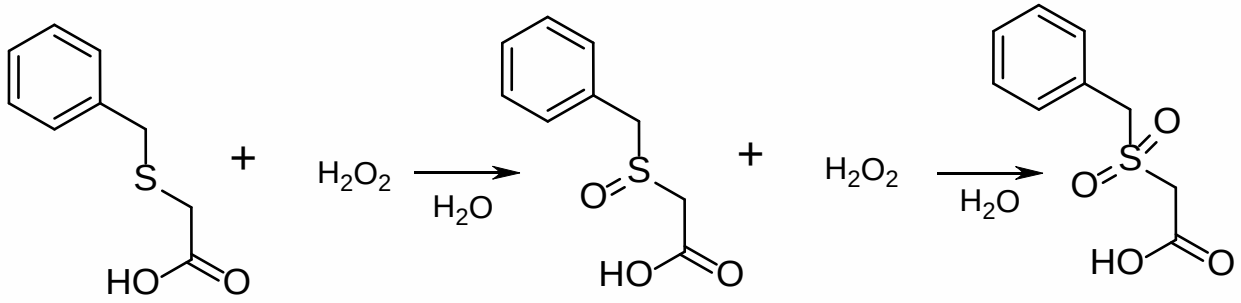
Case Study – Heat of Reaction Estimation versus Calorimetry

Oxidation of Benzyl Thioglycolic Acids

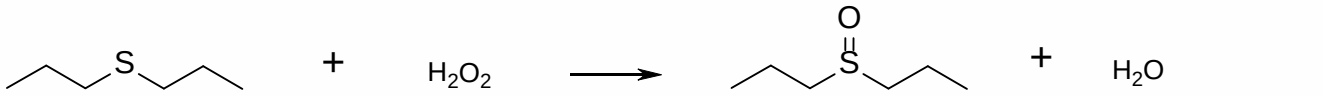


- Highly exothermic
- Consecutive oxidations amplify the concern
- Additional threat from potential peroxide decomposition

Ref: Knoechel, D.J.; Hewitt, B.D.; Lapekas, S.P. Oral Presentation, 12th RXE User Forum USA, Cambridge, MD, September 12-15, 2004

Case Study – Heat of Reaction Estimation versus Calorimetry

Heat of reaction estimation, using dipropyl sulfide as model compound



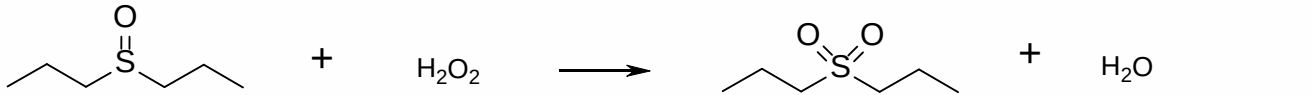
Phase: Liquid
ΔH_f^o = -169.9 kJ/mole

Phase: 5.7 pts Aq
ΔH_f^o = -191.0 kJ/mole

Phase: Liquid
ΔH_f^o = -329.4 kJ/mole

Phase: Liquid
ΔH_f^o = -285.8 kJ/mole

ΔH_{rxn} = (-329.4 kJ/mole + -285.8 kJ/mole) - (-169.9 kJ/mole + -191.0 kJ/mole) = -254.3 kJ/mole



Phase: Liquid
ΔH_f^o = -329.4 kJ/mole

Phase: 5.7 pts Aq
ΔH_f^o = -191.0 kJ/mole

Phase: Liquid
ΔH_f^o = -548.2 kJ/mole

Phase: Liquid
ΔH_f^o = -285.8 kJ/mole

ΔH_{rxn} = (-548.2 kJ/mole + -285.8 kJ/mole) - (-329.4 kJ/mole + -191.0 kJ/mole) = -313.6 kJ/mole

ΔH_{rxn} overall = -567.9 kJ/mole!!!

