Process Safety Scale-up Aspects of a Nitric Acid-Catalyzed Epichlorohydrin Hydrolysis Reaction

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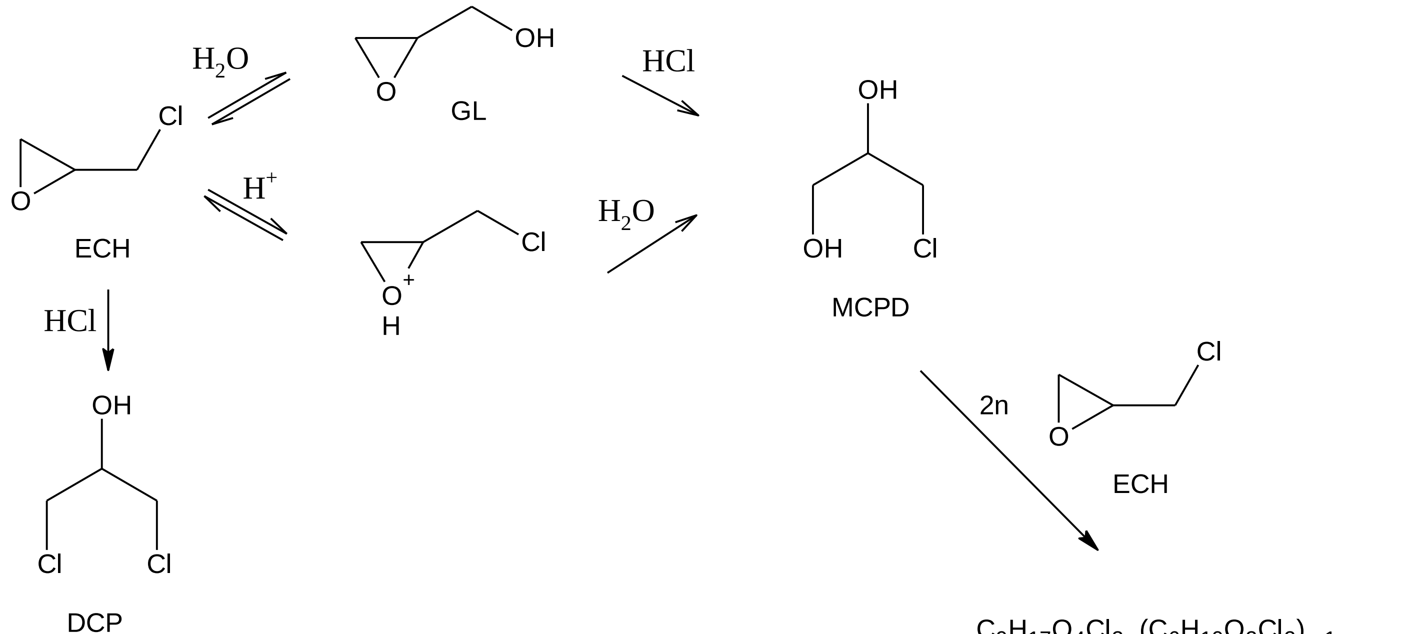
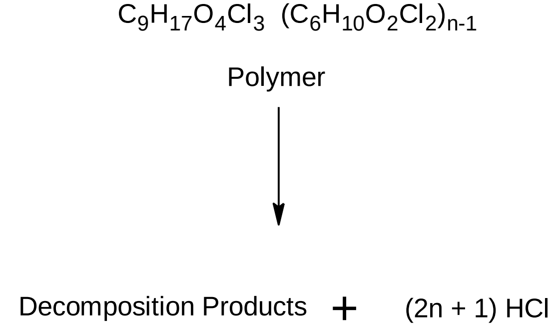
Outline

- EPI Hydrolysis – The Chemistry
- Reaction Calorimetry (RC) vs. Adiabatic Calorimetry (AC)
- RC, Energy Balance, Heat Rate Scale-Up and Initial Thermal Screening Findings
- Criticality Classification (Stoessel)
- Refining the Thermal Screening by DSC
  - Multiple Scans
  - AKTS Modeling
  - Thermal Activity Monitor (TAM) Results
- VSP2 Results
- Classification Summary
- ARC Results
- Instrument Sensitivity and TMR24ad
- Summary
- Acknowledgements
- Questions

The Chemistry: Acidic Hydrolysis of Epichlorohydrin





From J. Phys. Org. Chem. 2011, 24 1045–1050

From H. Fisher, personal comm.

Reaction Calorimetry (RC) vs. Adiabatic Calorimetry (AC)

RC

- Primarily used to characterize the desired process
- Measures heat (rate) under desired reaction conditions and calculates an adiabatic potential (ΔT_{ad})
- But that ΔT_{ad} is only due to measured heat at desired conditions
- ΔT_{ad} calculated using mCp at desired reaction conditions
- Heat Rate profile used to determine cooling capacity requirements for scale-up

AC

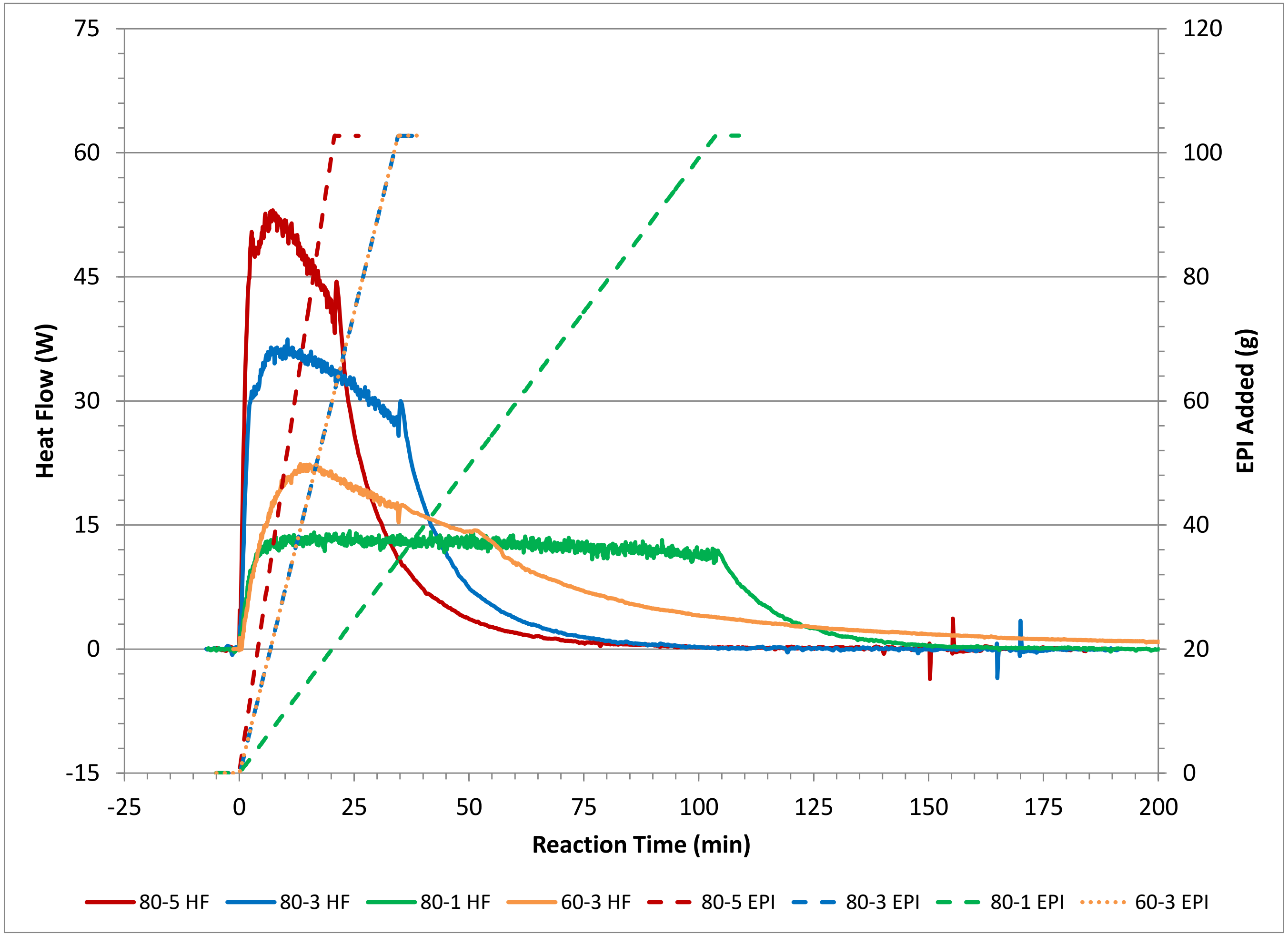
- In this context, used to characterize undesired or worst-case behavior
- Measures the temperature rise (correct for Φ) and calculates a heat
- Heat is at least due to desired reaction plus possible secondary reaction and more
- ΔT_{ad} realizes Cp(T)
- If desired heat only, ΔT_{ad} AC $<$ ΔT_{ad} RC
- Low Φ tests used for vent-sizing

Reaction Calorimetry
Epichlorohydrin Hydrolysis
Semi-batch Recipe

- Mettler-Toledo RC1 recipe – total charge ~380 g, 364 ml (385 ml stirred)
- Water – 72.4 % wt
- 69.0% Nitric acid – 0.5 % wt (0.02 mole eq.)
- 99.8% Epichlorohydrin – 27.1 % wt
  - Controlled Addition
  - 102.8 g at various addition rates
- Reaction Temperature – 60°C, 80°C

Epichlorohydrin Hydrolysis Semi-batch Process

- Composite Plot
- EPI accumulation increases with
  - faster additions
  - lower temperature



EPI Hydrolysis RC Data Summary

	80°C, 5 g/min	80°C, 3 g/min	80°C, 1 g/min	60°C, 3 g/min	80°C, 0.822 g/min
Reaction Mass (g)	380.18	379.86	379.86	379.90	379.8
Total Heat (J)	-85,803	-86,970	-86,338	-89,652	-91,578
EPI added (g)	102.74	102.74	102.76	102.76	102.68
EPI added (g-moles)	1.108	1.108	1.108	1.108	1.108
Heat of Reaction (kJ/mole EPI)	-77.4	-78.5	-77.9	-80.9	-82.7
Addition Time (hh:mm:ss)	00:20:55	00:34:45	01:43:45	00:34:43	2:06:09
% Accumulation	**33.2**	**24.0**	**11.0**	**58.8**	**9.5**
Pre-Reaction Cp (J/g°C)	4.360	4.365	4.361	4.210	4.378
Post-Reaction Cp (J/g°C)	3.823	3.758	3.782	3.648	3.819
ΔT_{ad}* (°C)	**59.0**	**60.9**	**60.1**	**64.7**	**63.1**
Dynamic ΔT_{ad}# (°C)	**19.6**	**14.6**	**6.6**	**38.0**	**6.0**

* Based on final mCp. #Assumes cooling is lost at end of the addition

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Energy Balances

Simplified Energy Balance
Input + Generation = Output + Accumulation

- Input – Sensible heat $= m_{add}Cp_{add}(T_r - T_{add}) / t$

- Generation – Heat from chemical reactions (includes ΔH of reaction, dilution, solution, mixing, crystallization)

  $= [\Sigma (\Delta H_{rx} * \# \text{ moles limiting reagent})] / t$ ← This comes from Reaction Calorimetry

- Output – Heat removed via reactor jacket, heat exchanger or condenser

  $= U*A (T_r - T_j)$ ← This comes from Equipment

- Accumulation – nonisothermal reaction mass

  $= m_r Cp_r dT_r/dt \sim m_r Cp_r(T_r i - T_r f) / t$

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Heat Removal by Jacket

- Scale up our generic example to 2000 kg EPI
- Assume a 12,000-liter reactor (diameter 2.4 m)
- Stirred volume ~7,250 Lit, A = 15.1 m^2
- Heat transfer coefficient for stirred tank – U*
  - Glass Lined Steel (GLS) = 300 W/m^2K
  - Hastelloy (HC) = 500 W/m^2K
  - ~~Stainless Steel (SS) = 1000 W/m^2K~~ (not used, acidic conditions, Cl^-)
- Available max ΔT = 50°C
- UA ΔT = 300 x 15.1 x 50 = 226,500 Watts

  = 500 x 15.1 x 50 = 377,500 Watts

Normalized cooling capacity rates 113.3, 188.8 W/kg EPI, respectively

* These are U values at the upper end of performance range

Heat Removal by Condenser

- From a Customer – “Oversized” condenser for ~10,000-liter tank

  Condenser has:

