PSCI

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Chemical Hazard Assessment and the Prevention of Runaway Reactions

Presented by

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Manager, Chemical Process Evaluation Group
DEKRA Insight

Welcome!

Course Instructor

- Swati Umbrajkar, Ph.D., CSP,
  - Process Safety Experience:
    - Manager, Chemical Process Evaluation Group
    - Test Engineer, Chemical Process Evaluation Group
  - Education
    - Ph.D., Mechanical Engineering
      New Jersey Institute of technology, Newark, NJ
  - Partial Membership list
    - AIChE
    - BCSP

Background

- Participants
  - ❖ Division
  - ❖ Position
  - ❖ Process Safety background
  - ❖ What do you hope to learn / accomplish at this course?
  - ❖ Are there any issues that need to be addressed?

COURSE PROGRAM

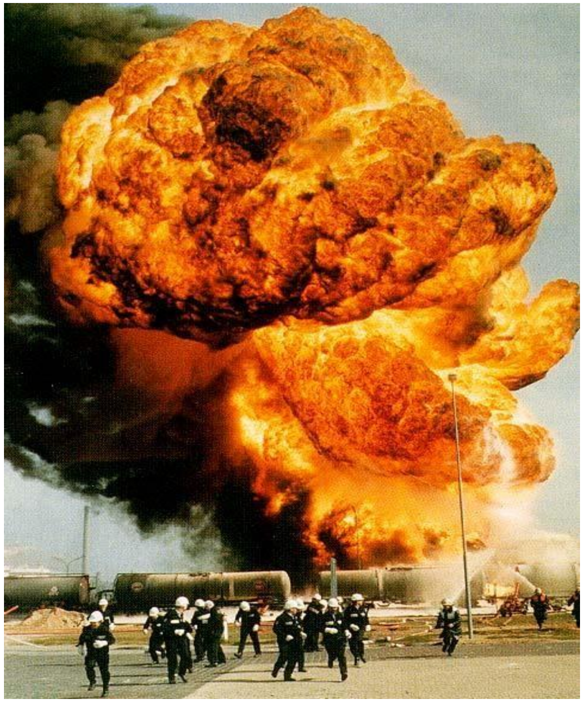
•09:00 am	1 Introductions
•09:15 am	2 Where hazards arise
•10:15 am	*Coffee*
•10:30 am	3 Chemical Reaction Hazards Assessment Strategy
•11:00 am	4 Fundamental Principles of Scale-Up and Thermal Runaway Reactions
•11:30 am	04 Small-Scale Screening Tests
•Noon	*Lunch*
•01:00 am	5 Identification of Highly Energetic Materials
•02:00 pm	6 Reaction Characterization through Calorimetry
•02:30 pm	7 Characterization of Thermal Runaway Reactions using Adiabatic Calorimetry
•03:30 pm	08 Safety Measure Selection
•03:45 pm	*Coffee*
•04:00 pm	09 Case Studies Chemical Reaction Hazards
•04:45 pm	10 Course survey and closing remarks
•05:00 pm	Adjourn

COURSE OBJECTIVES

- What you will learn?
  - To recognize the important characteristics of exothermic reactions and thermal instability
  - To identify potentially hazardous processing situations
  - What tests to do and interpret or apply the data
  - The safety measures that are available for control of exothermic reactions

- **PLEASE ASK QUESTIONS DURING THE SESSION!**

Where Hazards Arise
Reported Incidents and Legislation



Chemical Reactivity Hazards Management Alliance

- U.S. Occupational Safety and Health Administration (OSHA)
- U.S. Environmental Protection Agency (EPA)
- American Chemical Society (ACS)
- American Chemistry Council (ACC)
- Center for Chemical Process Safety (CCPS)
- Chlorine Institute, Inc. (CI)
- Mary Kay O'Connor Process Safety Center
- National Association of Chemical Distributors (NACD)
- Synthetic Organic Chemical Manufacturers Association (SOCMA)

- **http://www.osha.gov/dcsp/alliances/reactives/reactives.html**

New Jersey

- NJ Toxic Catastrophe Prevention Act (NJTCPA)
  - Added coverage of reactive chemicals in 2003

  - Two categories for coverage of reactive chemicals
    - Reactive Hazard Substances (RHS), a list of chemicals
    - Reactive Hazard Substance Mixture (RHSM), a list of functional groups

  - For covered materials, requires hazard assessment and evaluation of inherently safer technologies

Free resources

Office of Response and Restoration

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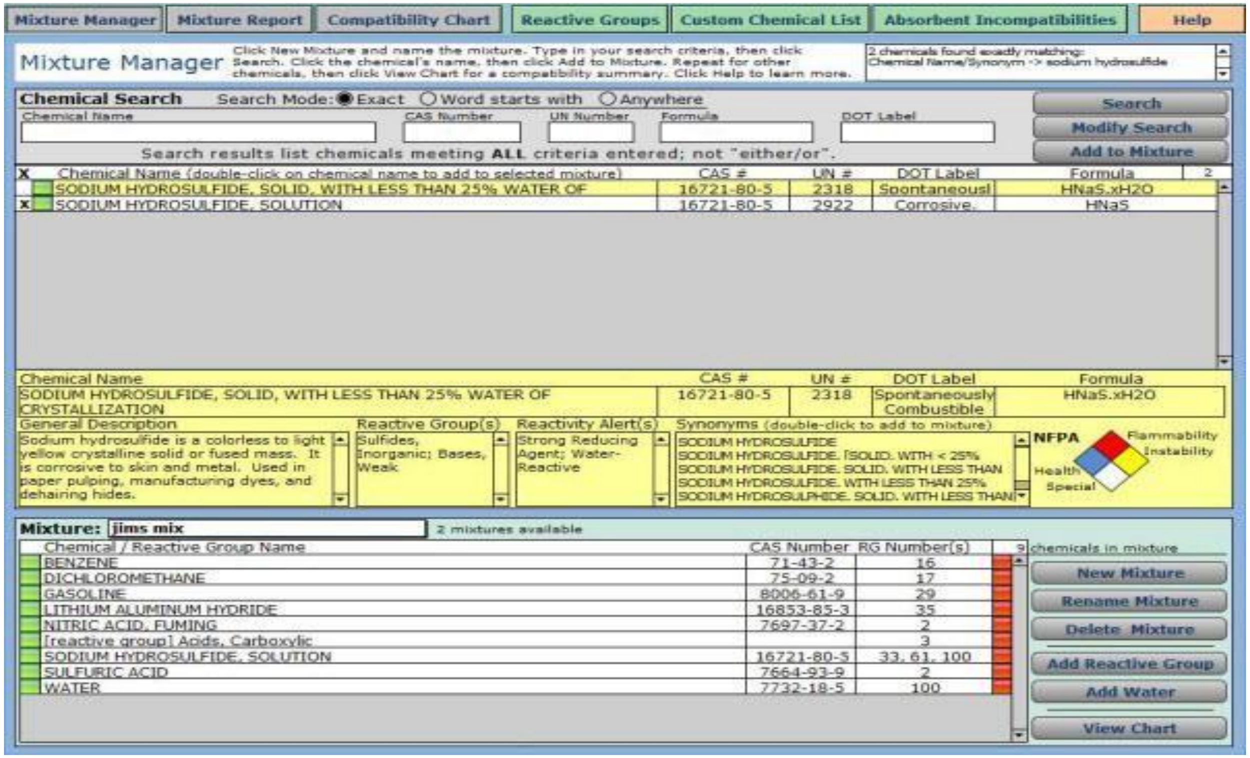
- National Oceanic and Atmospheric Administration (NOAA)
- The Chemical Reactivity Worksheet is a free program you can use to find out about the reactivity of substances or mixtures of substances (reactivity is the tendency of substances to undergo chemical change).
- It includes a database of reactivity information for more than 6,000 common hazardous chemicals; a way for you to virtually "mix" chemicals-to find out what dangers could arise from accidental mixing.
- The database includes information about the intrinsic hazards of each chemical and about whether a chemical reacts with air, water, or other materials. It also includes case histories on specific chemical incidents, with references.
- http://response.restoration.noaa.gov/index.php



Mixture Manager

Click New Mixture and name the mixture. Type in your search criteria, then click Search. Click the chemical's name, then click Add to Mixture. Repeat for other chemicals, then click View Chart for a compatibility summary. Click Help to learn more.

2 chemicals found exactly matching:
Chemical Name/Synonym -> sodium hydrosulfide

Chemical Search Search Mode: ● Exact ○ Word starts with ○ Anywhere

Chemical Name
CAS Number
UN Number
Formula
DOT Label

Search results list chemicals meeting **ALL** criteria entered; not "either/or".

X	Chemical Name (double-click on chemical name to add to selected mixture)	CAS #	UN #	DOT Label	Formula	2
	🟩 SODIUM HYDROSULFIDE, SOLID, WITH LESS THAN 25% WATER OF	16721-80-5	2318	Spontaneousl	HNaS.xH2O	
X	🟩 SODIUM HYDROSULFIDE, SOLUTION	16721-80-5	2922	Corrosive.	HNaS	

Chemical Name	CAS #	UN #	DOT Label	Formula
SODIUM HYDROSULFIDE, SOLID, WITH LESS THAN 25% WATER OF CRYSTALLIZATION	16721-80-5	2318	Spontaneously Combustible	HNaS.xH2O

General Description
Sodium hydrosulfide is a colorless to light yellow crystalline solid or fused mass. It is corrosive to skin and metal. Used in paper pulping, manufacturing dyes, and dehairing hides.

Reactive Group(s)
Sulfides, Inorganic; Bases, Weak

Reactivity Alert(s)
Strong Reducing Agent; Water-Reactive

Synonyms (double-click to add to mixture)
SODIUM HYDROSULFIDE
SODIUM HYDROSULFIDE. [SOLID. WITH < 25%
SODIUM HYDROSULFIDE. SOLID. WITH LESS THAN
SODIUM HYDROSULFIDE. WITH LESS THAN 25%
SODIUM HYDROSULPHIDE. SOLID. WITH LESS THAN

Mixture: **jims mix** 2 mixtures available

Chemical / Reactive Group Name	CAS Number	RG Number(s)	9 chemicals in mixture
🟩 BENZENE	71-43-2	16	🟥
🟩 DICHLOROMETHANE	75-09-2	17	🟥
🟩 GASOLINE	8006-61-9	29	🟥
🟩 LITHIUM ALUMINUM HYDRIDE	16853-85-3	35	🟥
🟩 NITRIC ACID, FUMING	7697-37-2	2	🟥
🟩 [reactive group] Acids, Carboxylic		3	🟥
🟩 SODIUM HYDROSULFIDE, SOLUTION	16721-80-5	33, 61, 100	🟥
🟩 SULFURIC ACID	7664-93-9	2	🟥
🟩 WATER	7732-18-5	100	🟥

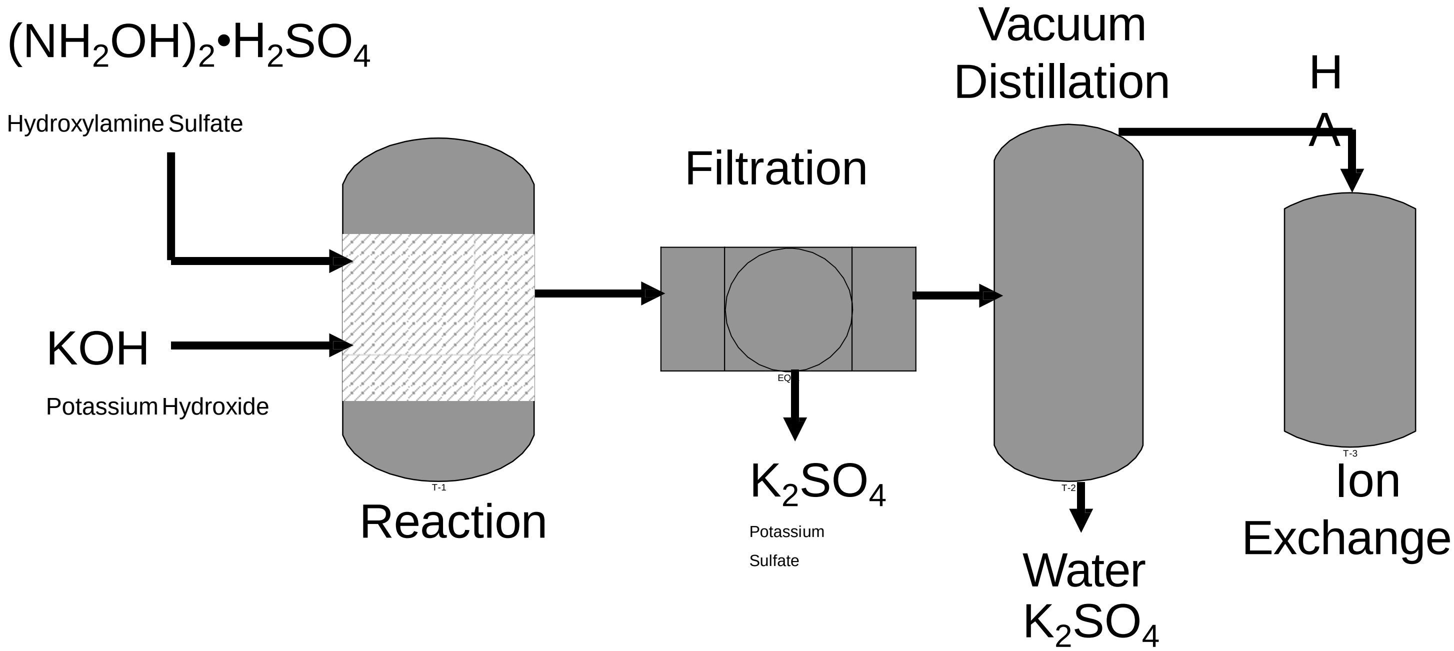
Reactive Chemical Incidents in the US (Partial)

Concept Sciences, Inc. (Allentown, PA)

- Hydroxylamine (NH_2OH) - Oxygenated derivative of ammonia
- Used in cleaners for semiconductor industry, manufacture of nylon, inks, paints, pharmaceuticals, agrochemicals, and photographic developers

Concept Sciences, Inc. Explosion

- Product: 50 wt% Hydroxylamine (HA) distilled with KOH
- Process



$(NH_2OH)_2 \bullet H_2SO_4$

Hydroxylamine Sulfate

KOH

Potassium Hydroxide

Reaction

Filtration

K_2SO_4

Potassium
Sulfate

Vacuum
Distillation

Water
K_2SO_4

HA

Ion
Exchange

Consequences

- 5 deaths (1 off-site), 14 injured
- 10 damaged buildings,
  - One was a day care center!
  - Several residences damaged
- $4 MM in damage
- Two mile flying debris
- Cloud of chemical residue
- Liquid KOH spilled into parking lot