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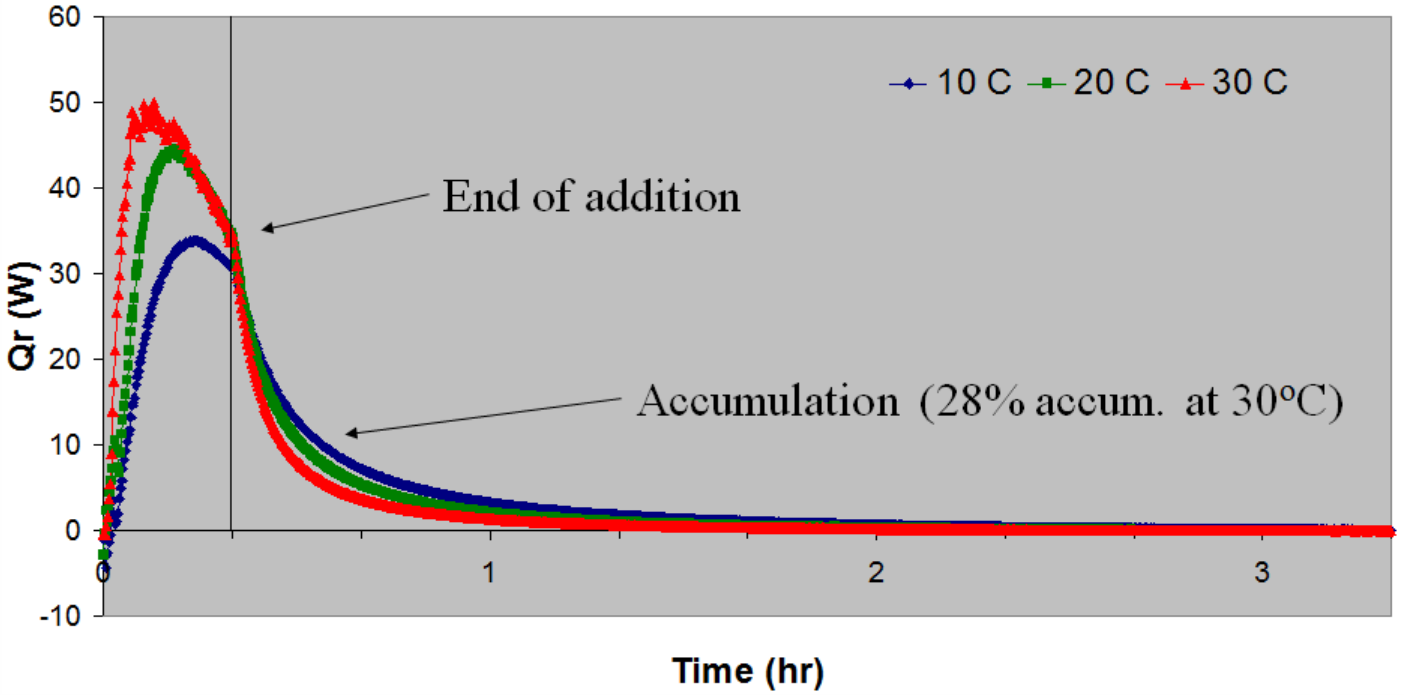
Case Study – Heat of Reaction Estimation versus Calorimetry

RC1 experiment, 1st eq 30% H_2O_2 added over 20 minutes



Ref: Knoechel, D.J.; Hewitt, B.D.; Lapekas, S.P. Oral Presentation, 12th RXE User Forum USA, Cambridge, MD, September 12-15, 2004