  “heat removal capacity of 38.4 K BTU / min with a water boil out”

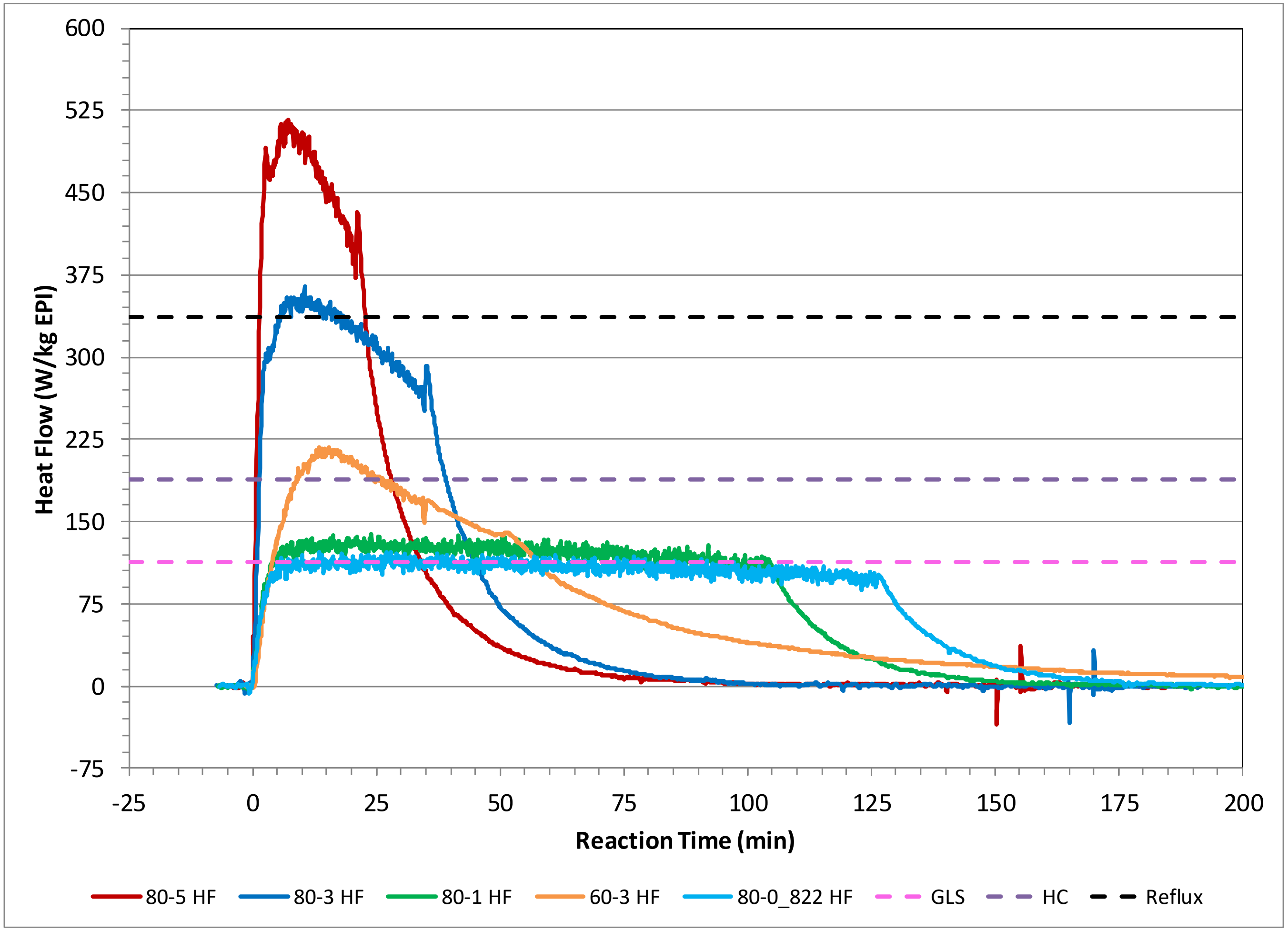
- 38.4 K BTU / min = 1076 kg water/hr = 674,635 W

- For our 2000 kg batch the normalized cooling capacity limit by reflux is:

  337 W/kg

Heat Removal with Scale-Up

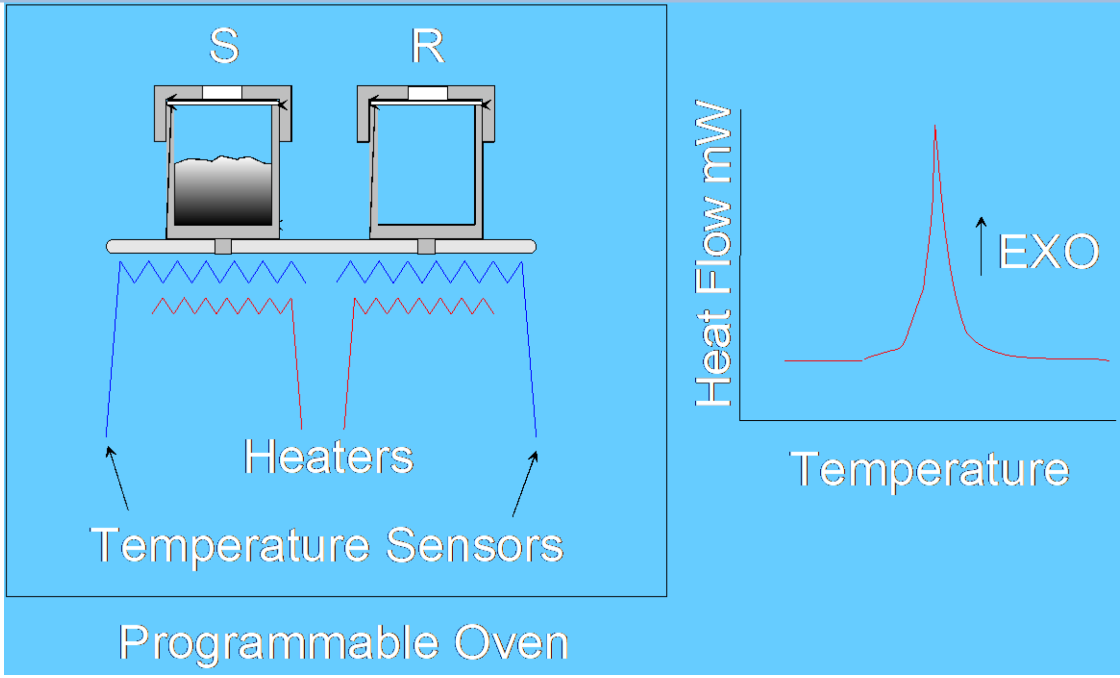
- 2000 kg EPI batch in 12,000 Liter vessel (stirred volume 7,250 lit)
- Compare Glass Lined Steel (GLS), Hastelloy C, Reflux
- Normalized cooling capacity lines for normalized UAΔT (113.3 W/kg, 188.8 W/kg and 337 W/kg for Reflux)
- Reflux (vacuum) can handle the 35 min addition at either 80°C or 60°C but not the 20 min addition at 80°C
- HC would require >1 hr addition at 60°C
- GLS would require at least 2 hr addition at 80°C



Thermal Screening Differential Scanning Calorimetry (DSC)

- Small Sample Size (1-10 mg)
- Typical Heat Rate 0.5-8°C/min
- Quantitative for Energy
- Screening only for onset T
- Swissi Pans (FAI is NA Distributor)

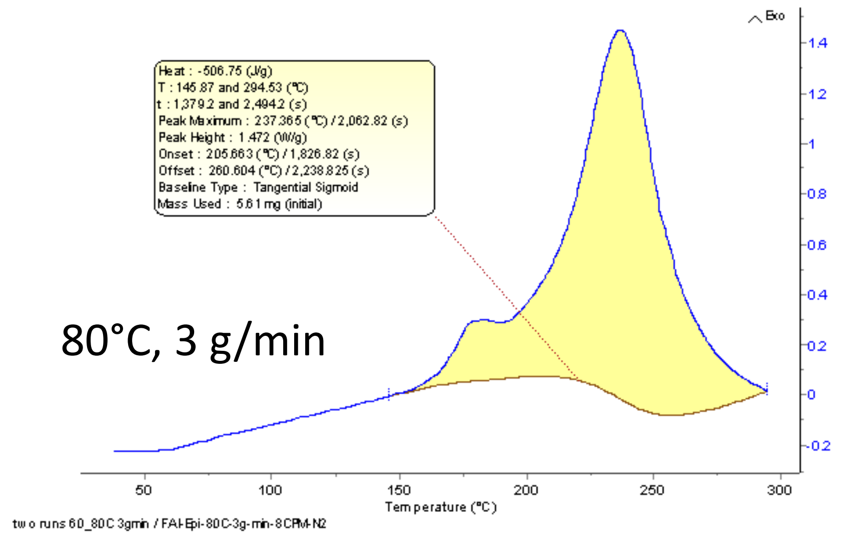
M20  M50 

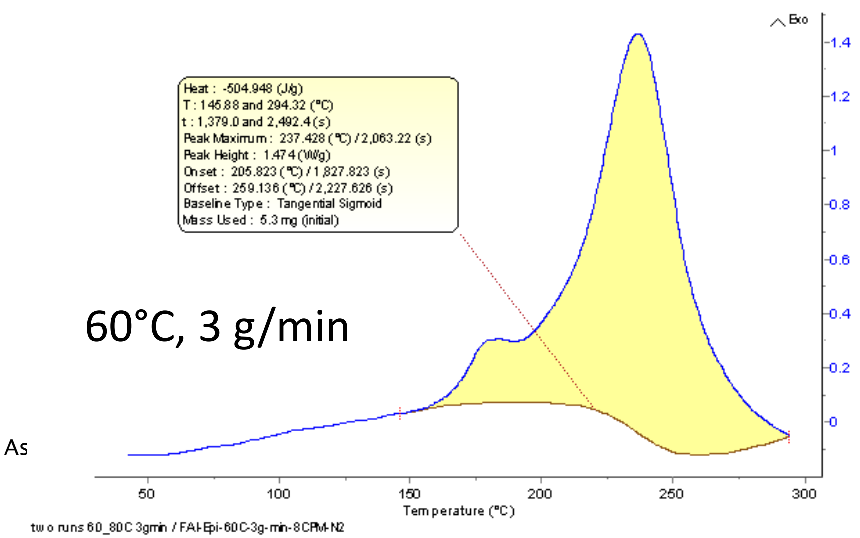


- The "onset" point is the temperature at which the thermal activity is first observed in a dynamic thermal measurement. Its value is a result of a balance between the sensitivity and scan rate of the instrument, the mass of the sample, the mass and conductivity of the sample cell and the kinetics and energy of the decomposition reaction. It is not an intrinsic property of the material and should not be treated as an absolute number.

Thermal Screening (DSC) of Select Post Reaction Mixtures

- DSC using 20μL M20 Swissi Crucibles
- Sealed in nitrogen atmosphere
- Scanning rate 8°C/min
- Results shown for 80°C, 3 g/min (5.30 mg) and 60°C, 3 g/min (5.61 mg) post reaction mixtures
- Exothermic energy >–500 J/g
- Onset ~ 146°C





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Scale Up Implications for EPI Hydrolysis

- Reaction Calorimetry shows
  - Plenty of intended heat of reaction to handle

- Thermal Screening (DSC) shows
  - Secondary reaction potential lying in wait

- Handling the intended heat of reaction is critical to process safety with scale up

- Adiabatic Calorimetry should show
  - Can intended energy lead to waiting energy in a loss of cooling scenario?

Stoessel Criticality Classes

- Criticality Classes from – Stoessel, F. (1993) What is your thermal risk?. *Chemical Engineering Process*, October, 68-75.

- IMHO, this methodology best serves the batch dominant chemical industry (incl. Ag and Pharma) during the development phase to highlight "*what can cause trouble?*"
  - Desired reaction
  - Undesired (Secondary) reaction
  - Vent Sizing Issues

- Serves as guide to direct needed change to improve process safety with development

Stoessel Criticality Classes (cont.)