What Was Left

Concept Science Inc (CSI) Explosion

- **Possible Causes**
  - Solid crystal HA very explosive
  - Heating with contaminants
  - Heat from friction in pump
- **Effects**
  - OSHA issued CSI several willful and serious citations
  - Federal grand jury indicted the president of CSI for alleged criminal violations of the PSM standard (later dismissed)
  - CSI went out of business

CSI Contributing Factors

- *Deficiencies in process knowledge* and documentation
- Insufficient process safety reviews for capital projects
- No standard engineering drawings
- Operating procedures not fully developed

Runaway Reaction – Morton International Inc., Patterson, NJ

- Dye manufacturing process
- Causes:
  - Lack of Process Safety Information
    - Exotherm onset temperatures not known
- Process hazard analysis inadequate
- Process changes
  - Batch size increase
- Previous temperature excursions not investigated

Results

Morton International, Inc.
Paterson, NJ
April 8, 1998

9 Injuries

“sounded like a train rumbling through”

Blender Explosion – Napp Technologies (Lodi, NJ)

- Blending Aluminum, Sodium Hydrosulfite
    - Water reactive

- Water entered blender

- Causes:
    - Inadequate Process Hazard Analysis
    - Inadequate Operating Procedures
    - Inappropriate equipment
    - Inadequate fire brigade training

Result

5 Fatalities,

4 Injuries

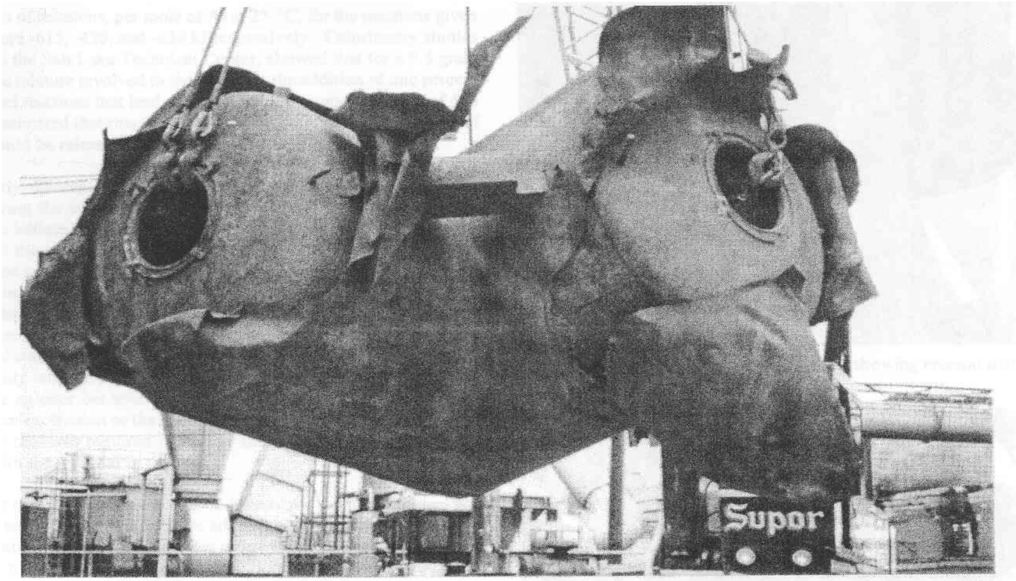


Figure 3: The damage to the blender in the accident was extensive. This photograph shows the 2 top loading ports on the blender, the shredded water jacket, and the hold-down tabs for the access covers.

Distillation Column Explosion - Mississippi

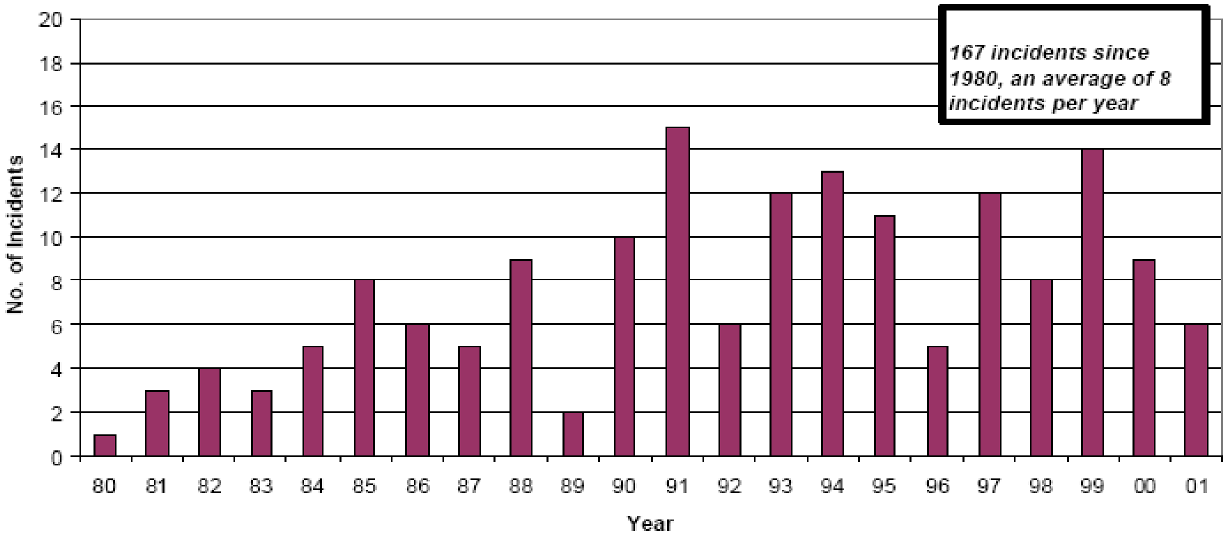
- Process shutdown, column isolated
- 1200 gallons of mononitrotoluene (MNT) in column
- Steam leaked through manual valve
- MNT decomposed

“One large fragment of the distillation column punctured a nearby para-MNT storage tank and ignited its contents, which burned for almost 3 hours. A *6-ton column segment was hurled 1,100 feet* and landed near a crude oil storage tank at a refinery across the highway.”

US Chemical Safety and Hazard Investigation Board Report - 2002

- 167 incidents in US between 1980 and 2001
- 48 resulted in one or more fatalities
- 108 total fatalities
- 50 incidents had public impact
- Over 50% of the incidents involved chemicals not covered by the OSHA PSM standard or the EPA RMP regulations
- Approximately 60% involved chemicals that were not rated for stability by the “NFPA diamond”, or which were listed as “no special hazard” – a “0” rating in the NFPA system

US Chemical Safety and Hazard Investigation Board Report - 2002

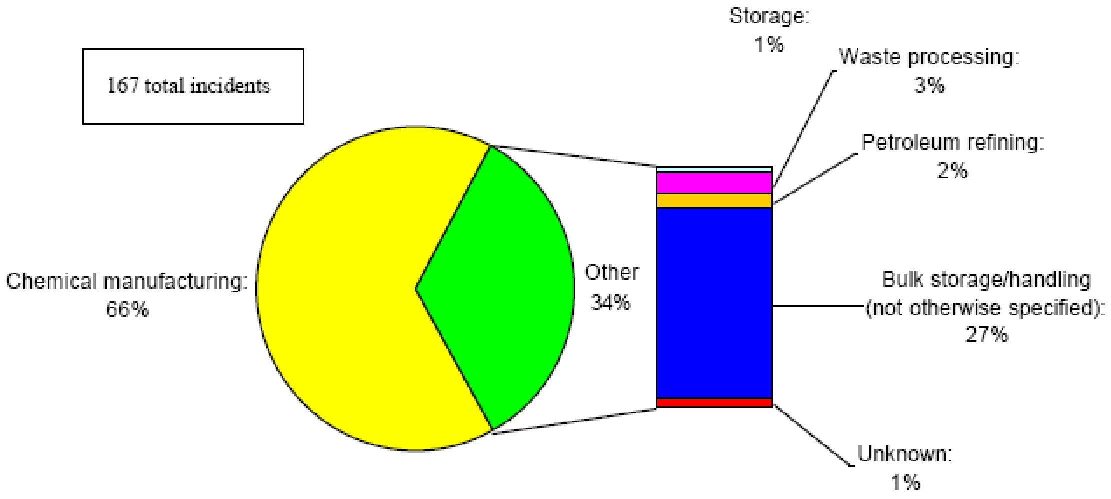


167 incidents since 1980, an average of 8 incidents per year

Figure 3. Total incidents by year, 1980–2001.

US Chemical Safety and Hazard Investigation Board Report – 2002

Process Operation



US Chemical Safety and Hazard Investigation Board Report – 2002

Incident Consequences

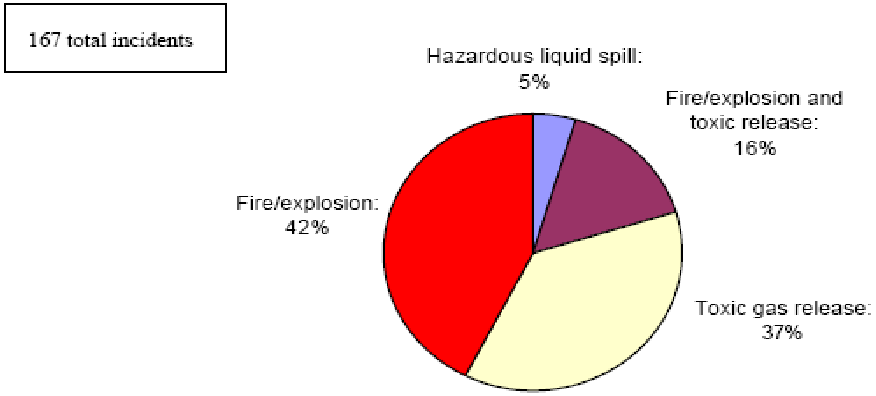
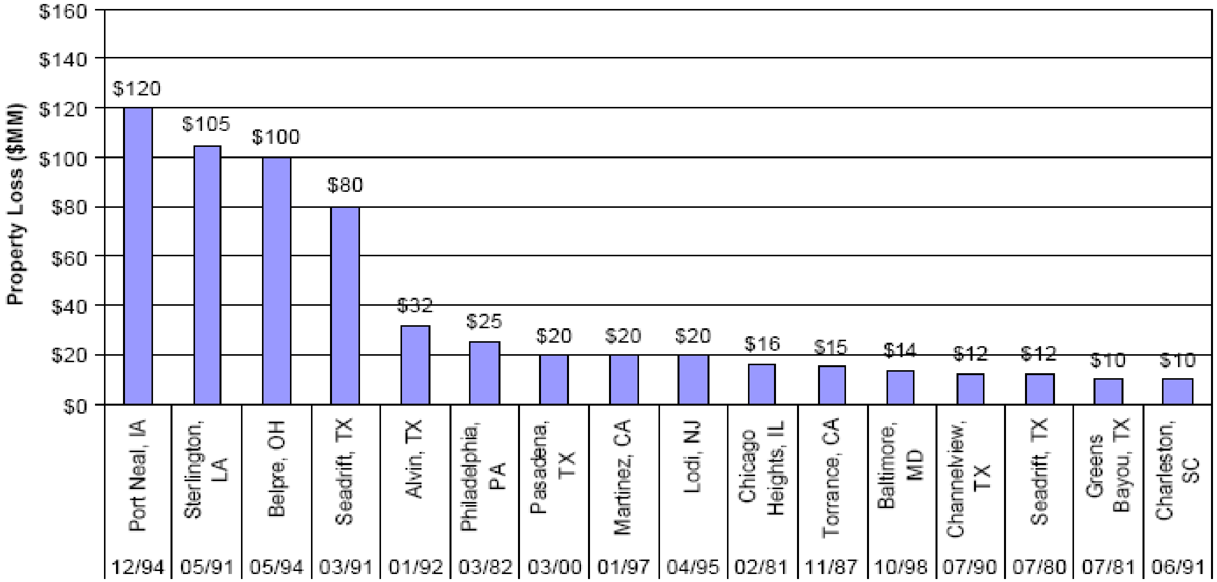


Figure 6. Categorization of consequences of incidents.

US Chemical Safety and Hazard Investigation Board Report – 2002 Property Damage



The Unpublished Laws of Loss Prevention

- First Law :
  - “He who ignores the past is condemned to repeat it”
- Second Law :
  - “Success in preventing loss is in anticipation of the future”
- An unacceptable basis of safety :
  - “We’ve been running this process for 20 years and never had an incident - there’s no need to do a hazard study!”