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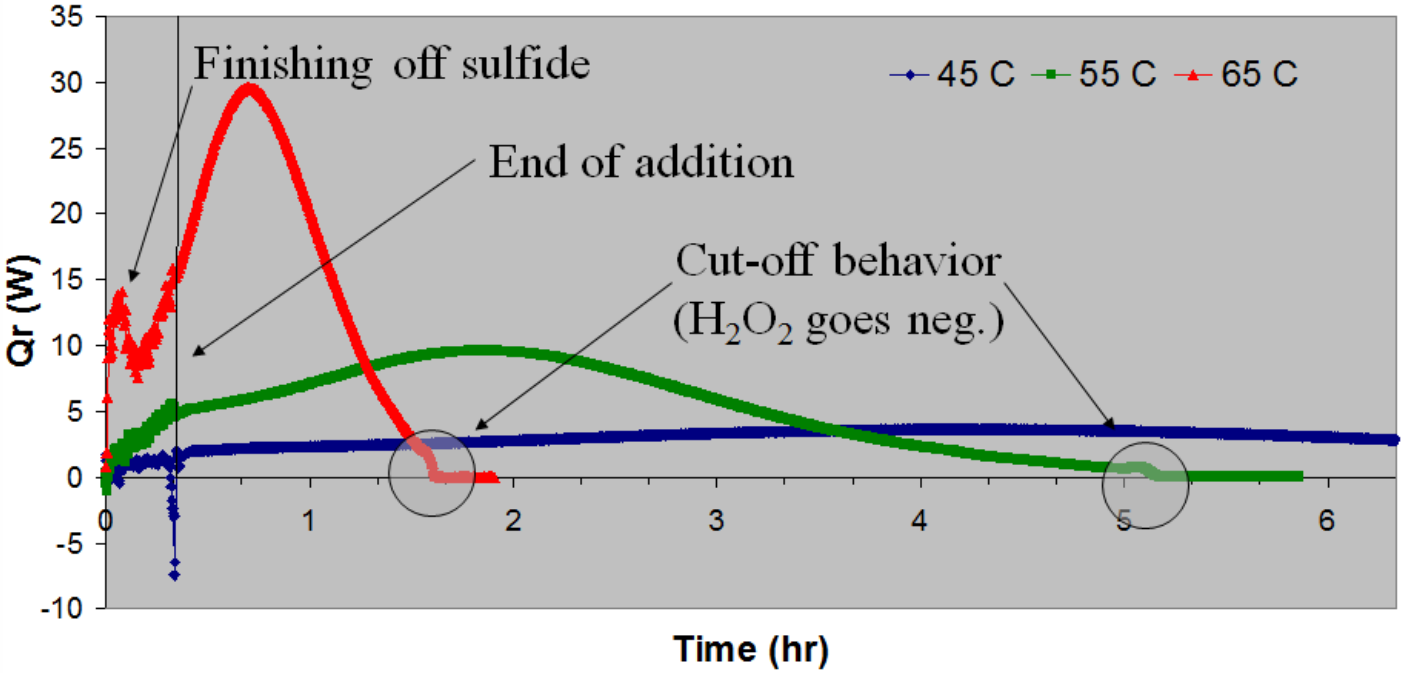
Case Study – Heat of Reaction Estimation versus Calorimetry

RC1 experiment, 2nd eq 30% H_2O_2 added over 20 minutes



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Case Study – Heat of Reaction Estimation versus Calorimetry

H_2O_2	T(°C)	Estimation (kJ/mole)	RC1 (kJ/mole)
1st eq	10		-239.3‡ †
1st eq	20		-229.3‡ †
1st eq	30	-254.3*	-221.8‡ †
2nd eq	45		-296.2†
2nd eq	55		-314.6†
2nd eq	65	-313.6*	-310.0†

* All estimations based on ΔH_f at 25°C
‡ Conversion corrected
† Tdos corrected

Estimation values show good agreement with RC1 results.

However, estimation gives no insight into the reaction kinetics and heat accumulation. This information is critical for developing a safe scale-up strategy.

Ref: Knoechel, D.J.; Hewitt, B.D.; Lapekas, S.P. Oral Presentation, 12th RXE User Forum USA, Cambridge, MD, September 12-15, 2004

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Summary

- It is critically important for facilities processing chemicals to have a thorough understanding of their reactive hazards.
- The amount of testing required is proportional to the potential severity of the hazard (e.g. high energy, large exotherms, increasing scale, etc.).
- A robust reactive hazard test program requires gathering and analyzing information from multiple tools.
  - Making decisions on single screening tests/methods can have unsafe consequences.

Piramal Pharma Solutions Global Process Safety Lab Network

RIVERVIEW
- ESTIMATIONS
- DSC
- TSu
- Phi-TEC I ARC
- µRC
- RC1

TORONTO
- ESTIMATIONS
- DSC
- ARSST
- SIMULAR

ENNORE
- ESTIMATIONS
- DSC
- ARSST
- RC1

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