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

- Process Temperature (Tp)

- Maximum Temperature of the Synthetic Reaction (MTSR)
  - $MTSR = Tp + \Delta T_{ad}$ (from RC)

- Decomposition Temperature (T_D)
  - Stoessel suggested to use TD24 or TMR24ad (DSC, ARC, other)

- And…

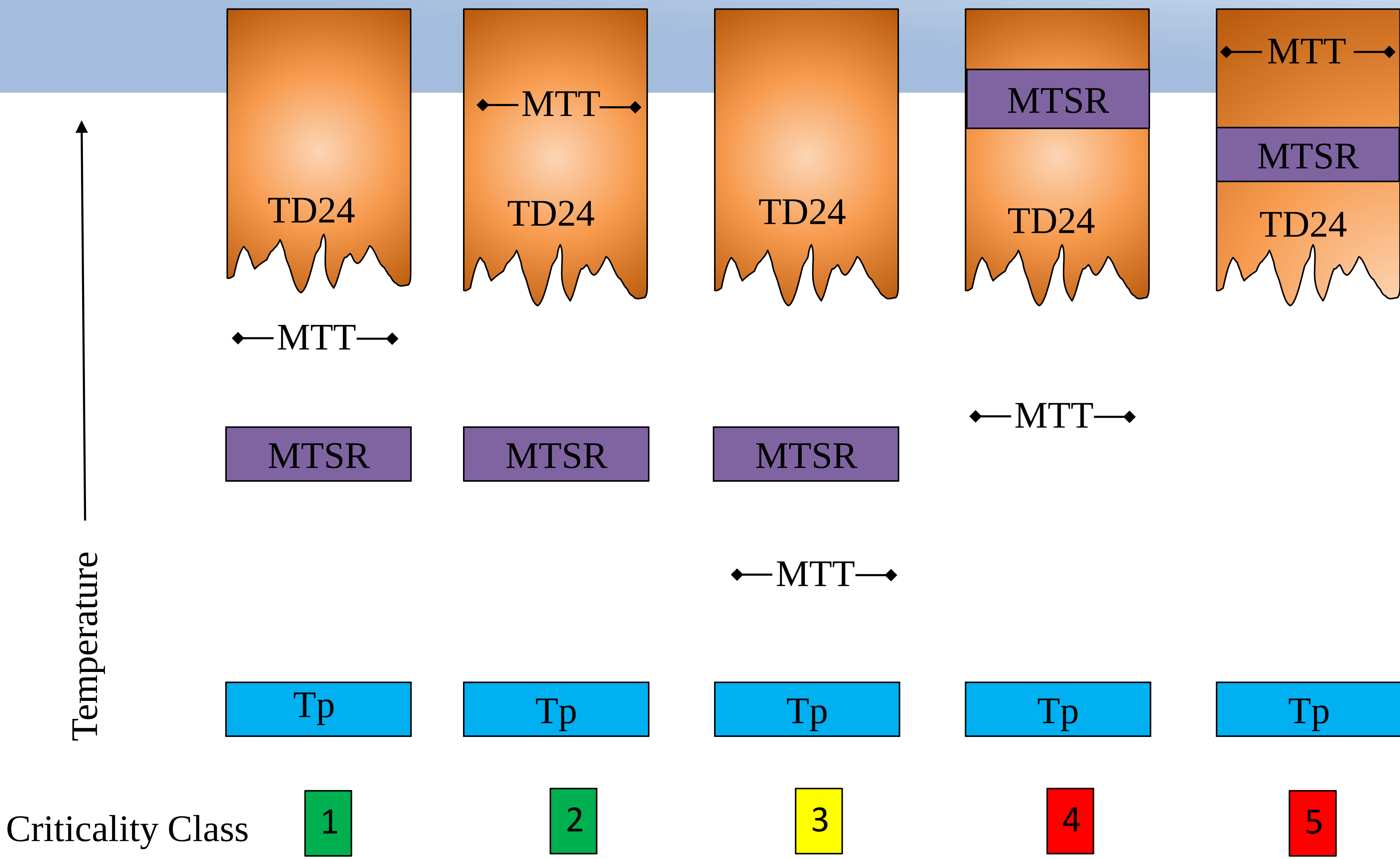
Maximum Technical Temperature (MTT)

- Open system – Boiling point of the reaction mass
  - Is it truly open?
  - Many batch reactors have large diameter risers leading to condensers
  - But condensers can flood

- Closed System – T corresponding to maximum permissible pressure
  - Sub-definition says T at set pressure of relief device
  - In DIERS we know it should be the temperature at the maximum accumulation pressure, typically 1.1 x MAWP
  - This comes from VSP2 data and a vent sizing calculation
  - Sometimes this data is not known until late in development

- Maximum temperature from jacket utilities?

Stoessel Criticality Classes



Summary of Classifications
(and what can be done to decrease class)

- Class 1 & 2 Inherently Safe
- Class 3 basis of safety depends
  - Vented – how much will boil?
  - Unvented – how much pressure?
- Class 3 > 1 by
  - Dilution
  - Higher BP solvent
- Class 4 > 3 by
  - Dilution
- Class 5 > 2 by
  - Dilution
- Class 5 > 4 by
  - Lower BP solvent
- Semi-Batch Operation
  - A controlled addition dynamically decreases accumulation of reagent, hence same effect as dilution
  - 5 > 2
  - 4 > 3 > 1

Criticality Classes – Observations

- China Guidelines for Commercial Production Process Approval recommends knowledge of TMR24ad
- The Criticality Class concept is presented as an all-in/loss of cooling context
- It is largely based on batch/semi-batch operations
- MTT must be thought about critically
  - Effects of two-phase flow, system classification (gassy, vapor, hybrid)
- Must adapt and be flexible to apply to continuous operation
- TMR24ad is a very conservative estimate of the beginning of the region in temperature where the undesired decomposition takes place
  - Conservative in the sense that some action is taken well before 24 hours elapses
  - But what burden do we place on our PHA and LOPA analysis picking such a conservative (Low T) value?

What Do We Know? | What Do We Need?

- From RC
  - Running at 80°C
  - $MTSR_{batch}$ = 80°C + 61°C = 141°C
  - $MTSR_{semibatch}$ = 80°C + 6°C = 86°C
- From DSC of post RC Sample
  - Secondary Activity
    - Onset ~146°C
    - More ΔT_{ad} (>130°C)

- DSC at different scan rates and TMR modeling for TMR24ad
- TAM for low T heat rate
- VSP2 for MTT for closed system

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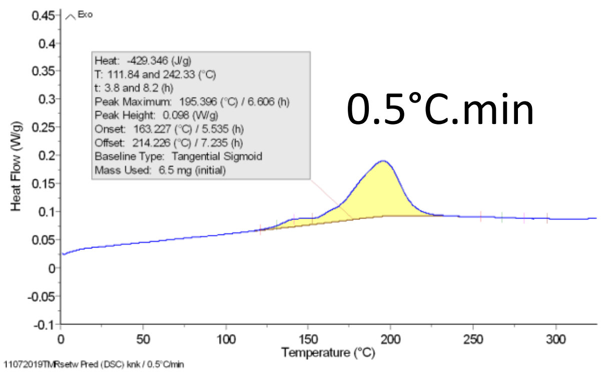
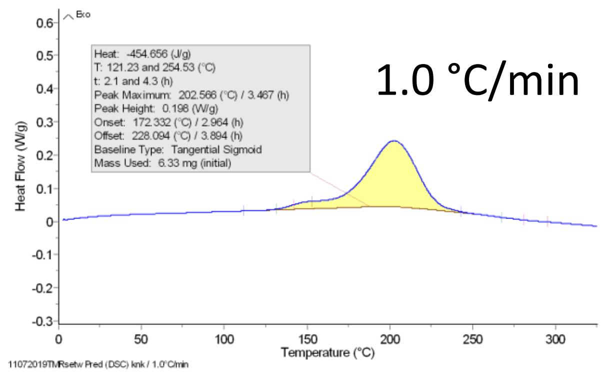
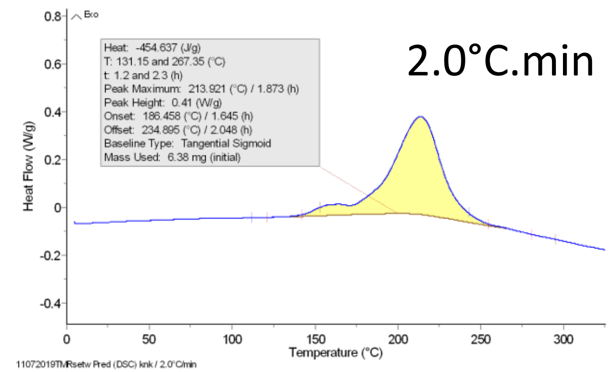
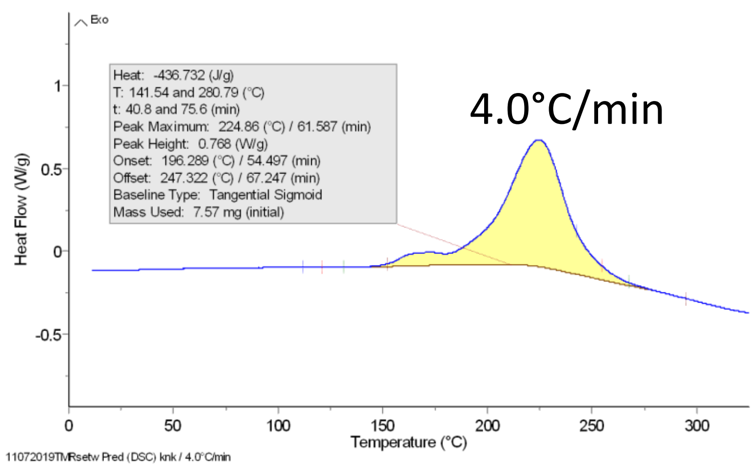
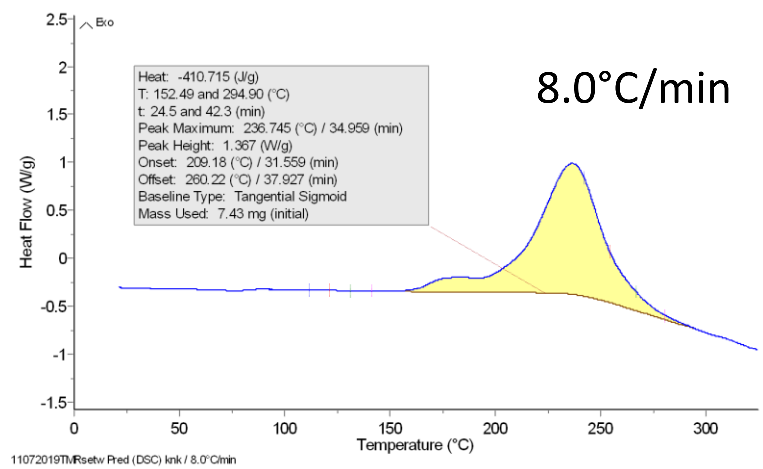
RC 80°C, 0.822 g/min DSC Scans











Thermal Screening by DSC Summary

DSC Run	DSC Results		
	Onset# (°C)	Q (J/g)	ΔT_{ad}* (°C)
80°C, 0.822 g/min 0.5°C/min	111.8 | 163.2	-429.4	114.6
80°C, 0.822 g/min 1.0°C/min	121.2 | 172.3	-454.7	121.3
80°C, 0.822 g/min 2.0°C/min	131.3 | 186.5	-454.6	121.3
80°C, 0.822 g/min 4.0°C/min	141.5 | 196.3	-436.7	116.5
80°C, 0.822 g/min 8.0°C/min	152.5 | 209.2	-410.7	109.6

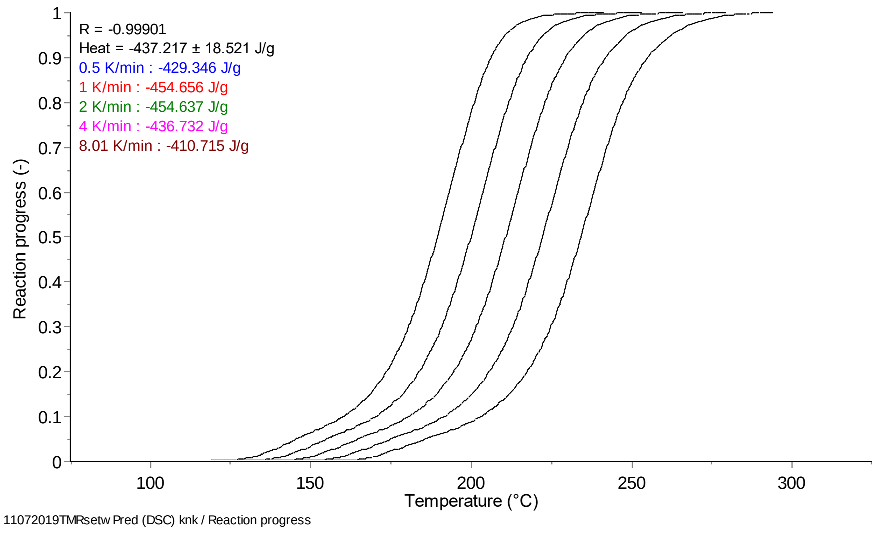
#1st Activity Onset | Extrapolated Onset. *Based on Cp = 3.748 J/g°C