Famous Last Words

" I didn't see an exotherm in the lab "

" I only saw a little bit of foaming "

" It goes a bit brown if you leave it in the oven too long "

Incidents : 1962 - 1987

- Survey conducted by Barton and Nolan from HSE records
- 189 Incidents reported to HSE from 1962 – 1987
- New Reporting Regulations introduced in 1985 : “Reporting of Injuries, Diseases and Dangerous Occurrences Regulations” (RIDDOR)

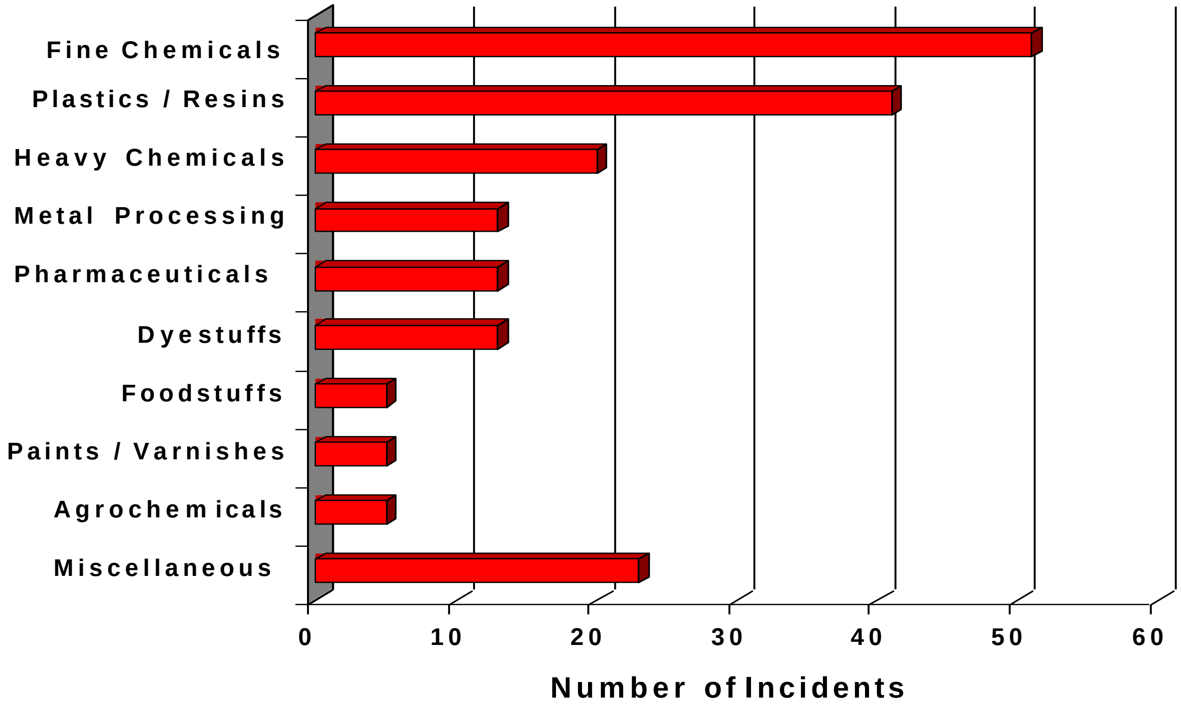
3 incidents in 1985

16 incidents in 1986

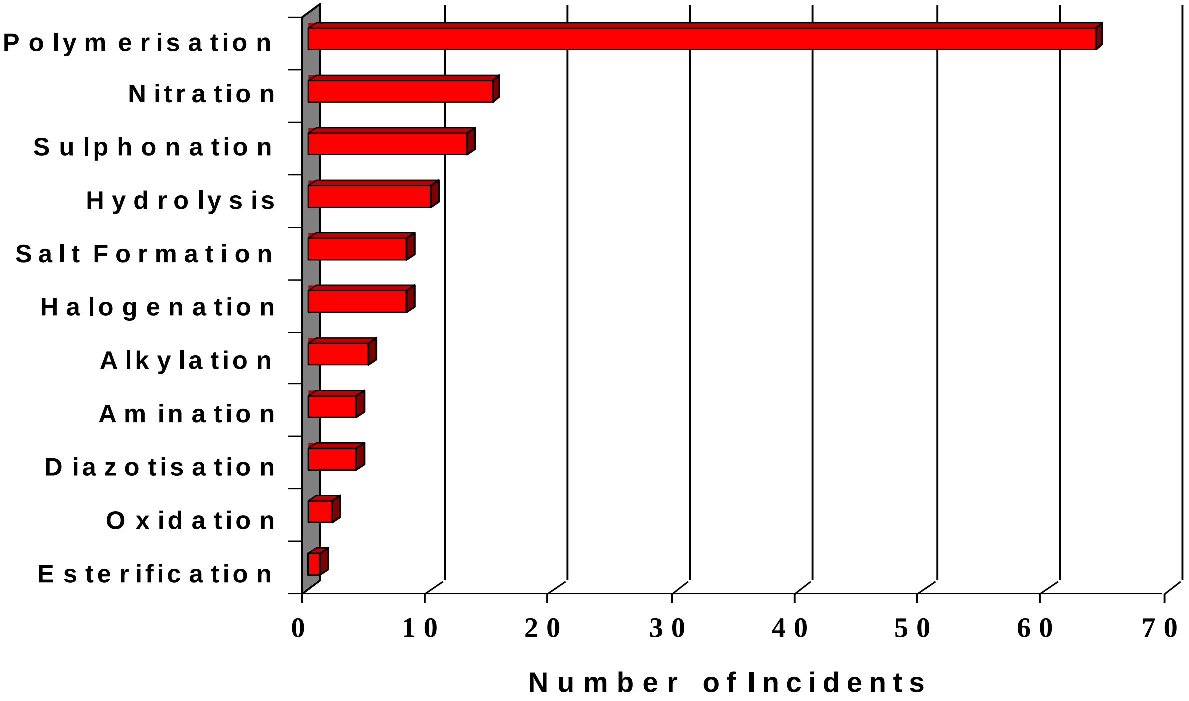
28 incidents in 1987

Barton, J.A. and Nolan, P.F., “Incidents in the Chemical Industry due to Thermal Runaway Chemical Reactions”, IChemE (Rugby, UK) Symposium Series 115 (Hazards X : Process Safety in Fine and Specialty Chemical Plants), Manchester, April 1989

Manufacturing Industry Involved



Chemistry Involved



Incidents (1962 - 1987)
PRIME CAUSES

- **PROCESS CHEMISTRY (34)**
  - No appreciation of heat of reaction
  - Product decomposition
  - Unstable by-products
  - Batch instead of semi-batch
  - Concentrations too high
  - Catalysis by vessel materials
- **MISCHARGING (35)**
  - Material added - too much, too fast, in wrong order
- **AGITATION (17)**
  - Inadequate specification
  - Mechanical failure / operator intervention

Recent Incidents (1962 - 1987)
PRIME CAUSES

- **TEMPERATURE CONTROL (32)**
  - Failure of cooling system
  - Steam related incidents
  - Probe wrongly positioned
  - Error in reading
  - Fouling of probes

- **RAW MATERIAL QUALITY (15)**
  - Water contamination
  - Impurities
  - Changed specification

Recent Incidents (1962 - 1987)
PRIME CAUSES

- **MAINTENANCE (25)**
  - Equipment leaks
  - Blockages
  - Reflux line closed
  - Utility failure
  - Water / residue contamination
  - Unauthorised modifications

- **HUMAN ERRORS (11)**
  - Written instructions not followed
  - Batch run off too early
  - Poor shift change communication

Recent Incidents (Etchells, HSE, 1986 - 1990)

- Further data has been collected since 1986 by the HSE, this data clearly shows how the change in reporting regulations brought more incidents to the surface :

BATCH REACTORS

–Mischarging of reactants	32
–Lack of thermochemical knowledge	18
–Inadequate temperature control	17
–Inadequate maintenance	9
–Inadequate agitation	16
–Raw material quality	12
–Operator error	5
–Other...	13

Recent Incidents (Etchells, HSE, 1986 - 1990)

- Additionally, other thermal related incidents were reported to the HSE in this period :

Laboratory incidents	50
Thermal decompositions in stills	8
Other thermal decompositions	24
Inadvertent mixing of incompatible materials in drums, tanks etc	39
Miscellaneous reaction hazards	26

- In this period there were a total of 269 incidents reported in the UK caused by thermal related hazards.

Recent Incidents: GENERAL LESSONS

Analysis indicates that incidents occur due to:

- Lack of proper understanding of the thermochemistry (heat of reaction) and chemistry (balanced chemical equation)
- Inadequate engineering design for heat transfer for the scale-up
- Inadequate control systems and safety back-up systems
  - – including emergency relief systems, process vent, etc.
- Inadequate batch procedures and insufficient operator training

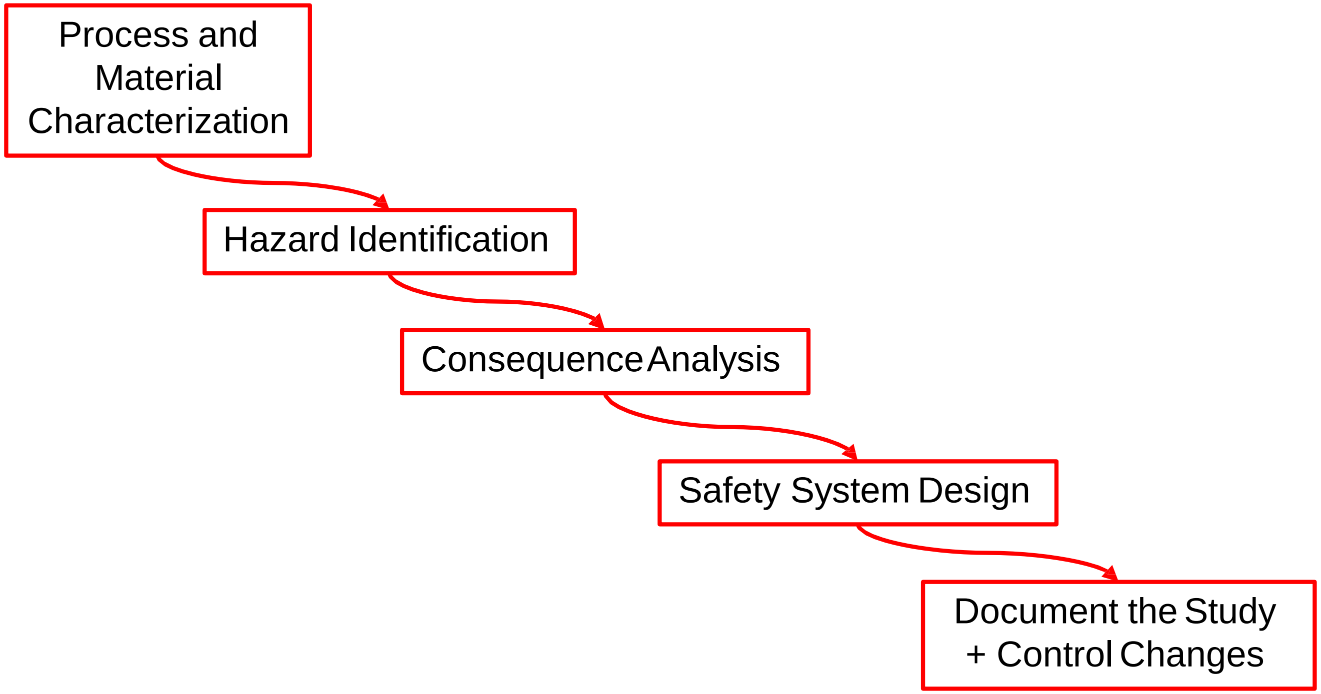
Risk, Safeguards, & Risk Reduction

- **Risk** - The possibility of a process safety incident/time
- The combination of undesired consequences with the likelihood (frequency) that the consequences (adverse event, cost, etc.) will occur.
- Risk = Likelihood x Consequence

- **Safeguards** can be preventative and mitigating
- **Prevention** reduces the **likelihood** of an incident occurring (control over mischarges to a reactor)
- **Mitigation** reduces the **consequence** of an incident (emergency relief devices)

- **Risk Reduction** = Likelihood ↓ x Consequence ↓

ASSESSMENT STRATEGY



Process and Material Characterization

Hazard Identification

Consequence Analysis

Safety System Design

Document the Study + Control Changes

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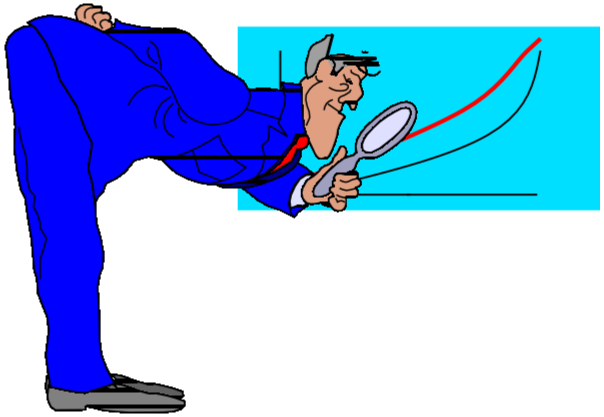
Chemical Reaction Hazards (CRH)

Assessment Strategy



Pharmaceutical & Fine Chemical Manufacture

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- **Typified by:**
  - Batch / semi-batch operations
  - Multi-product plant
  - Complex, developing chemistry
  - High frequency of change
  - Rapid response
- **Essential stages in safety evaluation**
  - Define the process
  - Quantification of the desired and adverse reactions of the process
  - Selection and implementation of safety measures
  - Monitoring safety performance and change control

Assessing Laboratory Hazards

- What process safety data is required at each stage of process development from:
    - chemical route identification
    - process development and optimization
    - scale-up (to pilot scale)
    - scale-up (to manufacturing scale)

- Basic principle should be to aim for **inherent safety**
    - Robust process: The process can be subject to reasonable changes. Small changes should not have a catastrophic consequence

Chemical Route Identification

- Consideration should be given to :
    - reaction conditions (as mild as possible)
    - materials (reactivity, flammability, toxicity, other hazards)
    - plant / equipment available

- Desk screening should be conducted to identify:
    - flammability, reactivity and thermal stability of identified reagents (from literature sources)
    - energetics of reactions (from computational calculations plus literature information on analogous processes)

Preliminary Laboratory Studies

- Confirm absence of potentially explosive groupings before any scale of operation.
  - If energetic groups are present, consider small scale explosivity tests (and take extra care in initial preparative work)

- Confirm flammability hazards are protected against.

- Use appropriate PPE (assess potential toxicity hazards).

- Predict thermal behavior (heat of reaction, adiabatic temperature rise, gas evolution, etc).
  - Select processing method accordingly (batch, semi-batch, reflux, etc)
  - Select solvent level and characteristics according to predicted behavior
  - Use mildest conditions possible

Process Development / Optimization

- At this stage, physical testing should begin:
  - preliminary thermal stability trials (DSC, Carius tube)
  - (possibly) reaction calorimetry

- Select reaction conditions that:
  - are well away from thermal limits of materials
  - prevent / minimize accumulation (aim for semi-batch operation for exothermic processes)
  - minimize potential for over pressurization

Pilot Scale Processing → Batch Directions Issues

- **Prior to pilot scale processing:**
  - confirm (accurately) thermal limits of process
  - confirm reaction kinetics (and set trips / cut-outs accordingly)
  - consider potential process deviations (using checklists or possibly HAZOP)
  - confirm adequate safety measures are present to mitigate risk from potential deviations
  - provide operator training on expected / unexpected events and actions to be taken in various scenarios

Testing Regime

- Initial testing should provide a solid overview of hazards. Detailed testing may be wasted by later process changes / optimization

- Regulatory testing can commence but is not normally necessary prior to pilot scale studies. Testing should therefore concentrate on providing data required for safe processing

- Dust and vapor flammability issues generally only become significant at pilot scale and beyond. However,
  - decisions made on materials and routes may have significant consequences at larger scales

Basic Process Information Requirements

- Reaction characterization and thermal stability analysis should be complete by the time pilot scale operations are commenced.
- For final scale-up, the following data is required:
    - identification of potential process deviations
    - consequence analysis for potential process deviations
    - specification of a detailed BASIS OF SAFETY

Scale-up Procedures
Identification of Potential Process Deviations

- Potential process deviations can only be identified with a detailed knowledge of the chemistry and plant

- Methods available for hazard include:
  - Hazard and Operability Studies (HAZOP)
  - Computer HAZOP (CHAZOP)
  - “What-if” analysis
  - Failure modes and effect analysis (FMEA)
  - Checklist analysis
  - Fault tree analysis

Identification of Potential Process Deviations Miscellaneous Failure Conditions in Batch Processes

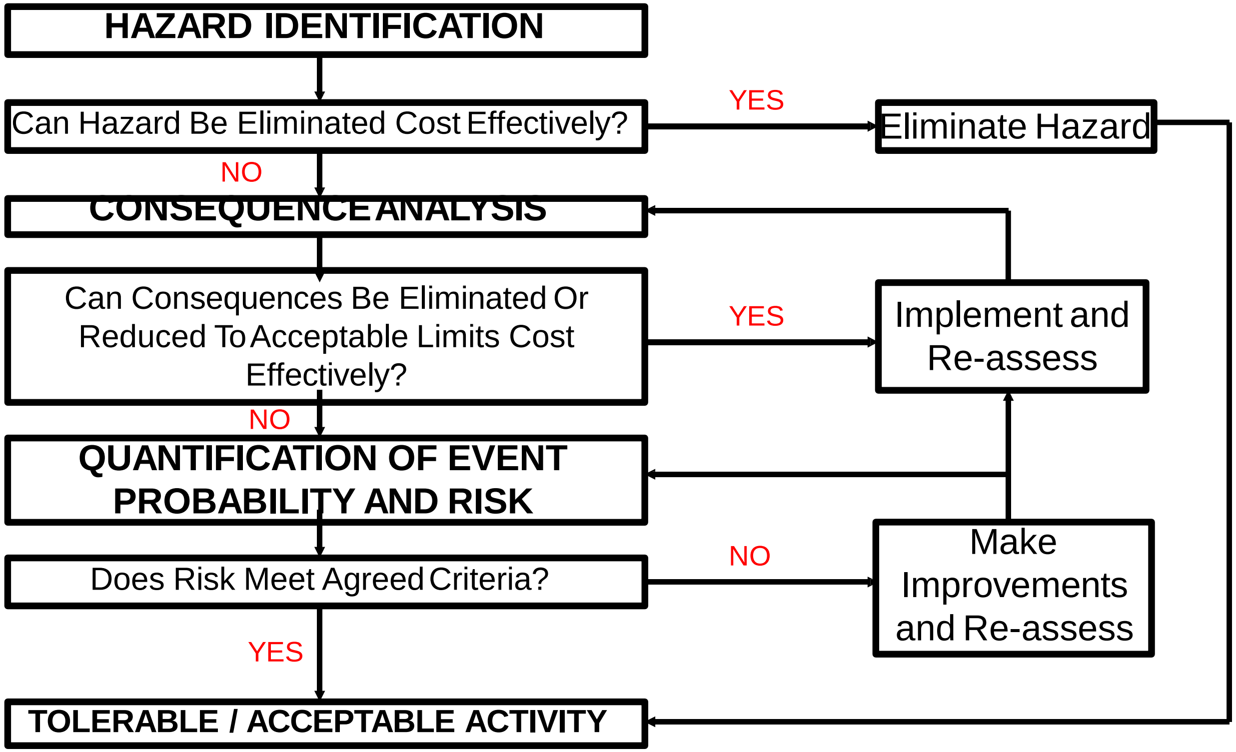
- Incorrect Reactants
- Impurities
- Reaction of Reactants with Equipment
  - Materials of Construction
- Corrosion by Reactants
- Too Much / Little Reactant
- Too Much / Little Solvent
- Unexpected By product
- Reactant Added Too Fast / Slow
- Reactant Added At Wrong Temperature
- Reactant Added To Wrong Temperature
- Too Much / Little Catalyst
- Wrong Order of Reactant / Catalyst Addition

Identification of Potential Process Deviations Miscellaneous Failure Conditions in Batch Processes

- Agitator Mechanical Failure
- Agitator Power Failure
- Agitator Inadequate Performance
- Coolant Failure - No Cooling
- Coolant Failure - Application of Heating
- Heating Failure - Overheating
- Temperature Too Low / High
- Pressure Too Low / High
- Blockage in Reflux Lines
- Condenser Cooling Failure
- Vacuum Failure
- Vacuum Broken With Air
- Excessive Storage Temperature
- Excessive Hold Time

Utilities Failures

- Consider the scenario(s) resulting from failure of :
  - Electrical Power
  - Cooling Water
  - Instrument Air
  - Chiller / Refrigeration Supply
  - Nitrogen
  - Steam
  - Hot Oil System
  - Process Water
  - Vacuum
  - Scrubber (ie. Emissions Treatment)
  - Fire fighting



HAZARD IDENTIFICATION

Can Hazard Be Eliminated Cost Effectively?

YES

Eliminate Hazard

NO

CONSEQUENCE ANALYSIS

Can Consequences Be Eliminated Or Reduced To Acceptable Limits Cost Effectively?

YES

Implement and Re-assess

NO

QUANTIFICATION OF EVENT PROBABILITY AND RISK

Does Risk Meet Agreed Criteria?

NO

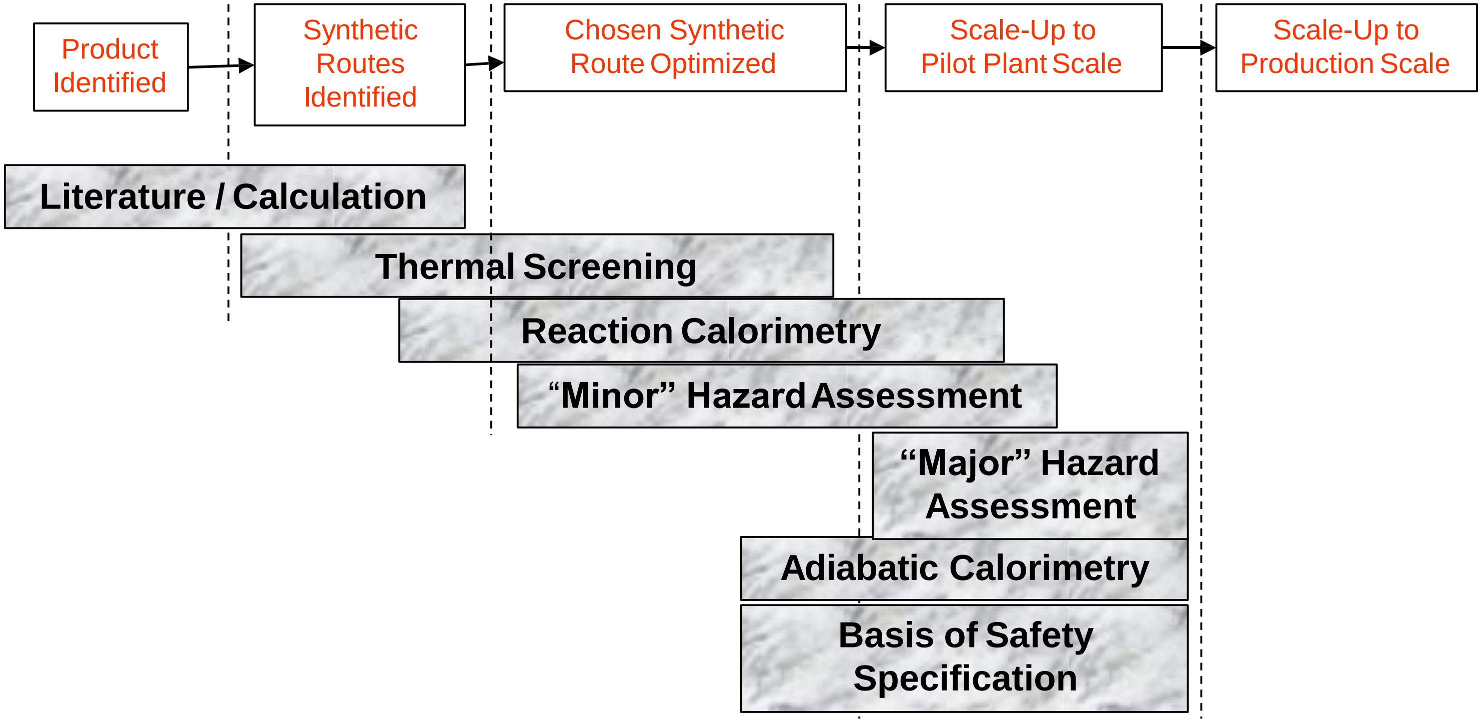
Make Improvements and Re-assess

YES

TOLERABLE / ACCEPTABLE ACTIVITY

Ref: Risk Assessment in the Process Industries, Pitblado R., Turney R.

CRH vs Process Lifecycle



Product Identified → Synthetic Routes Identified → Chosen Synthetic Route Optimized → Scale-Up to Pilot Plant Scale → Scale-Up to Production Scale

Literature / Calculation

Thermal Screening

Reaction Calorimetry

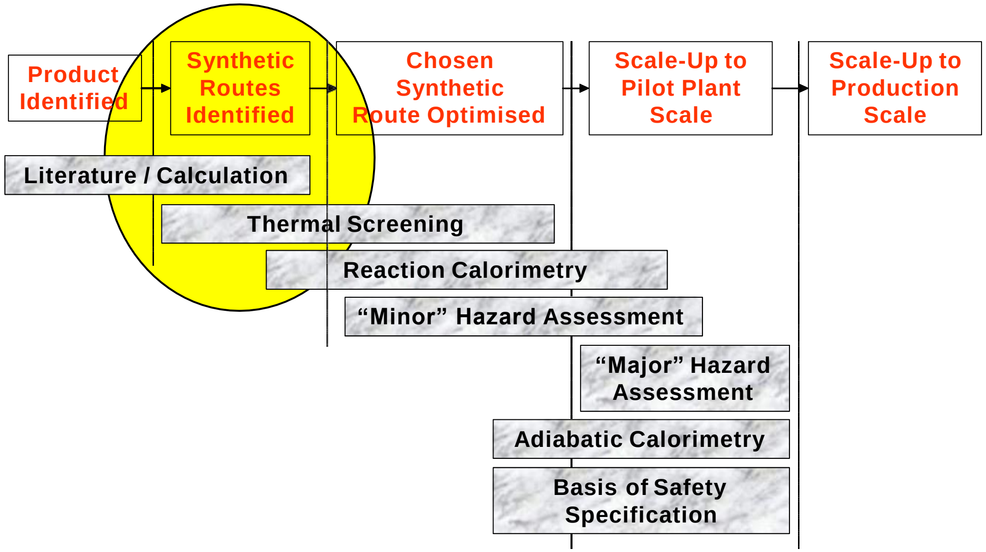
“Minor” Hazard Assessment

“Major” Hazard Assessment

Adiabatic Calorimetry

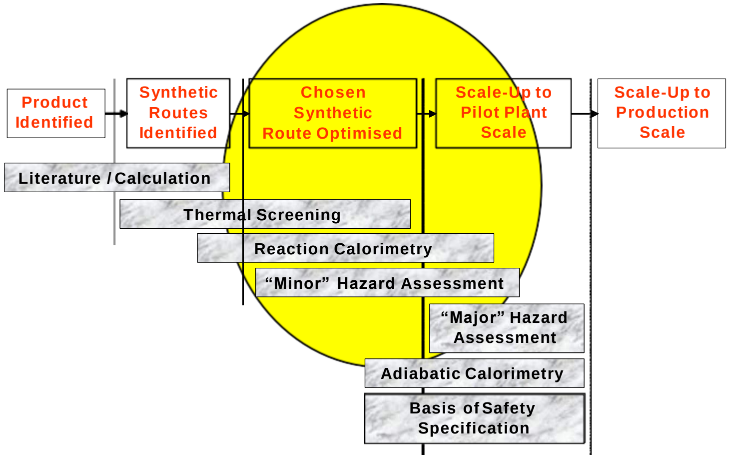
Basis of Safety Specification

Synthetic Route Selection



- synthetic pathway selected with regard to hazards
- potentially explosive groups identified
- chemical thermodynamics predicted
- thermal stability predicted
- Specific tools:
  - Literature, CHETAH, Functional group examination, oxygen balance, DSC, explosivity tests

Optimizing Synthetic Route



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Scale-Up to Pilot Plant Scale

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Literature / Calculation

Thermal Screening

Reaction Calorimetry

“Minor” Hazard Assessment

“Major” Hazard Assessment

Adiabatic Calorimetry

Basis of Safety Specification

Selecting Conditions

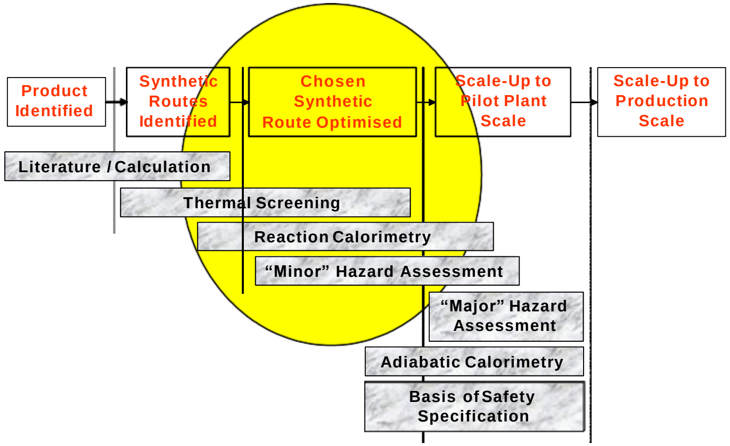
•thermal stability confirmed by small scale testing

- potentially explosive compounds tested
- reaction conditions selected
  - with regard to hazards
  - most suitable mode of processing identified
  - select solvents and other reagents with regard to safety

Optimizing Conditions

- Confirm thermodynamics and kinetics by reaction calorimetry (including pressure effects)
- Accurately define processing conditions
  - temperature limits (high and low)
  - sequences,