AKTS-Thermokinetics Software 'Thermal Safety Version'

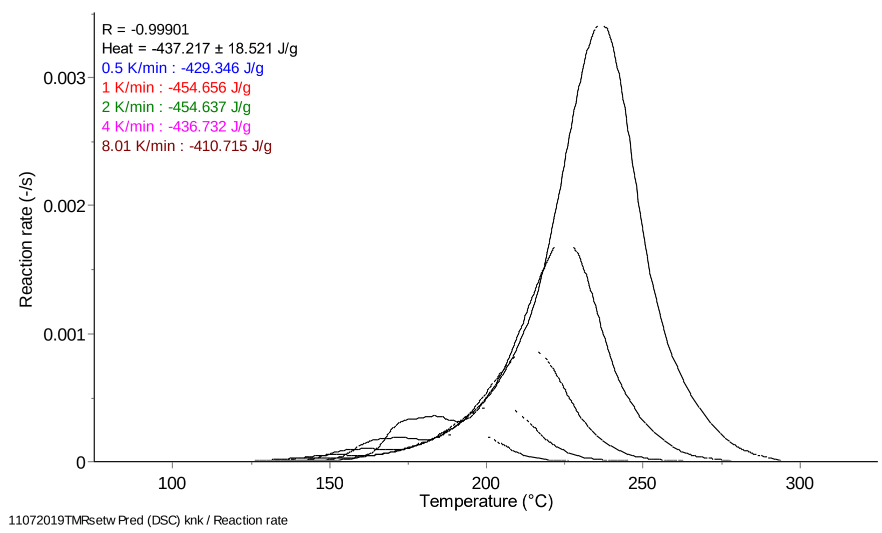
- Enables the calculation of Time-to-Maximum-Rate under adiabatic conditions (TMRad)
- Uses Isoconversional methods (model free)
  - Reaction model not required
  - Decomposition mechanism is unknown
- Typically uses multiple DSC scans with different scan rates:
  - But, can supplement with other instrument results to help with difficult cases
    - ARC
    - VSP2
    - Setaram C80
    - Thermal Activity Monitor (TAM)
      - to obtain low temperature isothermal rates – this means the kinetics are not extrapolated to where there is no data
    - THT μRC scanning experiments (150°C limit)

AKTS Evaluation Plots – DSC

Reaction Progress



Reaction Rates

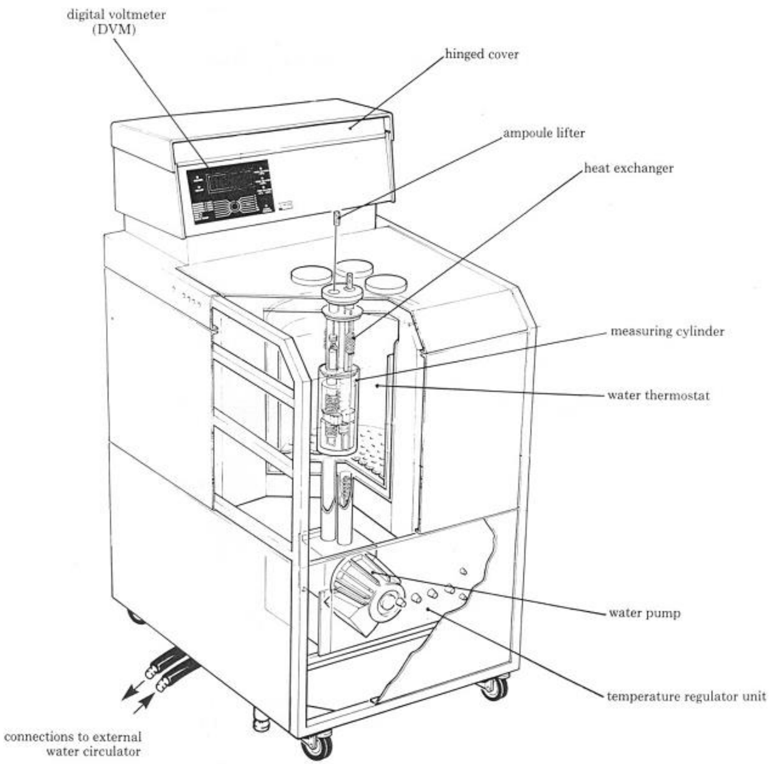


Thermal Activity Monitor (TAM)

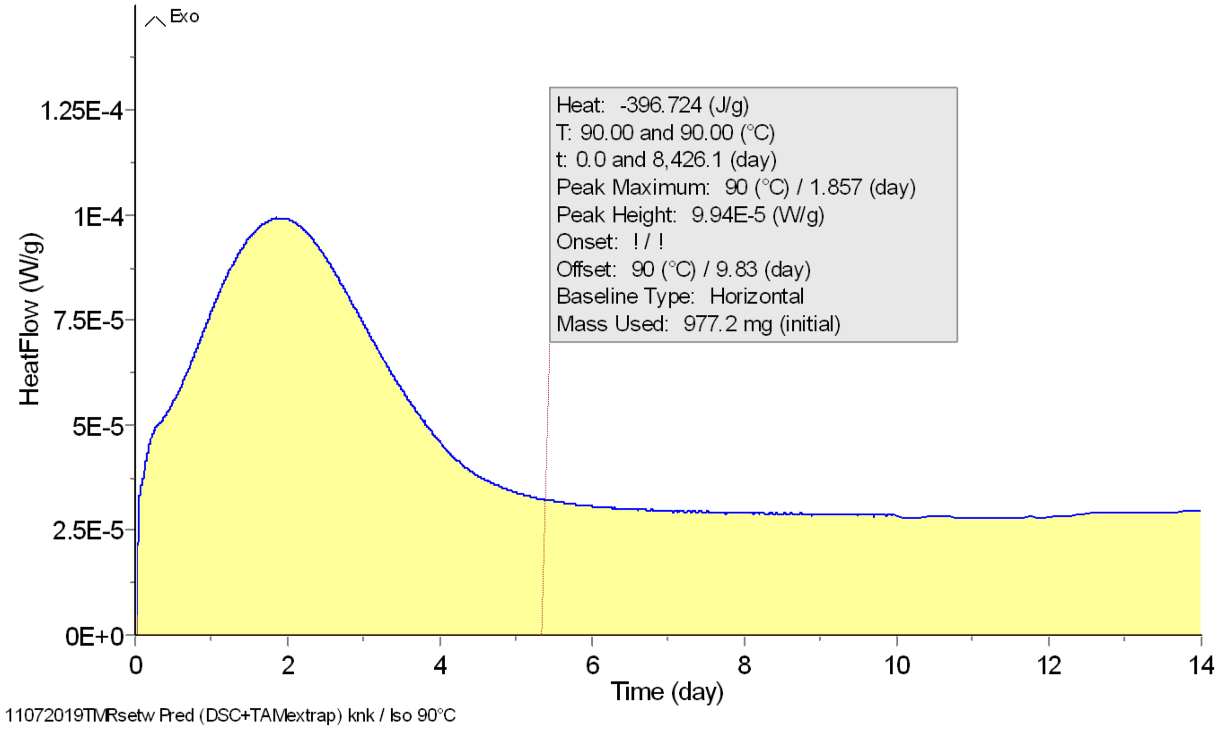
- Isothermal Microcalorimeter
- Provides heat flow data as a function of time
- Used to provide information on events that generate (low) heat
  - Shelf-life studies
  - Fermentation rates
  - Oxidation or corrosion rate
  - Interaction tests
  - Reaction kinetics
- Measure heat flow as low as 0.1μW
- Directly measure heat at temperature of interest

But…

- Tests can take a very long time to complete
- No pressure measurement

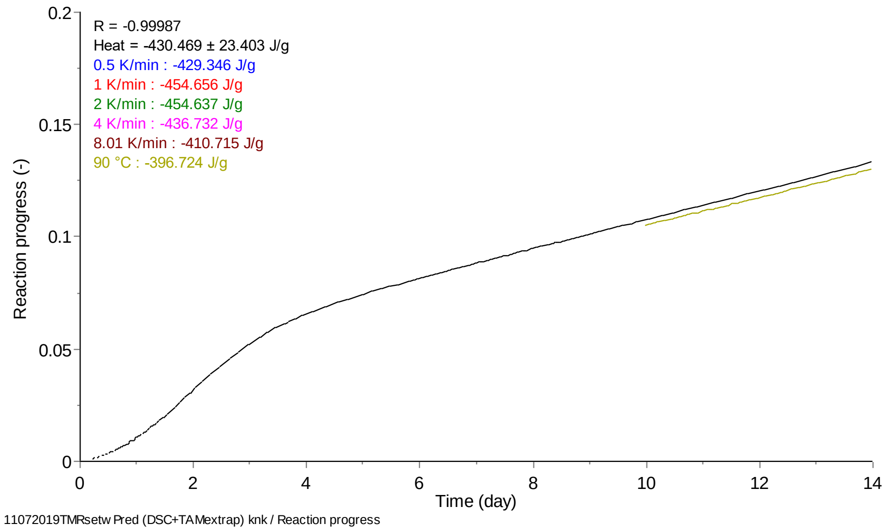


TAM Isothermal Test – 90°C
(Sample RC 80°C, 0.822 g/min)