Optimizing Synthetic Route



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Synthetic Routes Identified

Chosen Synthetic Route Optimised

Scale-Up to Pilot Plant Scale

Scale-Up to Production Scale

Literature / Calculation

Thermal Screening

Reaction Calorimetry

“Minor” Hazard Assessment

“Major” Hazard Assessment

Adiabatic Calorimetry

Basis of Safety Specification

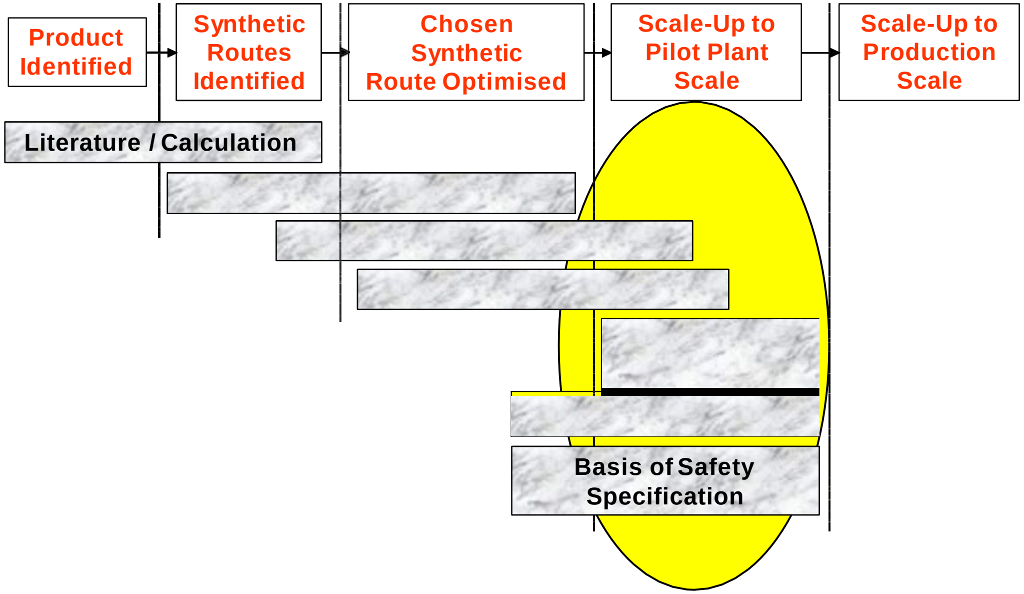
Preparing for Pilot Scale

- Predict consequence of common failure situations

Specific Tools

- Thermal stability screening (and more advanced thermal stability tests if required)
- Reaction calorimetry (+ evolved gas measurement)
- Minor hazard assessment (eg. checklists, what-if, etc)
- Preliminary adiabatic tests
- Specify basis of safety for pilot scale trials (for chemical reaction and Explosion hazards)

Pilot Scale Operations



Product Identified

Synthetic Routes Identified

Chosen Synthetic Route Optimised

Scale-Up to Pilot Plant Scale

Scale-Up to Production Scale

Literature / Calculation

Basis of Safety Specification

- Aim is to confirm robustness of process on scale-up
- Minor changes may occur
- Once successful pilot trial completed, conduct:
  - Confirmation that the data previously obtained is still valid
  - Major hazard assessment for production scale
  - Basis of safety review for production scale

Data Requirements Prior to Production Scale Operations

- $A + B \rightarrow C^1 \rightarrow D^2$

- C = Intermediate (not isolated) and D = Product (isolated)

- What data should exist?
  - Confirm that all previous stages have been completed fully
  - Thermal stability limits defined for A, B, C (in solution) and D (in solution and isolated) – also consider catalysts, solvents and any other additives
  - Reaction calorimetry / heat of reaction for the normal process (including accumulation potential)
  - Prediction of effects of all identified failure scenarios (“major” hazard assessment)
    - ➢ Adiabatic calorimetry for hazardous scenarios
      - Defined basis of safety for production scale
    - ➢ Documented hazard assessment and calculations

During Production Scale Operation

- Review any changes to the process or equipment
- Document any changes and document the safety review of the changes
- Confirm that safety review procedure has been followed and was effective
- Institute any changes to procedures to streamline or make more effective

Some Questions

1. Which is generally safer for exothermic processes - semi-batch or batch processing?
2. Reactivity data can be predicted True / False
3. Pure material flammability data can be predicted True / False
4. Physical safety testing should commence just before pilot plant production True / False
5. A written basis of safety should exist for all chemical processes operated at pilot scale. True / False
6. Experimental data is not necessary for the production of a basis of safety True / False

Checklist
Chemical Route Identification

- synthetic pathway selected with regard to hazards
- reaction conditions selected with regard to hazards
- potentially explosive groups identified
- chemical thermodynamics predicted
- thermal stability information predicted

Checklist
Preliminary Laboratory Synthesis

- thermal stability confirmed by small scale testing
- potentially explosive compounds tested
- reaction conditions selected
  - most suitable mode of processing identified
  - select solvents and other reagents with regard to safety

Checklist
Process Development / Optimization

- Confirm thermodynamics and kinetics by reaction calorimetry (including pressure effects)

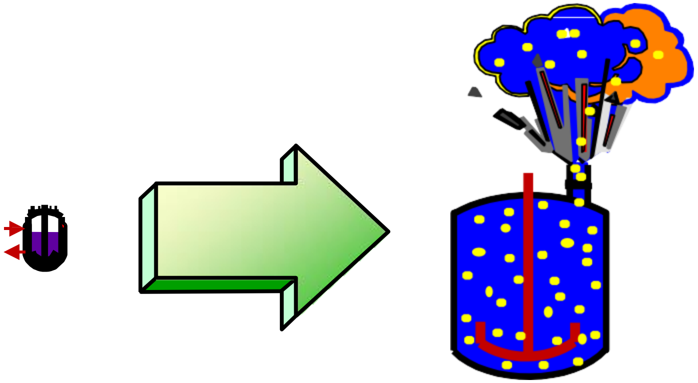
- Accurately define processing conditions
  - temperature limits (high and low)
  - sequences, concentrations, quantities and times

- Assess likely consequences of foreseeable deviations (and recommend safety measures where necessary)

Checklist
Pilot Scale Synthesis

- Conduct and document a detailed hazard assessment
- Ensure safety measures are in place and correctly configured
- Conduct additional calorimetry on process deviation scenarios (if necessary)
- Provide operator training on SOP and actions to be taken in the event of deviation scenarios
- Ensure operational hazards are identified and protected against (specifically, flammable atmospheres)

Fundamental Principles of Scale-up and Reaction Runaway



Definitions Relating to Thermal Hazards

- Causes of over pressurization
- Heat of Reaction
- Adiabatic Temperature Rise
- Arrhenius relationship
- Thermal runaway
- Phi factor
- Heat loss (changes with scale)
- Reagent accumulation
- Onset temperature (exothermic events)
- Safety factors (for thermal hazards data)

Hazards Arise from Pressure

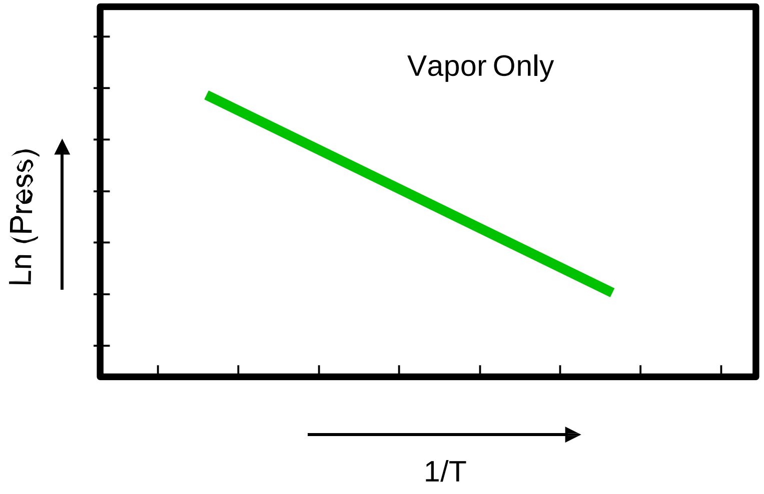
- When considering reaction hazards, temperature is rarely a hazard on its own. The impact of any temperature rise on the system is much more important.

- There are three potential sources of overpressure :-
  - Gas Generation from the normal process
  - Vapor pressure effects (as a consequence of heat from the normal process)
  - Heat from the normal process leading to secondary reactions at elevated temperature (causing gas and/or vapor pressure effects)

Vapor Pressure Effects

- ANTOINE PLOT (can be derived from sealed cell test data) Ln (Pressure) = A + (B / (C + Temp))

- For a pure vapor pressure system Ln (Pressure) $\propto$ (1/T)

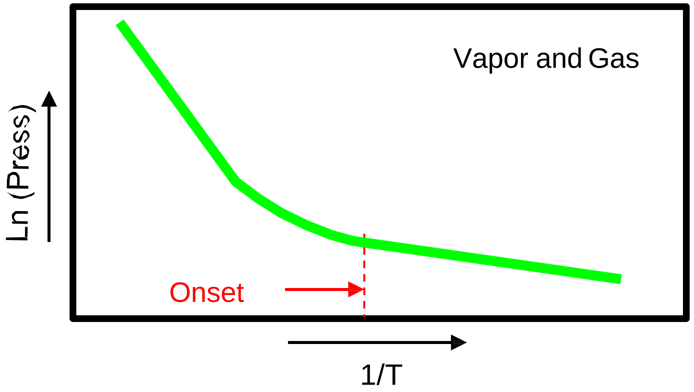


Vapor Pressure Effects

- Gas Generating System

  $\text{Ln (Pressure)} = A + (B / (C + \text{Temp})) + \tau$

- Where τ is a factor due to the generation of permanent gas
- Ln (Pressure) IS NOT $\propto$ (1/T)



HEAT OF REACTION

- ΔHr (measured in kJ.mol^{-1})

- For the reaction :-

$$A+B \rightarrow \text{Products}$$

- The HEAT OF REACTION is the quantity of heat released or absorbed as products are formed.

—-ve Exothermic, Heat released.

—+ve Endothermic, Heat absorbed.

HEAT OF REACTION

• Acid / Base Neutralization	- 60 kJ.mol^{-1}
• Esterification	
– Methanol / Acetic anhydride	- 67 kJ.mol^{-1}
• Hydrolysis	
– Diethylpropylmalonate	- 97 kJ.mol^{-1}
• Diazotization	
– Substituted amine hydrochloride	- 117 kJ.mol^{-1}
• Methylation	
– Complex acid chloride	- 104 kJ.mol^{-1}
• Grignard Reaction	- 200 kJ.mol^{-1}

... On its own, its not very useful!

ADIABATIC TEMPERATURE RISE

- The total temperature rise in a reacting system due to exothermic activity were there no heat loss to the surroundings.

ΔTad (measured in K)

$$\Delta \text{ Tad} = \Delta \text{ Hr.N} / (\text{m.Cp.}\Phi)$$

Where :-	N	No Moles of reactant (mol)
	Cp	Heat capacity ($J.kg^{-1}.K^{-1}$)
	Δ Hr	Heat of reaction ($J.mol^{-1}$)
	m	Mass in reactor (kg)
	Φ	Phi factor (see later)

REACTION RATE

ARRHENIUS RELATIONSHIP

$$k = A.\exp^{(-E/RT)}$$

Where :- k Rate constant

k	Rate constant
A	Frequency factor
E	Activation energy
R	Gas constant

Rate of heat production is dependent on reaction rate (for pseudo 1st order reaction) by

$$dQ/dt = k.\Delta Hr.m$$

Where :- dQ/dt = Rate of heat production

k = Rate Constant (1st Order)

m = Quantity of reagent available at time t

REACTION KINETICS

- Do not confuse ΔHr and E_A (they have the same units)
  - ΔHr is the overall energy change during a process
    - High ΔHr = a lot of energy change
    - Low ΔHr = little energy change
  - E_A is the energy required to initiate the change
    - Low E_A = facile reaction (occur at lower temperatures and / or pressures)
    - High E_A = difficult reaction (only occurs at higher temperatures and / or pressures)

KINETICS OF HEAT RELEASE / LOSS

- HEAT *RELEASE* RATE
  - from an exothermic reaction increases EXPONENTIALLY with temperature
- HEAT *LOSS* RATE
  - from a chemical reactor increases linearly with temperature

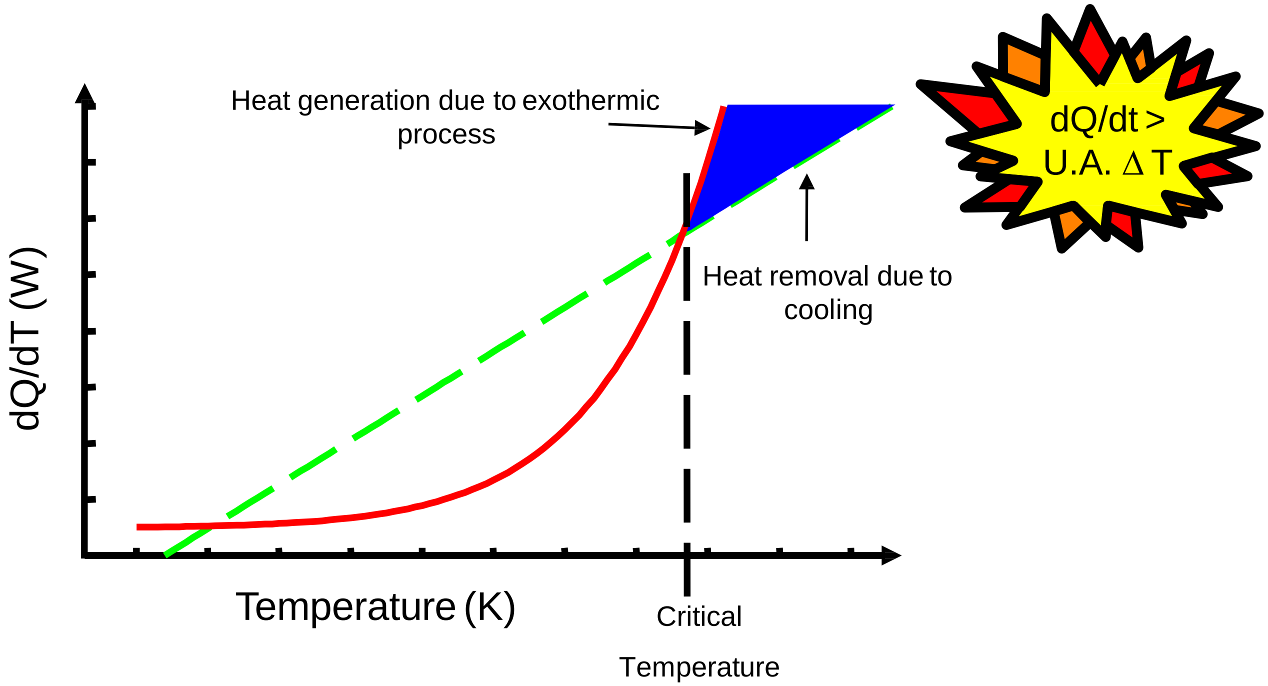
$$dQ/dt = U.A.\Delta T$$

U = Heat transfer coefficient ($W.m^{-2}.K^{-1}$)

A = Heat transfer area (m^2)

ΔT = Temperature difference between contents and jacket

THERMAL RUNAWAY



Reaction out of control → Thermal Runaway

THERMAL RUNAWAY

A THERMAL RUNAWAY is the progressive production of heat from a chemical process and occurs when the rate of heat production exceeds the rate of heat removal.