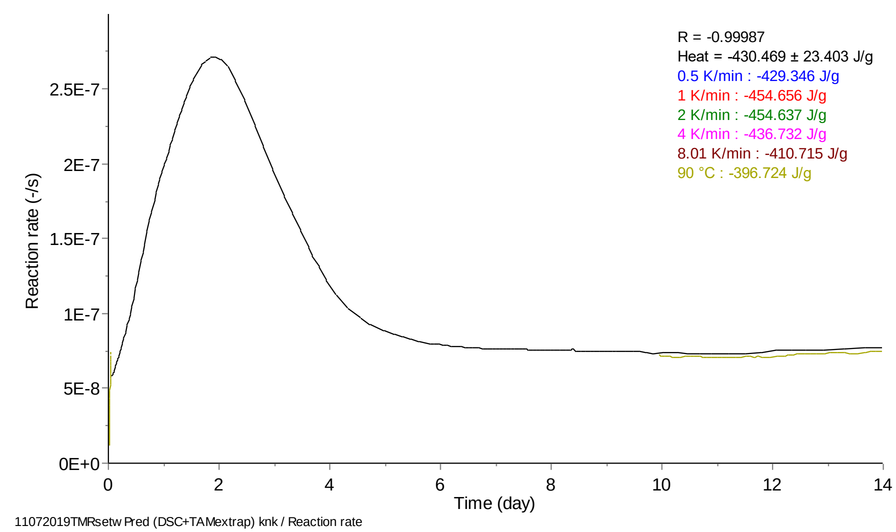


AKTS Evaluation Plots – TAM

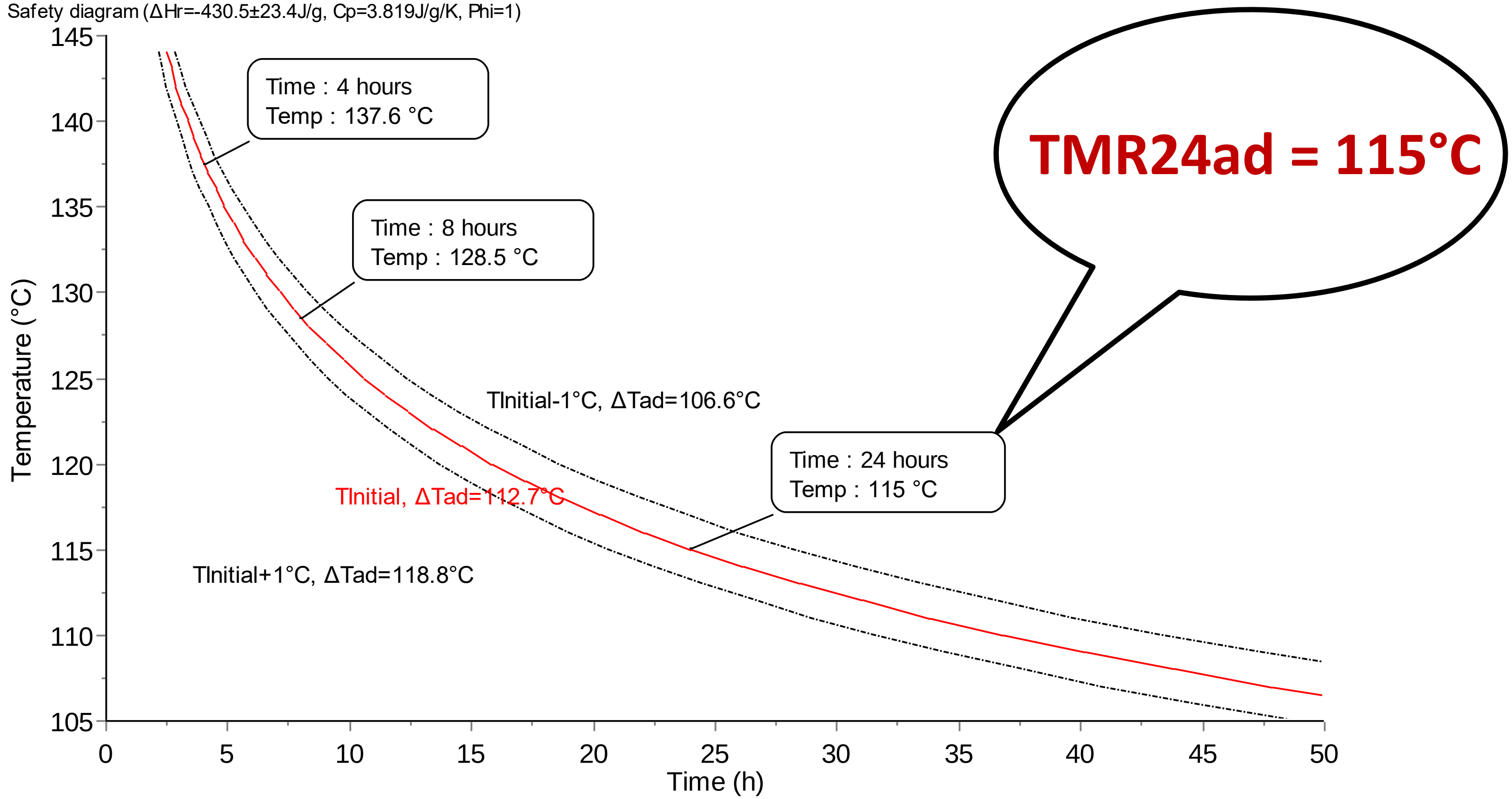
Reaction Progress



Reaction Rate



Time–to–Maximum–Rate Plot (TMR)
(Derived from DSC + TAM)



11072019TMRsetw Pred (DSC+TAMextrap) knk / Safety diagram (DeltaHr=-430.5±23.4J/g, Cp=3.819J/g/K, Phi=1)

EPI Hydrolysis Criticality Class Open System

- Straight Batch
  - Tp = 80°C
  - MTT (open) = 100°C
  - TMR24ad = 115°C
  - MTSR = 141°C

MTSR >TMR24ad > MTT > Tp

Class 4

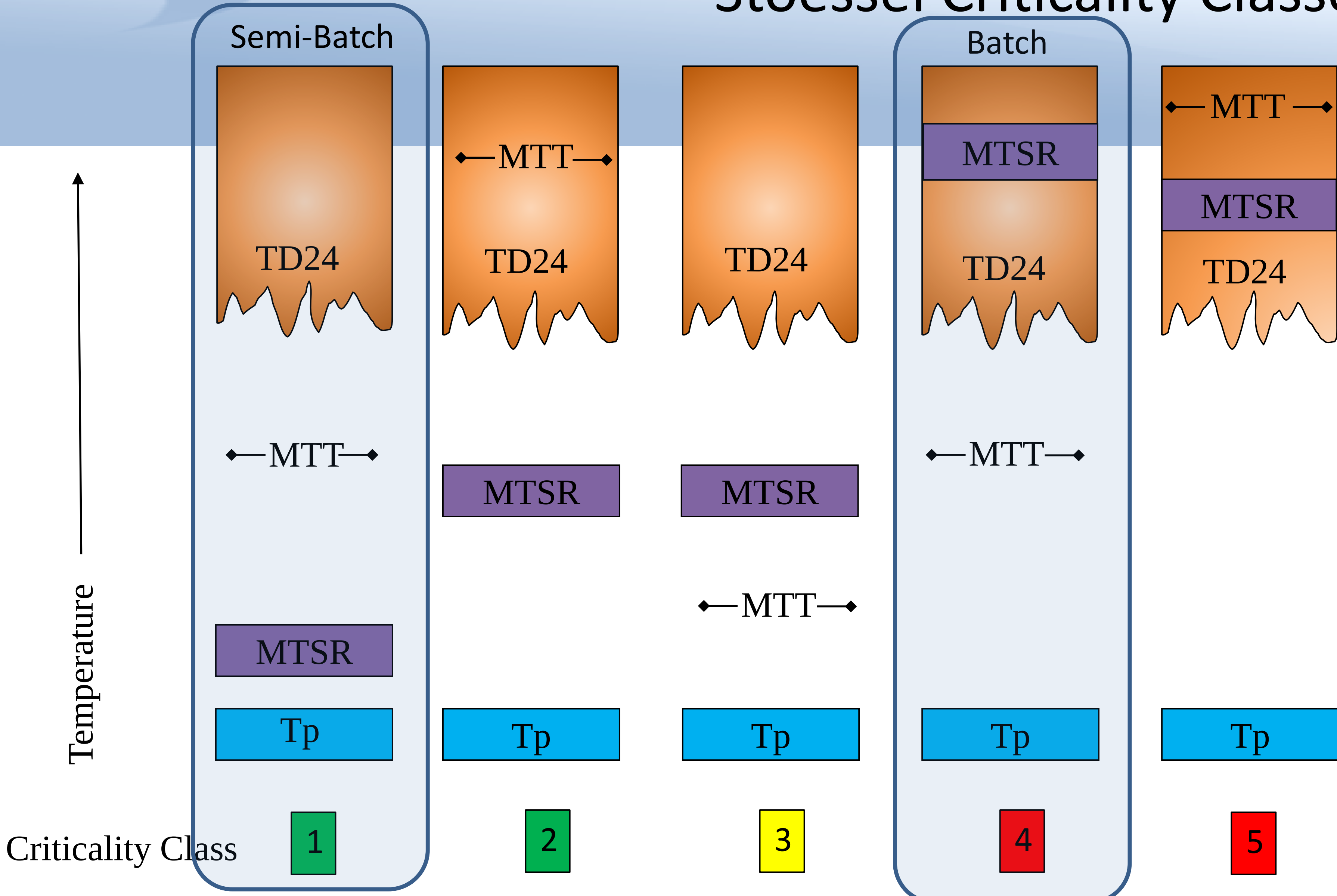
- Semi-Batch (2.1 hr Add)
  - Tp = 80°C
  - MTSR = 86°C
  - MTT (open) = 100°C
  - TMR24ad = 115°C

TMR24ad > MTT > MTSR > Tp

Class 1

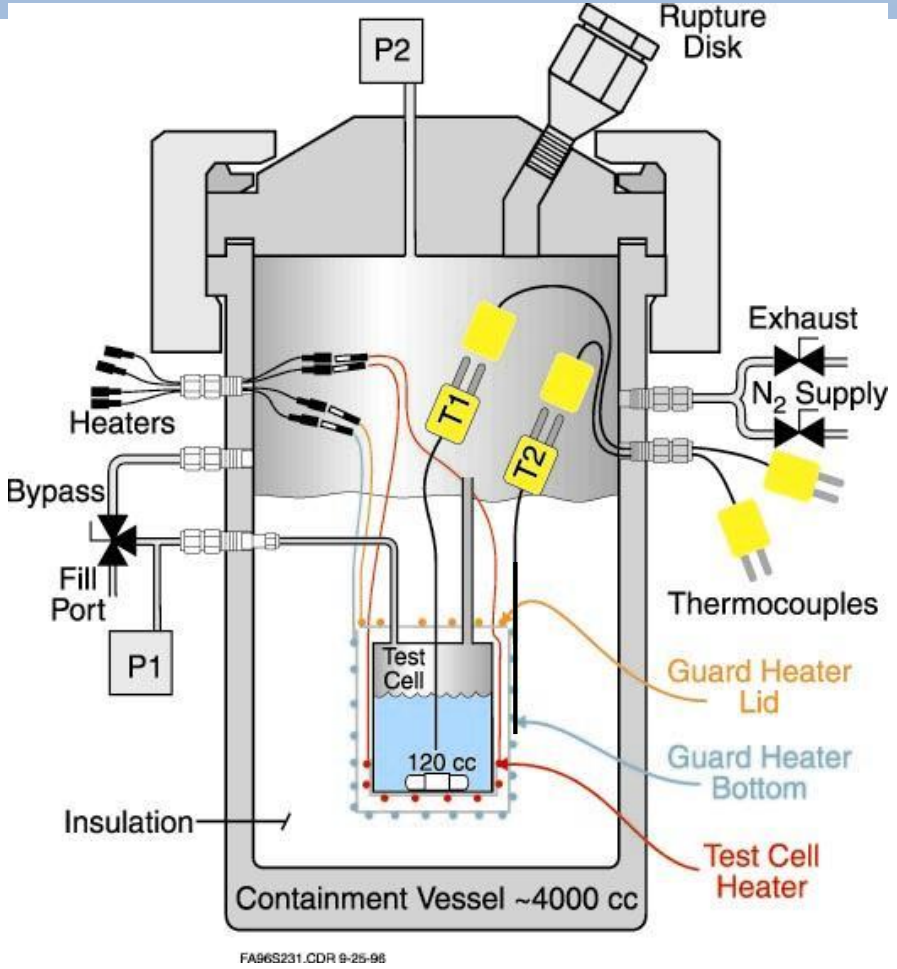
Can only be considered Class 1 if, when cooling is lost, the EPI addition is stopped

Stoessel Criticality Classes



Adiabatic Calorimetry
VSP2 Vessel & Test Cell Cross-Section

- Low thermal inertia
- Automatic pressure balancing
- Direct measurement of sample temperature, up to 4 temperature channels (from -70°C to 1000 °C)
- Measure up to 4 Pressures (FV to 2000 psig)
- Open or closed cell tests
- 120 ml max cell volume
- 4-liter containment volume
- 0.2°C/min Sensitivity

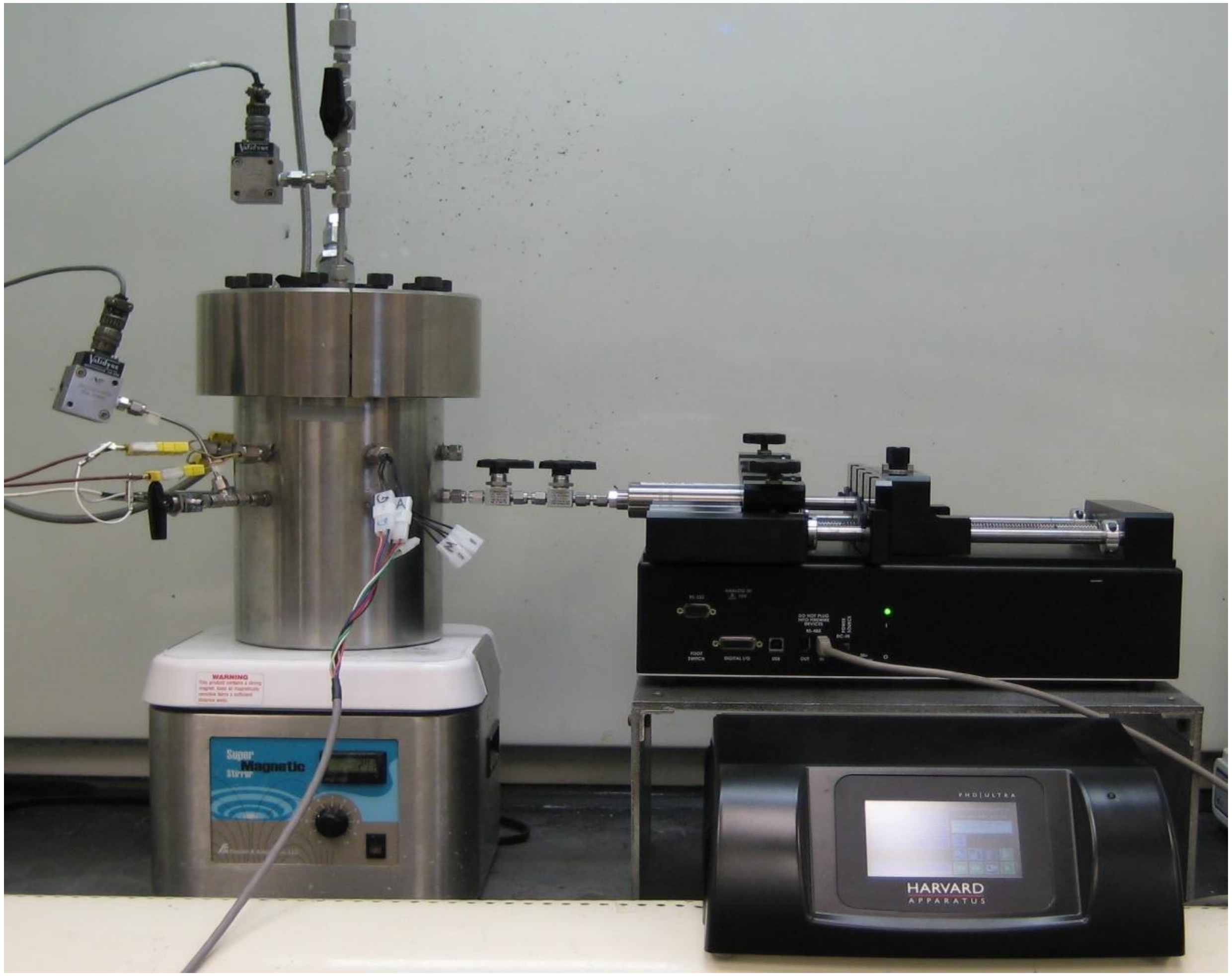


Epi Hydrolysis–VSP2 Loss of Cooling
Test Details

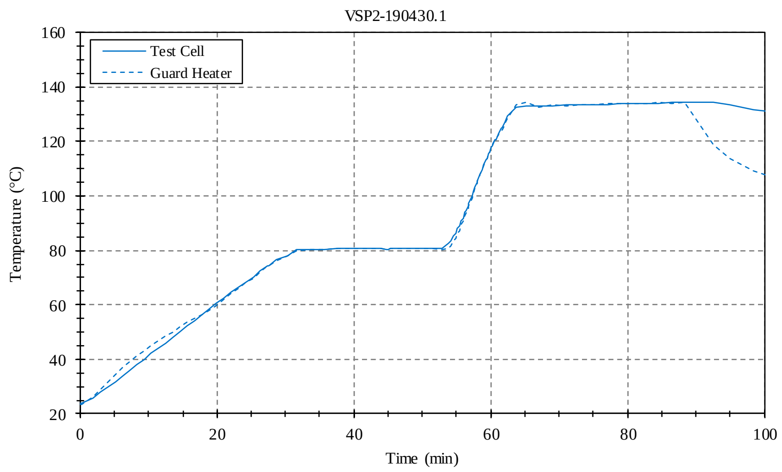
Chemical ID	Density (g/ml)	VSP2 Charge (g)	Concentration (wt. %)
DI Water	1.00	58.0504	72.42
Nitric Acid	1.41	0.4270	0.53
Epichlorohydrin	1.18	21.68	27.05
Total	1.05	80.16	100.0

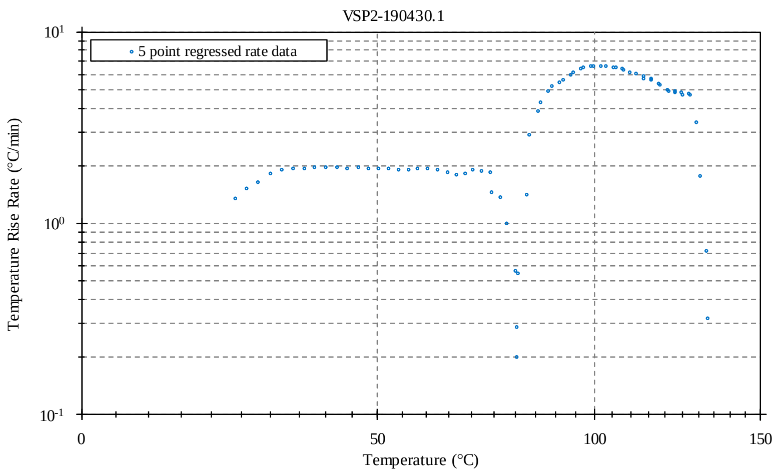
- Water and nitric acid heated to 80°C
- Epichlorohydrin (23°C) metered in over 10 minutes

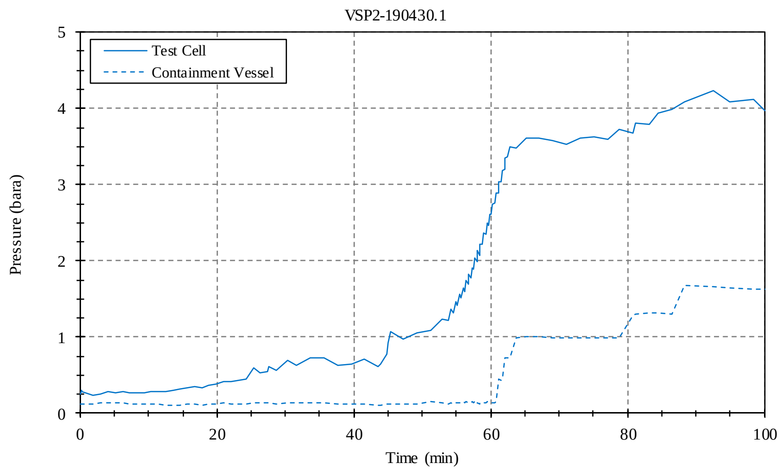
High Pressure Metering Syringe

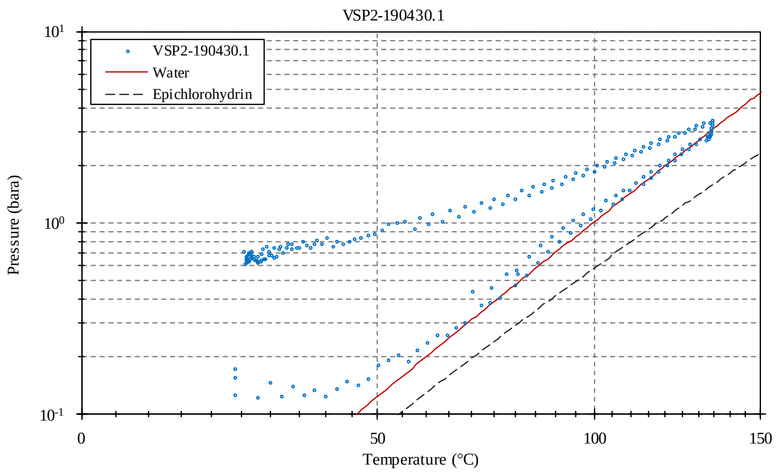


Epi Hydrolysis–Loss of Cooling
(10-min EPI Add)