Kinetic Complications….

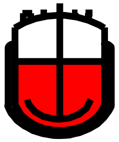
- Beware assuming simple kinetics for :
  - autocatalytic reactions
  - heterogeneous reactions
    - mass transfer may be rate determining
    - phase transfer agents may dictate rate
  - complex reactions (multiple steps / routes)

PHI FACTOR

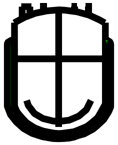
$$A + B \longrightarrow \text{Products}$$

- The heat generated in an exothermic reaction is consumed in three ways

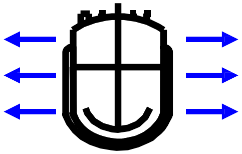
To raise the temperature of REACTION MASS



To raise the temperature of the REACTOR



Heat loss to the ENVIRONMENT



PHI FACTOR

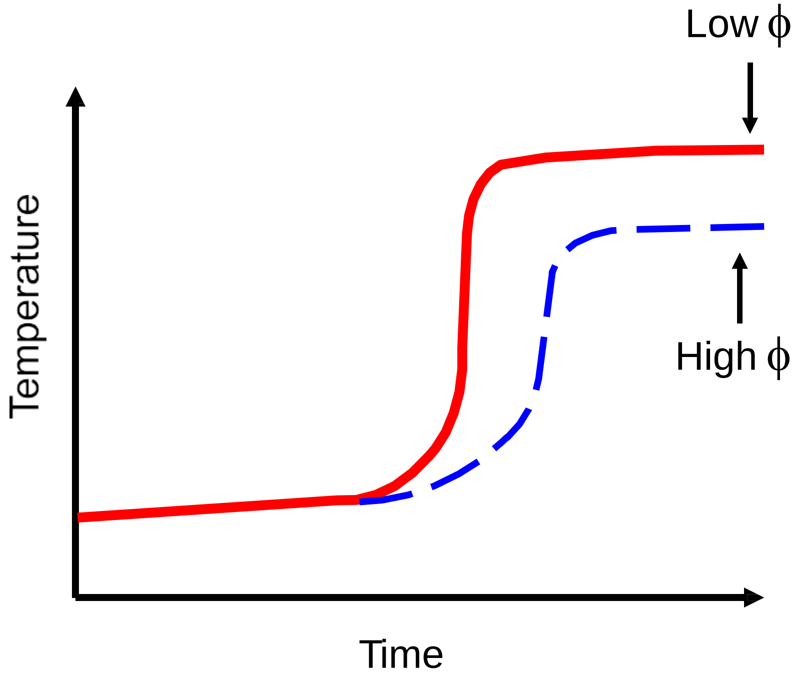
$$\phi = 1 + \frac{(\text{Mass of Container} \times \text{Heat Capacity Container})}{(\text{Mass of Sample} \times \text{Heat Capacity Sample})}$$

NB : Heat Losses not considered

– 1 m³ Glass lined reactor (Jacket empty)	ϕ 1.41
– 10 m³ Glass lined reactor (Jacket empty)	ϕ 1.13

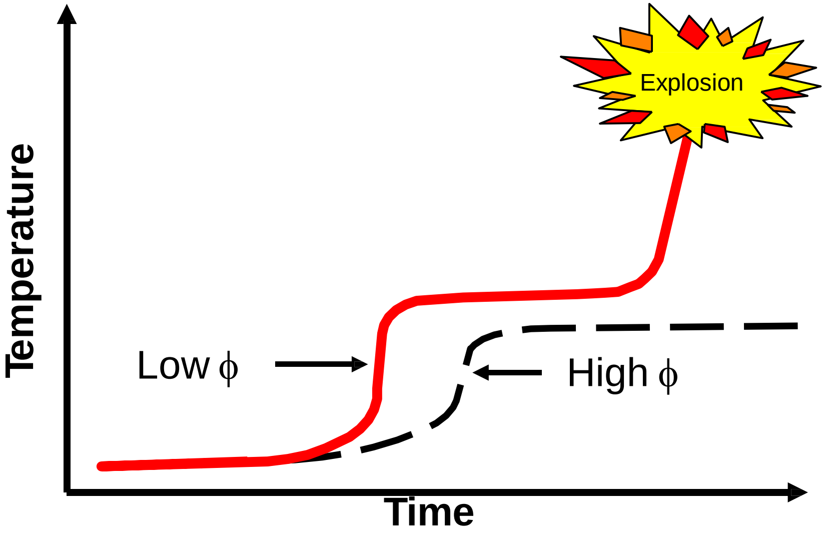
– 10g Carius tube screening test (best)	ϕ 2.50
– Accelerating Rate Calorimeter (best)	ϕ 1.50
– Adiabatic Pressure Dewar Calorimeter (best)	ϕ 1.05

PHI FACTOR



- TMR High ϕ > Low
- dT/dt ϕ Low ϕ >
- T_{ad} High ϕ Low ϕ
- dP/dt > High ϕ Low
- P_{MAX} ϕ > High ϕ
  Low ϕ > High ϕ

PHI FACTOR



Probability of

SECONDARY DECOMPOSITION
Overpressurisation
Loss of Containment

Heat Loss Considerations

Vessel	Time taken for 1°C drop at 80°C
25 m^3 reactor	233 minutes
12.7 m^3 reactor	59 minutes
2.5 m^3 reactor	21 minutes
10 cm^3 test tube	11 seconds
100 cm^3 beaker	17 seconds
1 l glass Dewar	62 minutes
1 l Dewar with -1 K oven	247 minutes

Scaling-Up Badly…

1974

Phenol-formaldehyde resin process. First batch at increased scale after numerous successful pilot batches

TESTING

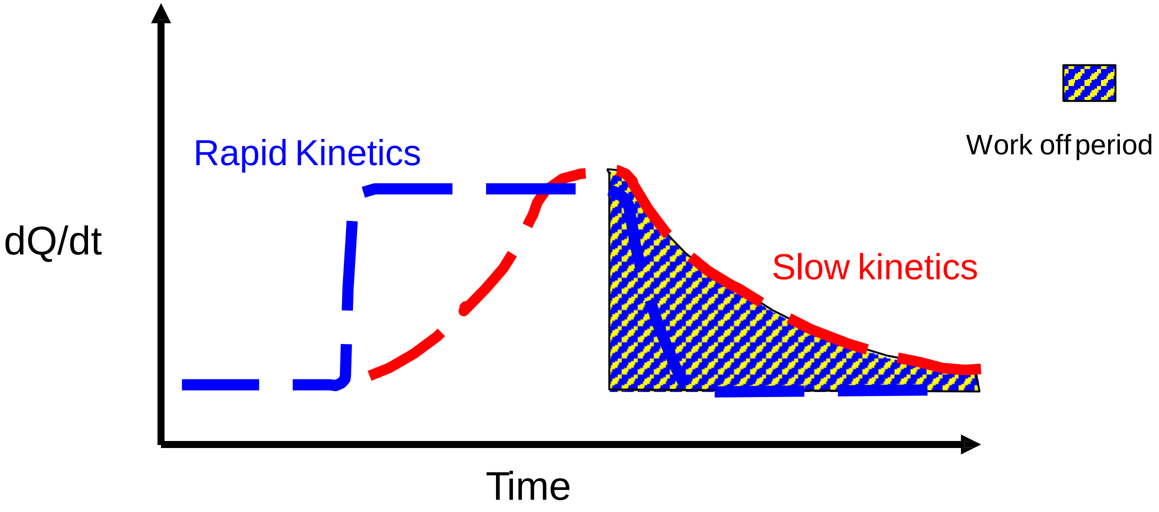
Testing should:

- Consider the consequences of all conceivable process deviations.
- Be conducted under plant scale heat loss conditions (or have an appropriate safety factor applied).
- Replicate plant conditions in all ways possible (including use of plant materials, consideration of materials of plant construction, etc).

REACTANT ACCUMULATION

A condition where :

Rate of Reactant Addition > Rate of reaction



REACTANT ACCUMULATION

Determined by process analysis

Causes (Not exhaustive) :

- Wrong kinetic assumptions
- Inefficient agitation
- Poor temperature control
- Impurities
- Incorrect initiation

The Concept of "Onset Temperature"

- The onset temperature is the temperature at which a reaction can be detected under the prevailing heat loss and phi factor conditions of the test.

- For a given reaction, it is equipment dependent and not a constant!

- Normally quoted as the temperature at which the rate of self-heating exceeds a threshold value.

Safety Factors

- Safety factors are applied to data collected in high phi factor or high heat loss test equipment.
  - 50 - 100 K for screening tests.
  - 10 - 50 K for adiabatic tests.
- Always apply a conservative factor to account for kinetic deviations between reaction types.
- Beware of autocatalytic reactions or processes with an induction or inhibition period.
- Consider air availability when assessing results

Some Questions

1. Is it important to differentiate between gas generating reactions and those that exert vapor pressure? Yes / No / Sometimes
2. The heat of reaction tells you, directly, how hot a reaction will get? Yes / No
3. A Grignard reaction will always be more hazardous than an acid / base neutralization? Yes / No
4. For any given reaction the heat of reaction is more or less constant. True / False
5. Comparing activation energies will indicate which reaction starts at a lower temperature. True / False

6. Reaction rate increases by a *maximum* factor of 2 for every 10 K increase in temperature for a first-order reaction True / False

7. The phi factor relates to atmospheric heat losses only. True / False

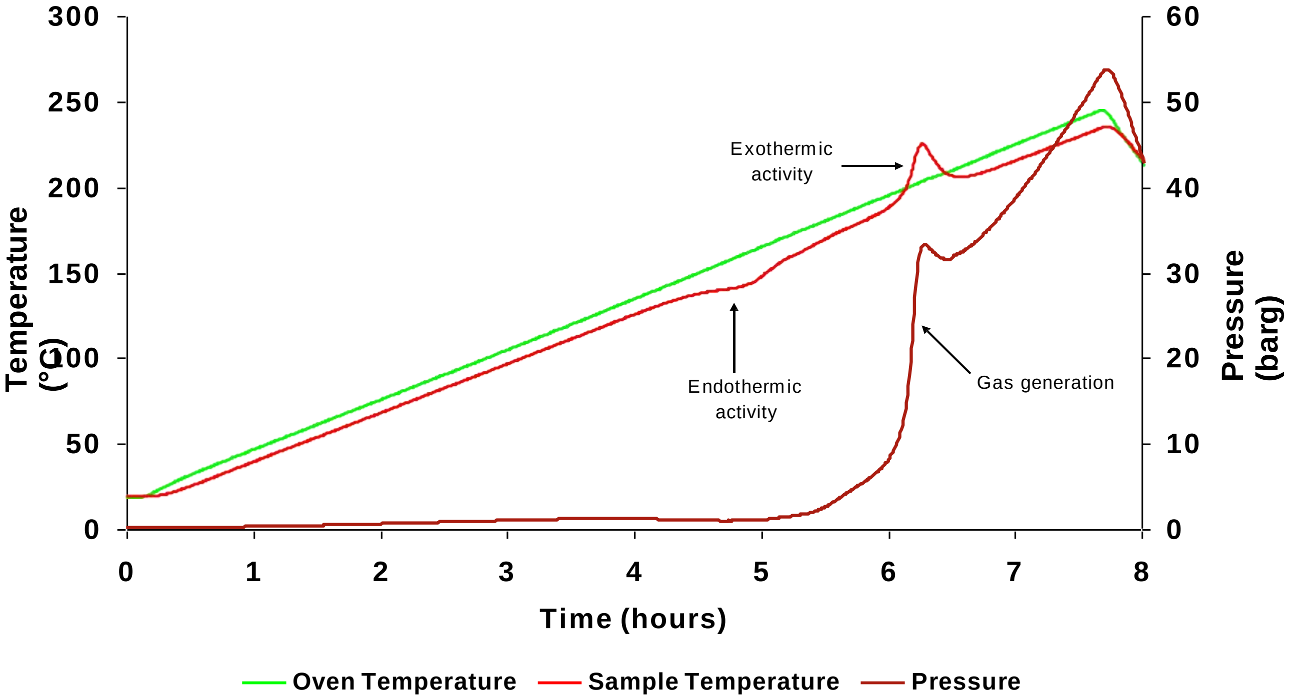
8. Vent sizing should always be based on high phi factor adiabatic calorimetry data. True / False

9. Larger reactors generally have lower phi factors and atmospheric heat losses than smaller reactors True / False

10. When testing, only low phi factor apparatus should ever be used True / False

11. Reactant accumulation in a semi-batch exothermic process is a bad thing True / False

Small Scale Screening Tests
(For Liquids, Mixtures and Solids)

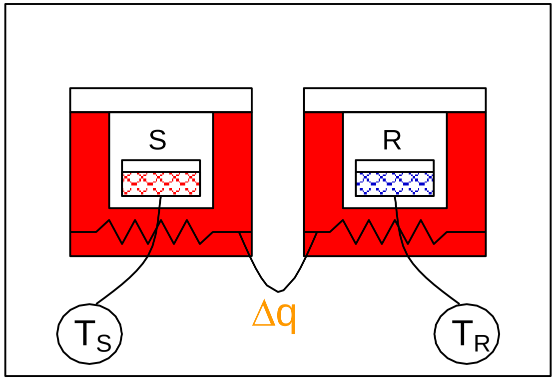


Preliminary Thermal Screening Methods (For Liquids, Mixtures and Solids)

- Tests are designed to
  - ✓Be rapid and small scale
  - ✓Give an initial indication of exothermic event onset, magnitude and associated pressure effects
  - ✓Identify highly energetic compounds

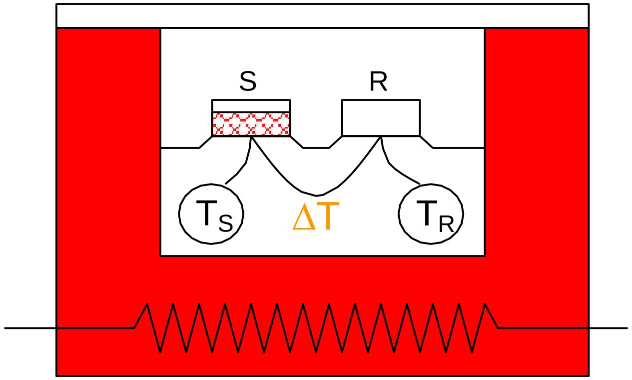
- Examples of commercial small scale screening methods are
  - ☞DSC (Differential Scanning Calorimetry)
  - ☞DTA (Differential Thermal Analysis)
    - Carius Tube Screening Test, Rapid Screening Device (RSD), Thermal Screening Unit (TS^{u})
  - ☞RSST (Reactive System Screening Tool)

Differential Scanning Calorimetry



Power compensation DSC

- Ts matched to Tr by direct element heat control
- Direct measure of q



Heat Flow DSC

- q calculated indirectly from ΔT and R_{TH} (thermal resistance of plate)

Differential Scanning Calorimetry

ICTA (International Confederation for Thermal Analysis) standards dictate exothermic peaks are plotted upward.

DIN standard 51005 dictates that exothermic peaks are plotted downward. Always identify which way round data is plotted!

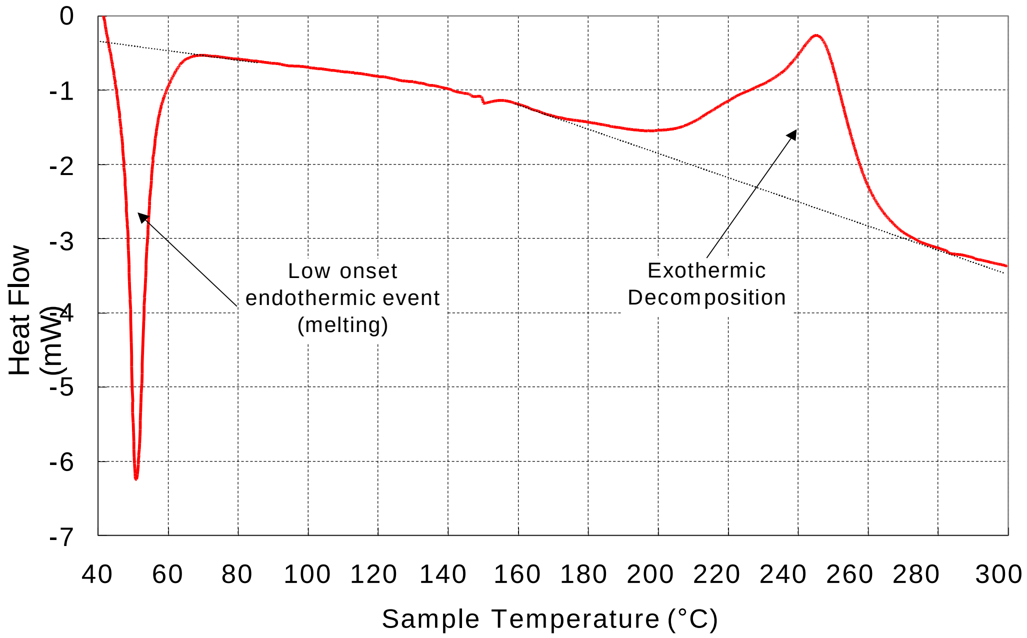
Advantages

- Quantified energy data
- Small sample size
- Wide variety of pans available
- Very rapid
- Can extract kinetic data

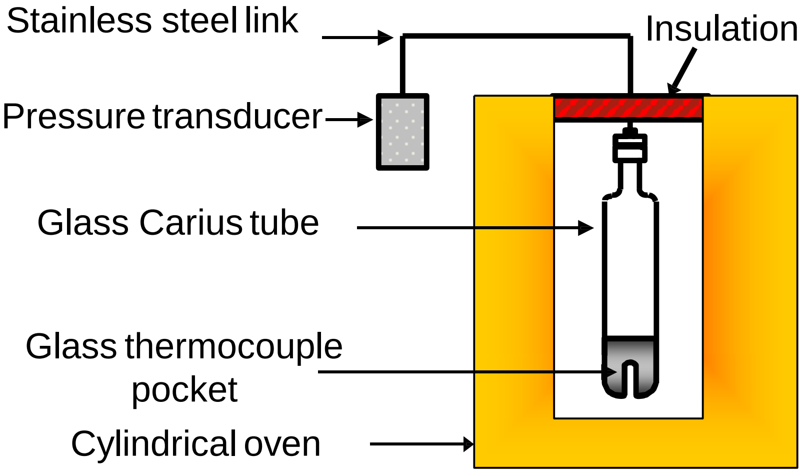
Disadvantages

- High thermal inertia
- Small sample size
- No agitation
- No pressure data

DIFFERENTIAL SCANNING CALORIMETRY



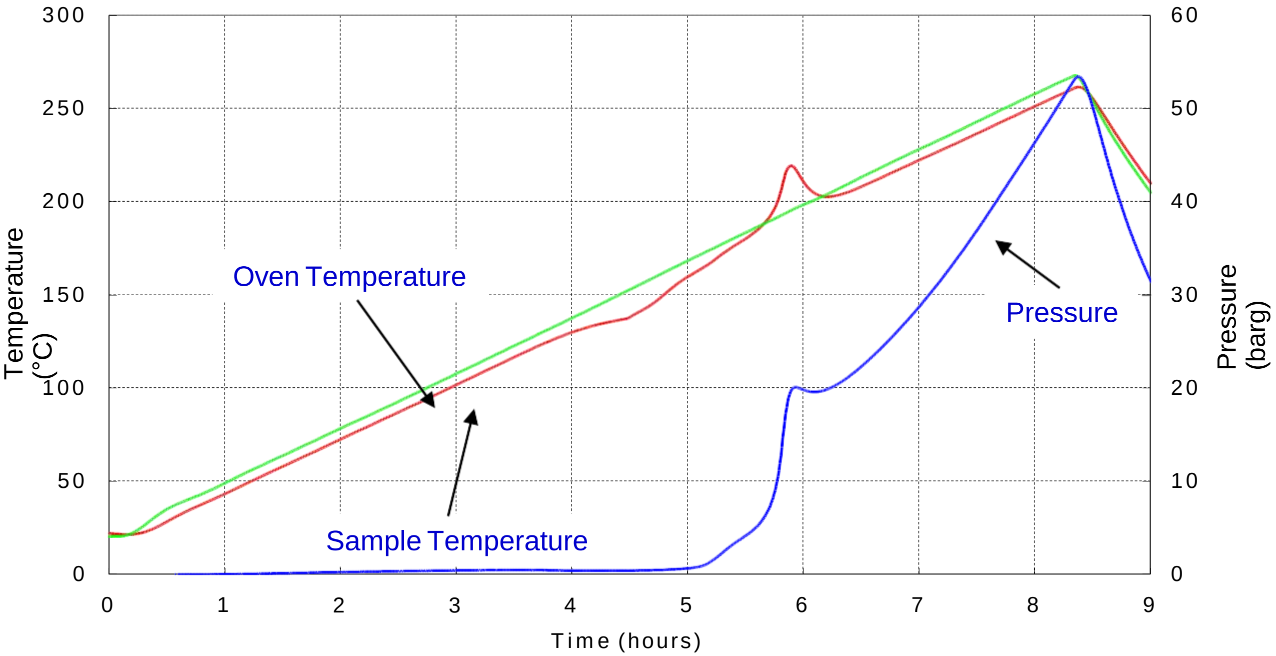
Carius Tube Screening Test



NB : Same principle applied to Radex apparatus, RSD and TS*u*

- Advantages :-
  - →Pressure data available.
  - →Glass tube (no contamination)
  - →Large sample size
  - →Reduced phi (2)
  - →Agitation possible
  - →Semi-batch addition possible.
- Disadvantages :-
  - →No quantified energy data.

CARIUS TUBE DATA
NaCl / Glucose (50:50)

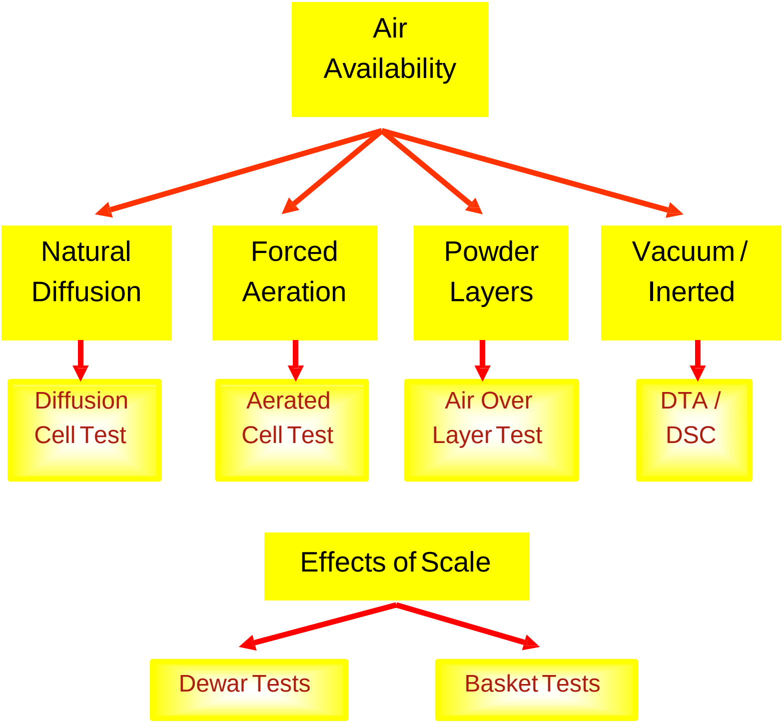


Advanced Thermal Stability Testing Methods

- Advanced methods of thermal stability analysis are available:
  - Tests specific to powder handling / drying / storage
  - Adiabatic methods
  - Self-Accelerating Decomposition Temperature (SADT) determination methods

- Screening tests :
  - are generally high heat loss
  - are not generally adiabatic
    - (and hence cannot be scaled up directly without significant safety factors)
  - do not consider the effect of air on stability
  - are generally rapidly ramped (and hence lack sensitivity)

Powder Thermal Stability Testing



Air Availability

Natural Diffusion
Forced Aeration
Powder Layers
Vacuum / Inerted

Diffusion Cell Test
Aerated Cell Test
Air Over Layer Test
DTA / DSC

Effects of Scale

Dewar Tests
Basket Tests

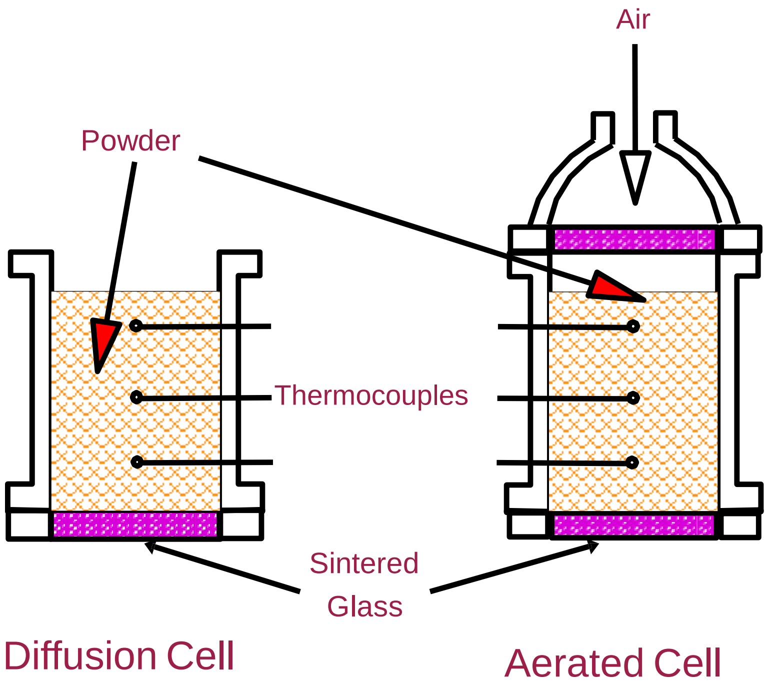
- Powders present additional hazards due to the significant effects of :
  - scale
  - heat transfer effects
  - air availability
  - time of exposure
  - purity
  - Geometry

- Special testing methods have been specifically developed to cover thermal stability assessment of powders

Powder Thermal Stability Tests

- Diffusion Cell Tests used for simulation of:
  - bulk powder
  - storage + drying

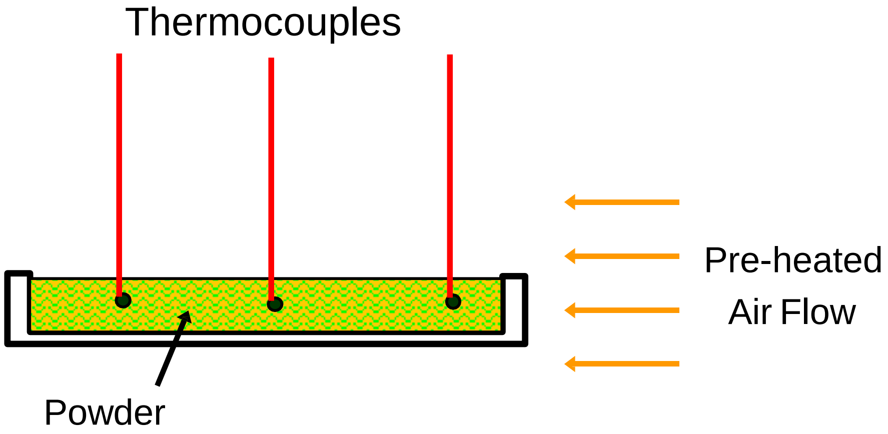
- Aerated Cell Tests used for simulation of:
  - fluid bed dryers
  - well aerated bulk powder
  - effects of increased air availability.



Powder Thermal Stability Tests

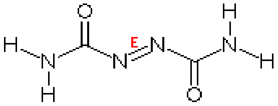
- Air Over Layer Test.