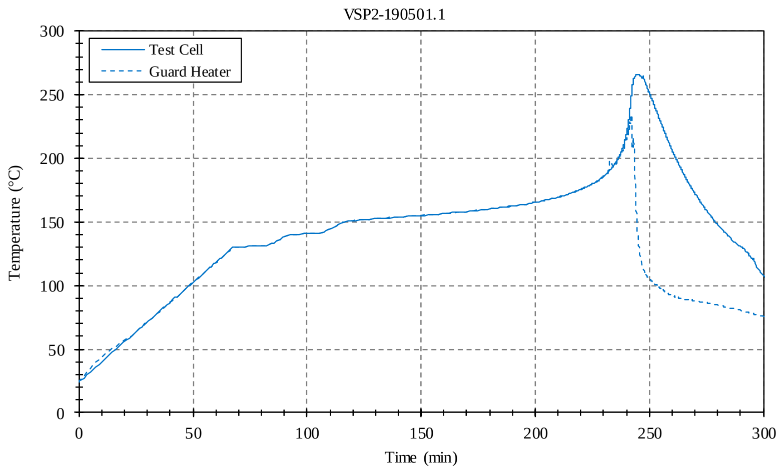


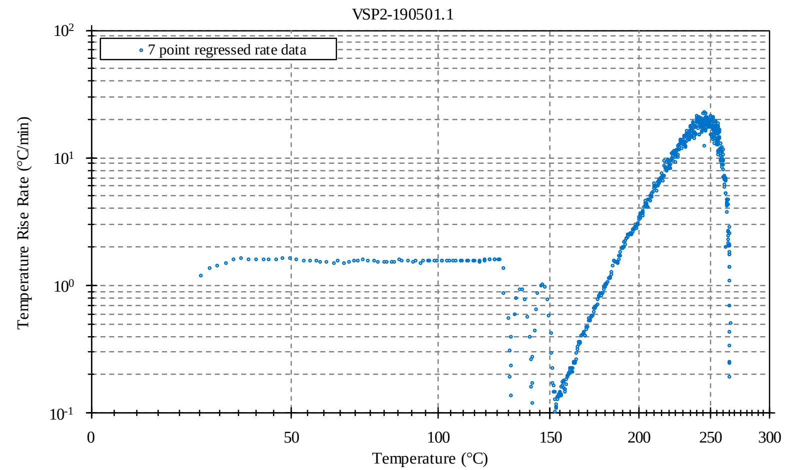


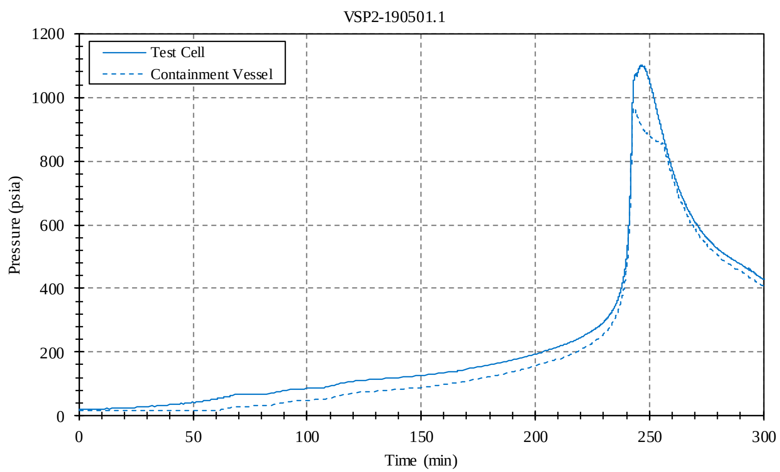


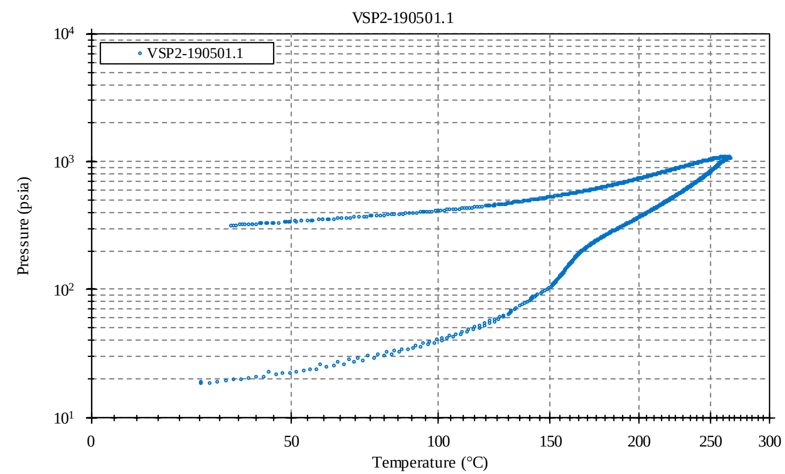


Epi Hydrolysis-HWS After Loss of Cooling

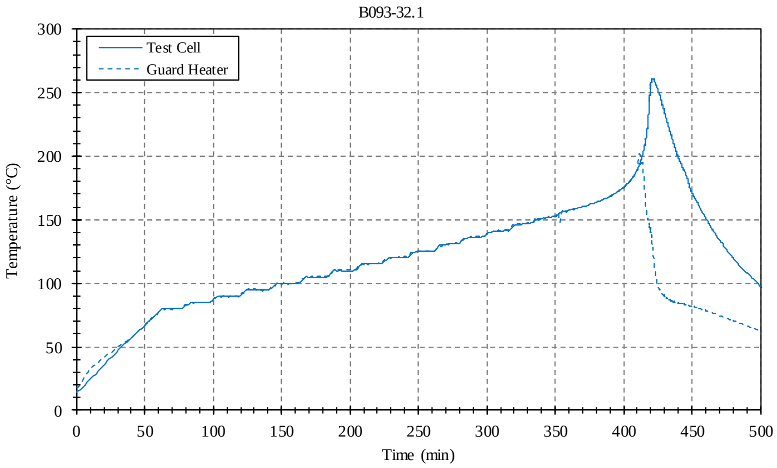


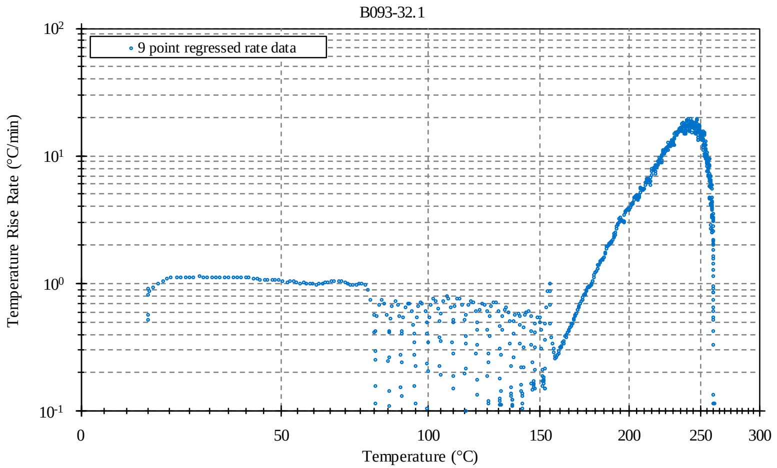


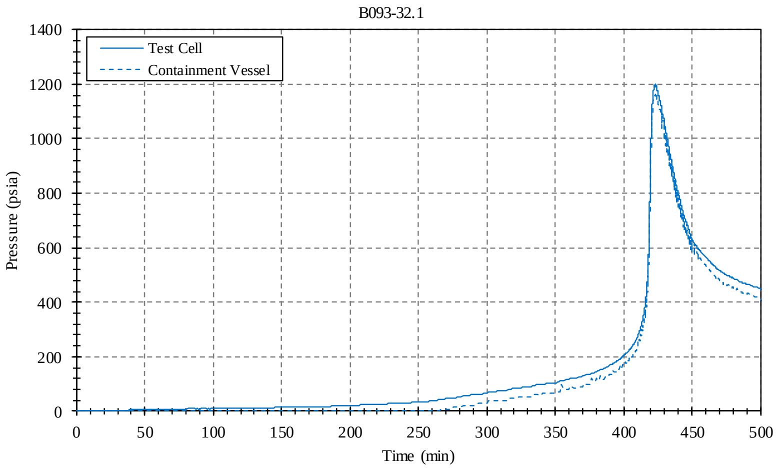


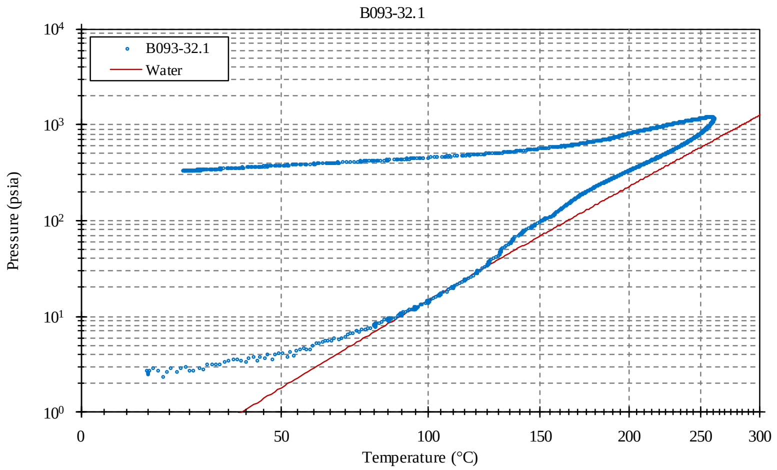


Epi Hydrolysis–HWS After RC at 80°C









From VSP2

- From LOC during short addition, ΔT_{ad} (meas) = 55°C
  - (Φ=1.07) ΔT_{ad} (Φ corr) = 59°C
- Recall projected ΔT_{ad} from RC was 61°C
- Onset from HWS post VSP2 experiment – 150°C
- Onset from HWS post RC – 160°C
- So what is MTT for a closed system?
  - MAWP for GLS typically 6 bar g (87 psig, 101.7 psia)
  - FAI recommendation
    - Set relief pressure as low as possible without affecting the process
    - Or assume 40% overpressure from set pressure based on 1.1 x MAWP on absolute basis. Set pressure = 78.8 psia
    - From VSP2 (RC) P vs T curve – 78.8 psia corresponds to 142.6°C
    - Process suggests to have temperature at set pressure in the 100-120°C range

EPI Hydrolysis Criticality Class MTT = 142.6°C, Set Pressure 78.8 psia

- Straight Batch
  - Tp = 80°C
  - TMR24ad = 115°C
  - MTSR = 141°C
  - MTT (closed) = 142.6°C

MTT > MTSR > TMR24ad >Tp

Class 5

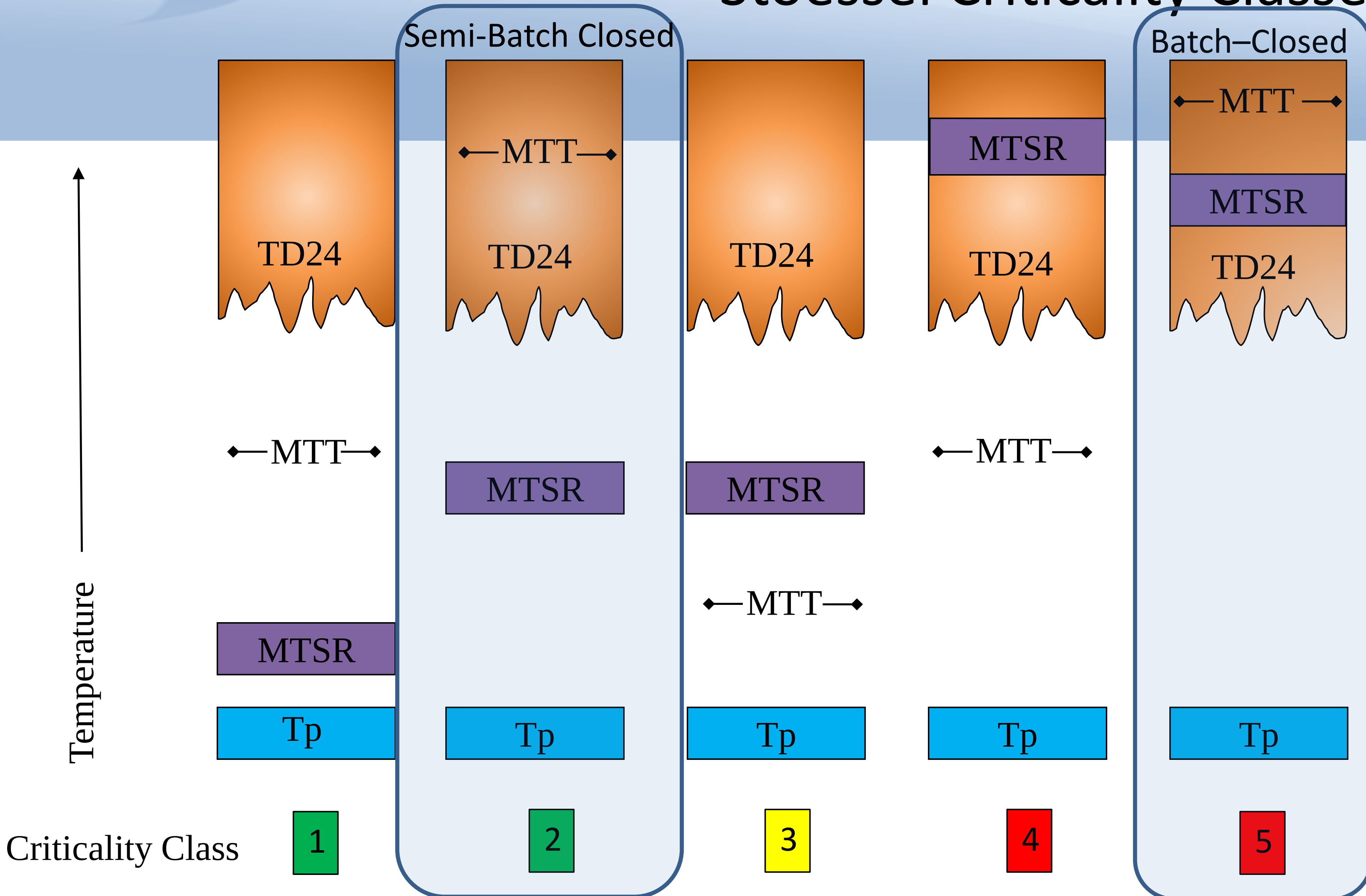
- Semi-Batch (2.1 hr Add)
  - Tp = 80°C
  - MTSR = 86°C
  - TMR24ad = 115°C
  - MTT (closed) = 142.6°C

MTT > TMR24ad > MTSR > Tp

Class 2

Can only be considered Class 2 if, when cooling is lost, the EPI addition is stopped

Stoessel Criticality Classes



EPI Hydrolysis Criticality Class MTT = 110.0°C, Set Pressure 20.1psia

- Straight Batch
  - Tp = 80°C
  - MTT (closed) = 110.0°C
  - TMR24ad = 115°C
  - MTSR = 141°C

MTSR > TMR24ad > MTT > Tp

Class 4

- Semi-Batch (2.1 hr Add)
  - Tp = 80°C
  - MTSR = 86°C
  - MTT (closed) = 110.0°C
  - TMR24ad = 115°C

TMR24ad > MTT > MTSR > Tp

Class 1

Can only be considered Class 1 if, when cooling is lost, the EPI addition is stopped

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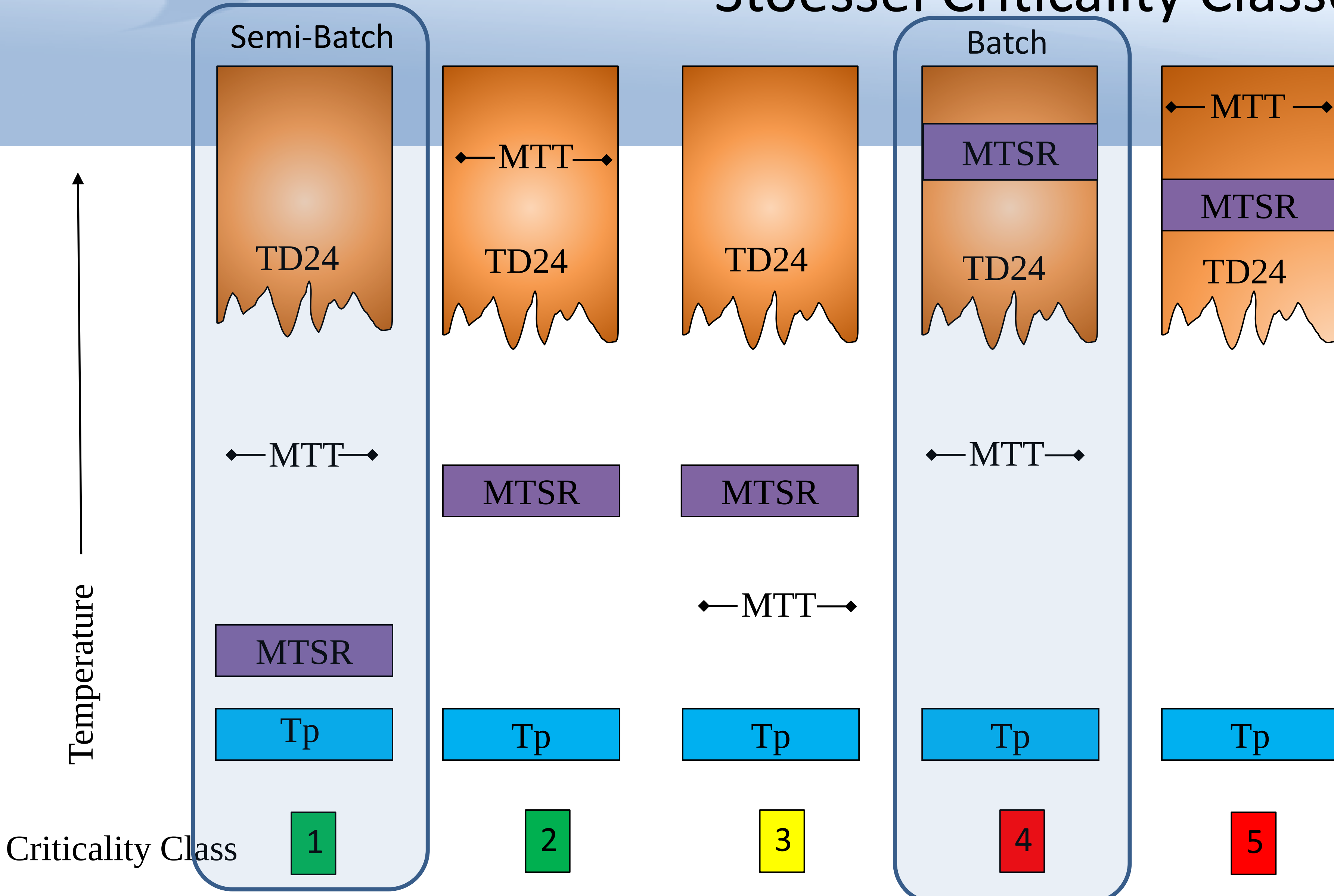
Stoessel Criticality Classes



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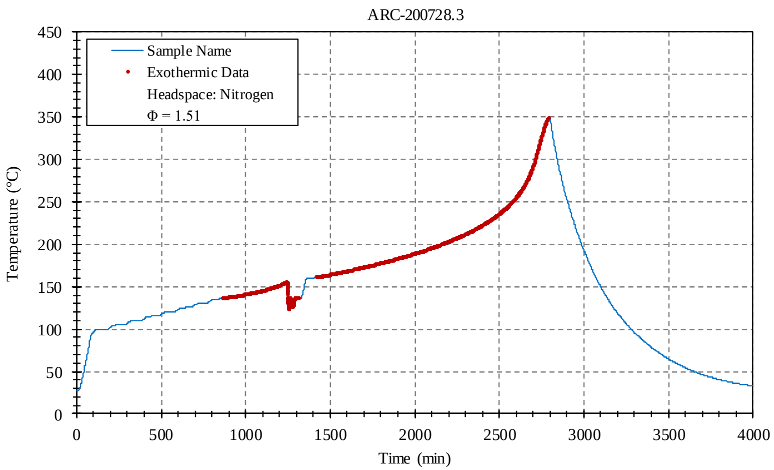
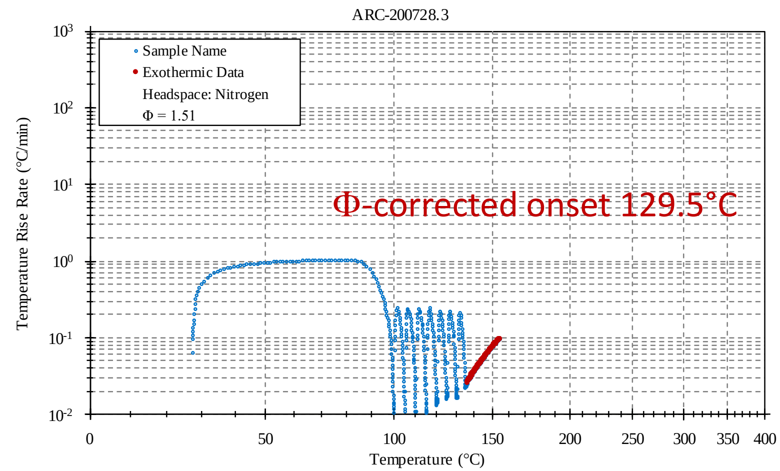
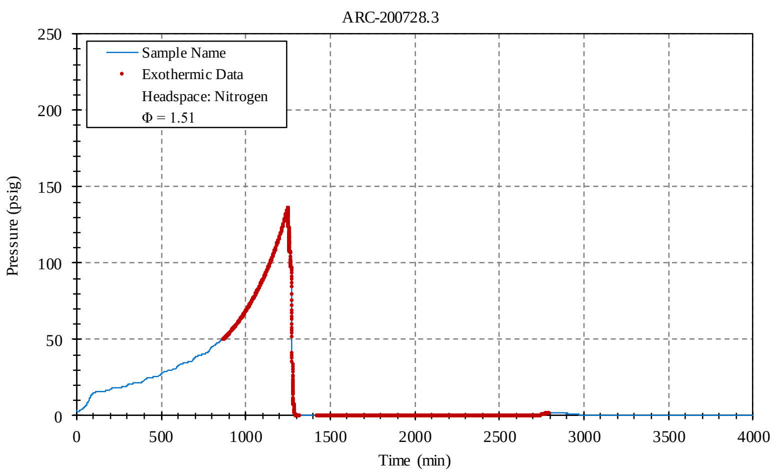
Criticality Class Summary

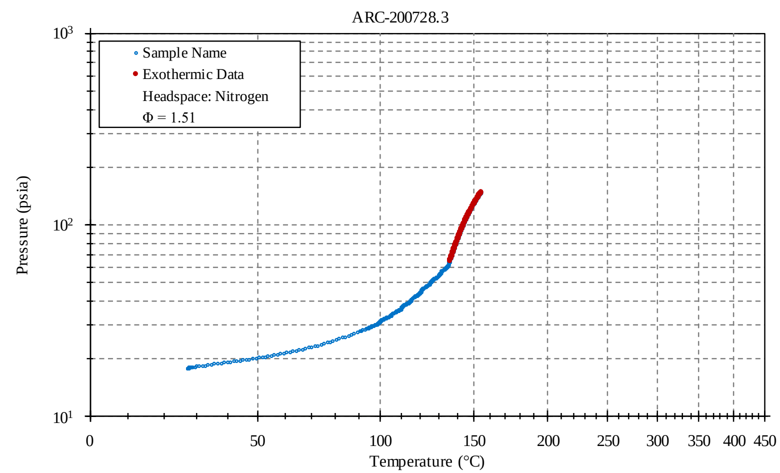
- Batch Open – Class 4
- Semi-Batch Open – Class 1
- Batch Closed – Class 5 or 4 depending on set pressure
- Semi-Batch Closed – Class 2 or 1 depending on set pressure
- For Semi-Batch Closed (MTT = 110°C), there is an addition time that would increase MTSR such that TMR24ad > MTSR > MTT > Tp – Class 3
- So what is the Criticality Class?
  - That depends on how you want to implement this process
    - Layers of protection
    - Set pressure on relief device
    - Flow restrictors

Accelerating Rate Calorimetry (ARC) Post-RC 80°C 0.822 g/min (0.02°C/min Sensitivity)









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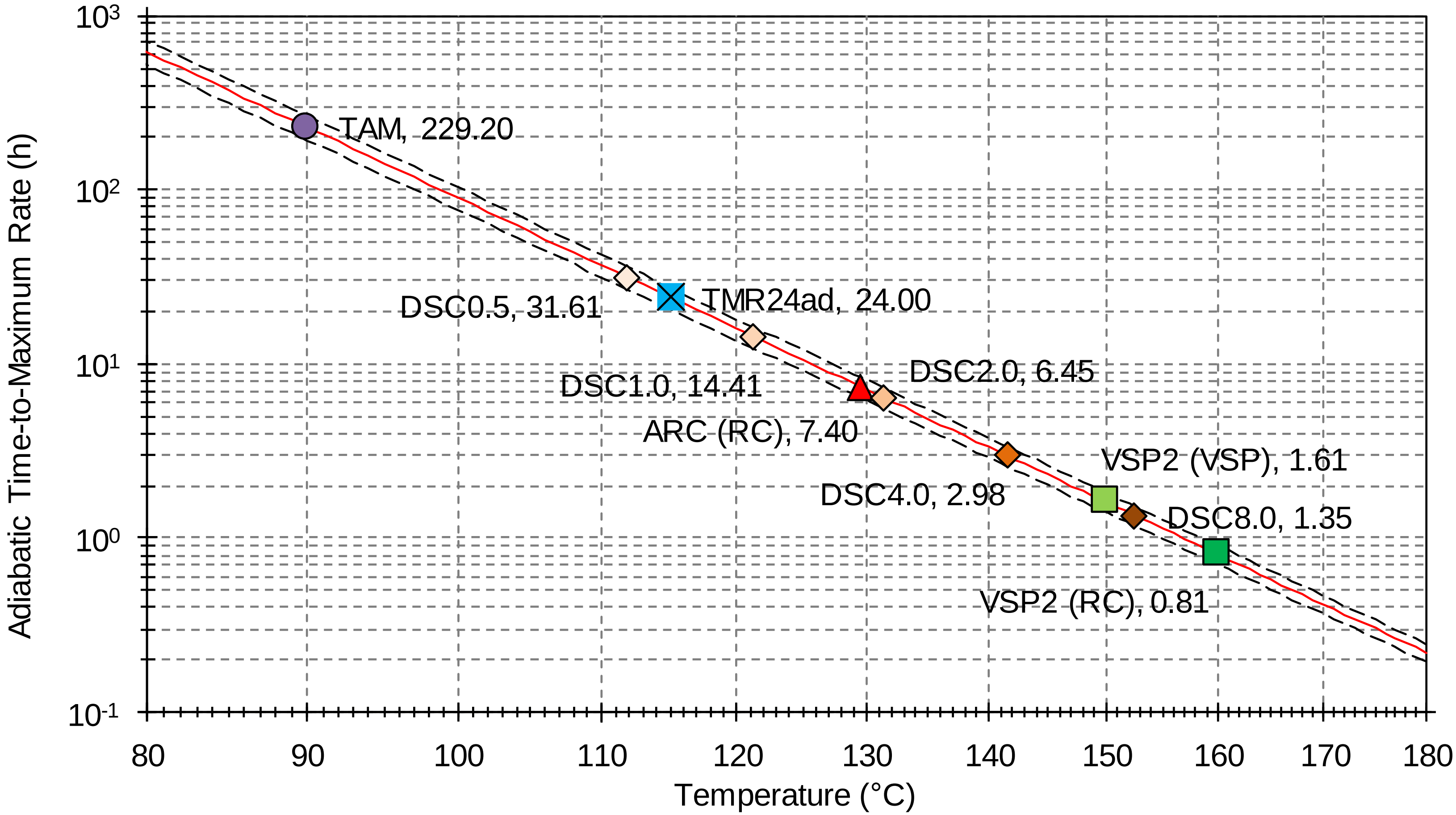
Instrument Sensitivity and TMR



TMR24ad Dilemma

- Validation at TMR24ad temperature (115°C for EPI hydrolysis) not likely by VSP2 and ARC
  - Running a ramp & hold at 115°C and seeing no onset does not mean all is good. It just means the sensitivity of the instrument isn't up to the task
  - If an HWS experiment were run in either instrument with longer wait times, onset would likely decrease, but not that much lower

- If wanting to validate with VSP2 and ARC, do so at higher T
  - ARC (0.02 °C/min), try TMR8ad
  - VSP2 (0.2 °C/min), try TMR2ad

Summary – Data Source for Criticality Class Determination

- Reaction Calorimetry (Desired Chemistry)
  - Heat Flow rate
    - Batch vs Semi-Batch
    - Degree of Accumulation
  - Adiabatic temperature rise projection – MTSR

- DSC and TAM with AKTS modeling provide Time-to-Maximum Rate Curve and TMR24ad

- VSP2 / Vent Sizing provides MTT Closed

- Ultimate Criticality Class depends on mitigation choices

Summary – Other

- While TMR (via AKTS) from DSC is effective, adding TAM
  - Provides a temperature point below TMR24ad
  - Validates the <u>extrapolated</u> kinetic model (same mechanism)
  - Refines the kinetics at early conversion

- TMR24ad is often way below the sensitivity of our typical lab instruments onsets (VSP2, ARC, DSC)
  - Validation of TMR24ad model with VSP2, ARC should be at higher temperature (in range of TMR8ad to TMR2ad)

- For EPI Hydrolysis, MTSR from Φ–corrected VSP2 is 2°C lower than RC Projection due to Cp(T)

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