- Used for :
  - simulation of powder layers
  - tray dryers
  - layer deposits



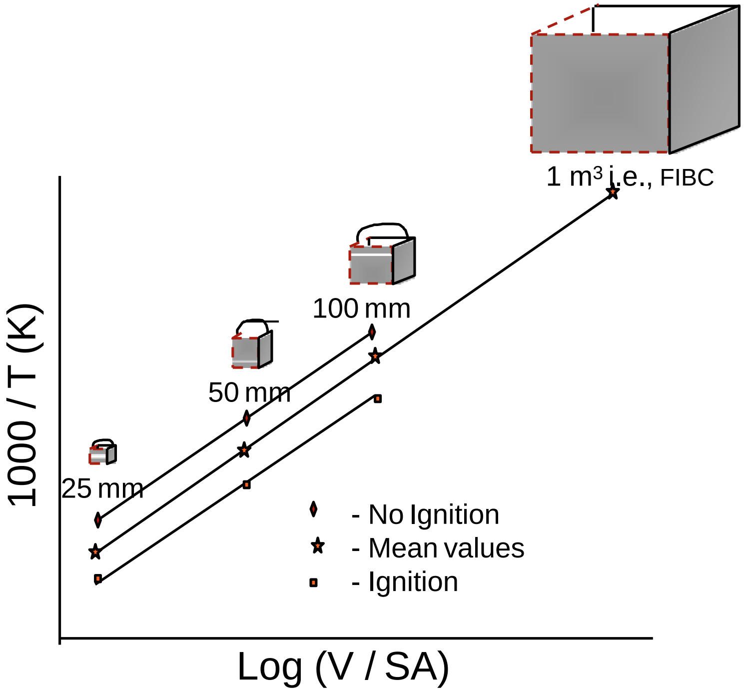
Air Over Layer Test

Comparison of Data
Chilworth Technology Study (1997)



	Citrus Peel	Azodicarbonamide
Carius Tube	115	145
DSC (air)	223	179
DSC (nitrogen)	>250	179
ARC	165	135
Diffusion Cell	114	169
Aerated Cell	101	168

Basket Tests



- Used for extrapolation for decomposition onset temperature determination (and duration time)
- Selected baskets used in UN Class 4.2 (self-heating substances) classification tests. Packing Class II or III
- Most sensitive method (with Dewars) for powder thermal stability data collection

Adiabatic Methods

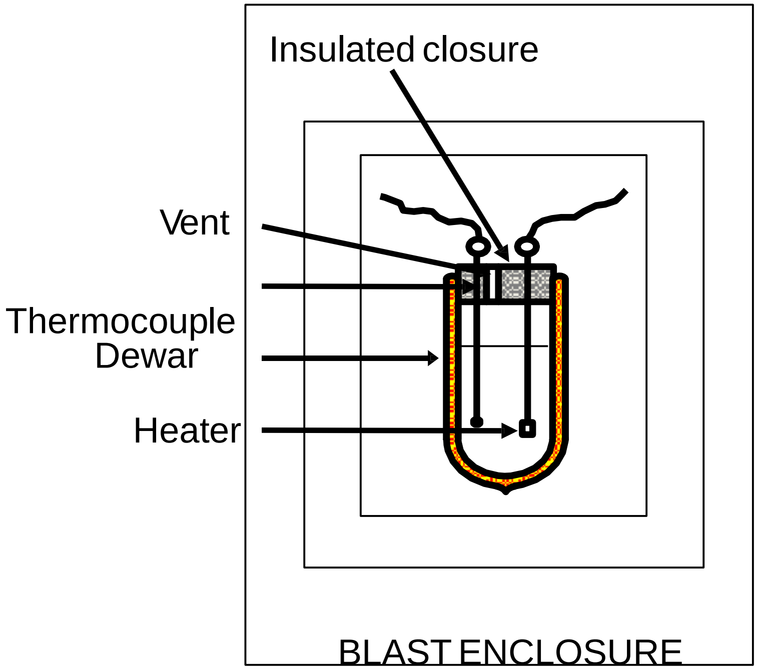
- Adiabatic testing methods are designed to simulate the heat loss and thermal inertia conditions experienced at large scale.
- Data directly scaleable.
- Available methods include:
  - Adiabatic Dewar calorimetry (Glass or metal)
  - Adiabatic calorimetry
  - Accelerating Rate Calorimetry
- Methods discussed later

SADT Methods

- The self-accelerating decomposition temperature is defined as the temperature at which the rate of heat production from a reaction exceeds the rate of heat loss from the sample receptacle. The SADT is not a constant!

- Standard UN Methods exist:
  - UN Test H.1 United States SADT test 75°C → 60°C → X°C
    - suitable for materials transported in packages (Isoperibolic)
  - UN Test H.2 Adiabatic Storage Test -20 °C → 220°C >0.1 K/m
    - suitable for materials transported in packages, IBC's and tanks
  - UN Test H.3 Isothermal Storage Test -20 °C → 200°C >0.1 K/m >
    - suitable for materials transported in all types of containers
  - UN Test H.4 Heat Accumulation Storage Test 75°C → 60°C → X°C
    - suitable for materials transported in packages, IBC's and small tanks (Isoperibolic)

UN Test H.4
Heat Accumulation Storage Test



- Calibrate Dewar heat loss (ensure in good correlation with intended container or specified level)
- Oven set to SADT test temperature
- Observe sample for 7 days
- If T_{exo} is > 6 K above T_{oven}, repeat at 5°C lower
- SADT determined within 5 K
- Method used for UN Division 4.1 (self-reactive substances classification)

Heat Losses of Typical Receptacles

200 Liter tank of water	56 mW.kg^{-1}.K^{-1}
3,400 Liter tank of water	18 mW.kg^{-1}.K^{-1}
20,000 Liter tank of isododecane	1.7 mW.kg^{-1}.K^{-1}
38 Liter tank of dicyclohexyl phthalate	35 mW.kg^{-1}.K^{-1}
110 Liter tank of dicyclohexyl phthalate	22 mW.kg^{-1}.K^{-1}

- Example: a container of water having a heat loss of 10 mW. kg^{-1}.K^{-1} will have a cooling rate at 80°C of 0.52 K.hr^{-1}

Summary

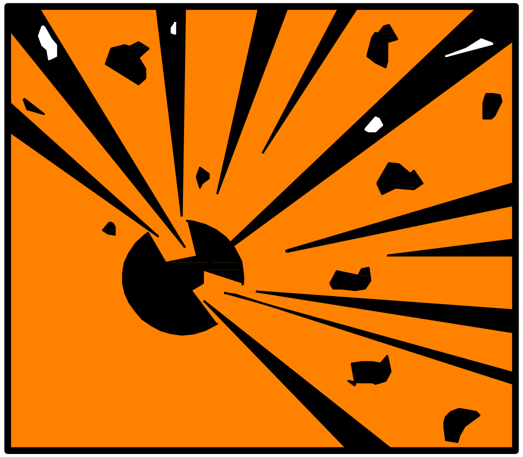
- Conduct literature search / desk screening before any new synthesis.
- Always deal with potential explosivity issues at very small scale.
- At least determine thermal stability using screening methods early in process development.
- Select the most appropriate test method
- Use conservative and appropriate safety margins.
- Detailed thermal stability analysis only likely to be feasible once larger volumes produced.
- Powders require special methods.
- Most sensitive methods are Dewar, basket and SADT methods.

Useful reference :S.M. Rowe, “Thermal Stability : AReview of Methods and Interpretation of Data”, Organic Proc. Res. & Dev., 2002, 6, pp 877 – 883.

Some Questions

1. Thermal instability onset temperatures can be predicted. True / False
2. Thermal instability onset temperatures are specific for a chemical and are independent of testing condition or apparatus True / False
3. DSC requires large safety margins. True / False
4. DSC measures pressure. True / False
5. Carius tube data can be used for vent sizing calculations True / False
6. Carius tube gives quantified energy release data True / False
7. For fluid bed drying applications, Carius tube data is acceptable True / False

Identification of Highly Energetic Materials



Identification of Highly Energetic Materials

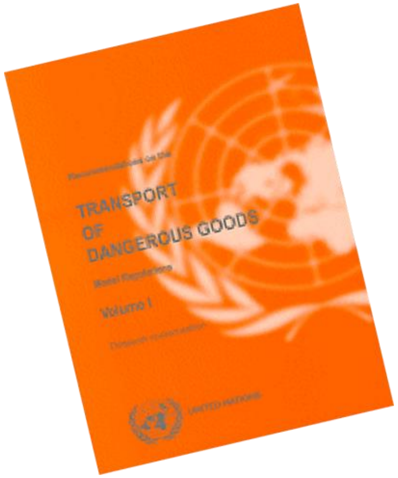
- At any scale of operation, it is critical (from a safety and quality perspective) to ensure that the following properties of materials are adequately assessed:
  - explosivity
  - thermal stability
  - fire properties (pyrophoricity, flammability of solids).

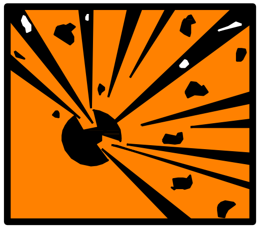
- This section explains how the most serious of these (Explosivity) can be assessed prior to laboratory work (and also outlines small scale tests for confirmation).

A Strategy for Assessment of Explosivity Hazards

- The following stages of assessment should be applied when examining new compounds for explosivity / thermal stability hazards:
  - Desk screening / literature review
  - Small scale screening for:
    - ☞ explosive properties
    - ☞ thermal stability properties
  - Detailed experimental characterization (including regulatory classification tests)

Explosivity



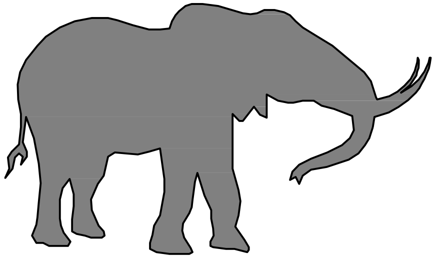


- Explosive compounds are classified as those which can detonate (decompose at a propagation rate above the speed of sound) if initiated by:
    - ○ thermal sources
    - ○ mechanical sources (friction / impact)
    - ○ explosive shock

- Samples which can deflagrate rapidly (i.e. below the speed of sound) may also be considered explosives (Class 1)

- Small scale test methods should be employed (initially)

Less Formal Definition….



“An explosion is like an elephant; difficult to define, but easily recognized when you are confronted with one”

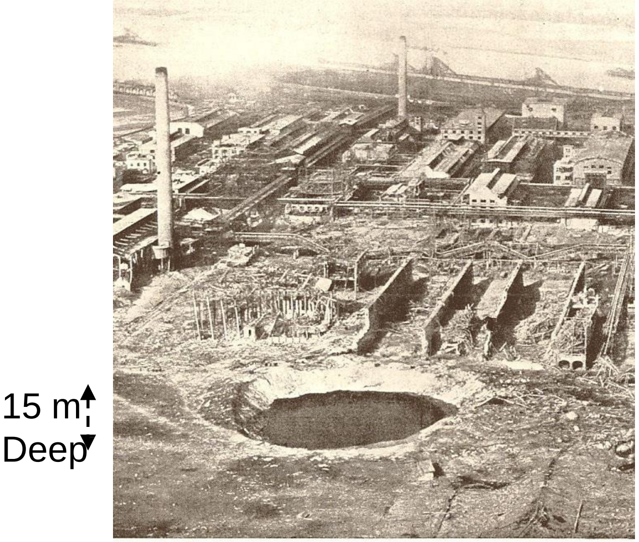
A detonation is a chemical reaction, which passes through the sample at well in excess of sonic velocity. It is a shock wave accompanied by the chemical reaction which sustains it.

High Order Detonations	4-9 km/s
Low Order Detonations	1.5-3 km/s

Nitroglycerin	7.58 km/s
Ammonium nitrate	1 - 3.9 km/s

1 km/s = 2,236 mph

Ammonium Nitrate Explosion

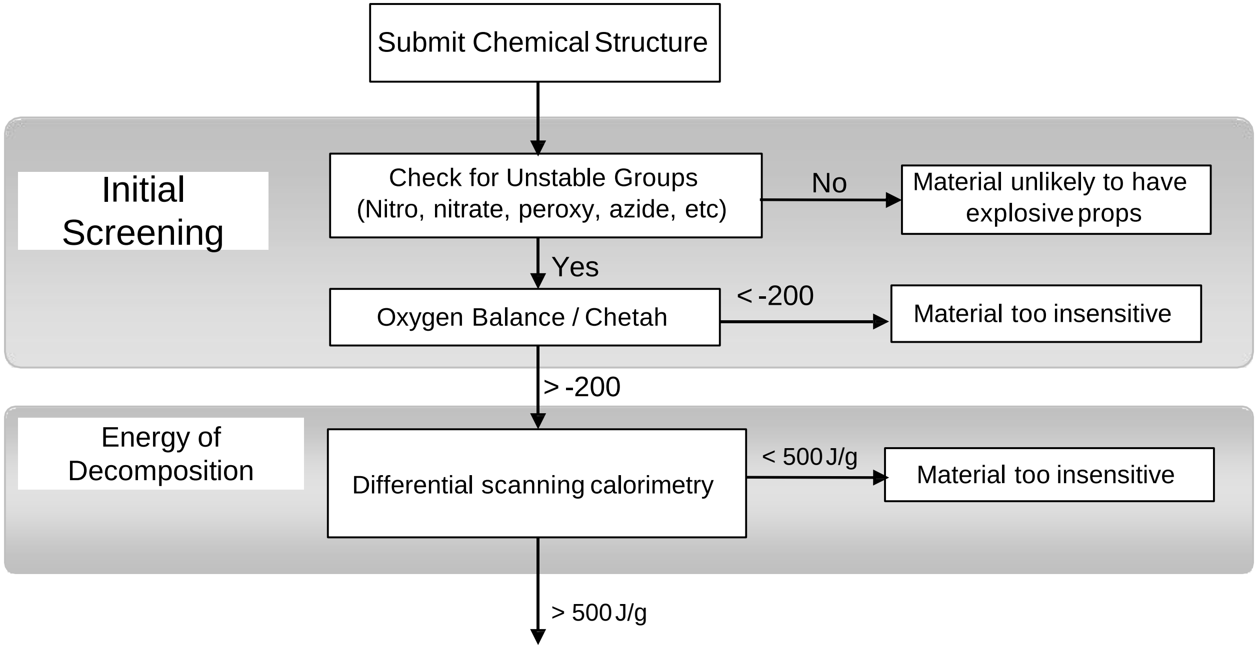


Herd der Exploſion und der Umfang der Zerſtörung im Oppauer Werk der Ba
fabrik (B. A. S. F.). Im Vordergrunde der durch die Sprengwirkung entſ
Trichter von 125 m Länge, 90 m Breite und 19 m Tiefe, über dem der S

- Literature states “ammonium nitrate explodes by percussion or at 70°C”

- Oppau, Germany (1921)
  - Ammonium nitrate / sulfate waste (4500 tonnes) stored outside and caked
  - Blasting powder used to break-up cake
  - Destroyed the works
  - Destroyed 1,000 nearby houses
  - 430 Fatalities
  - Damage in Frankfurt 80 km away
  - Toulouse, Fr. explosion (Sept 2001) very similar

Strategy for Assessing Explosivity



Submit Chemical Structure

Initial Screening

Check for Unstable Groups (Nitro, nitrate, peroxy, azide, etc)

No

Material unlikely to have explosive props

Yes

Oxygen Balance / Chetah

< -200

Material too insensitive

> -200

Energy of Decomposition

Differential scanning calorimetry

< 500 J/g

Material too insensitive

> 500 J/g

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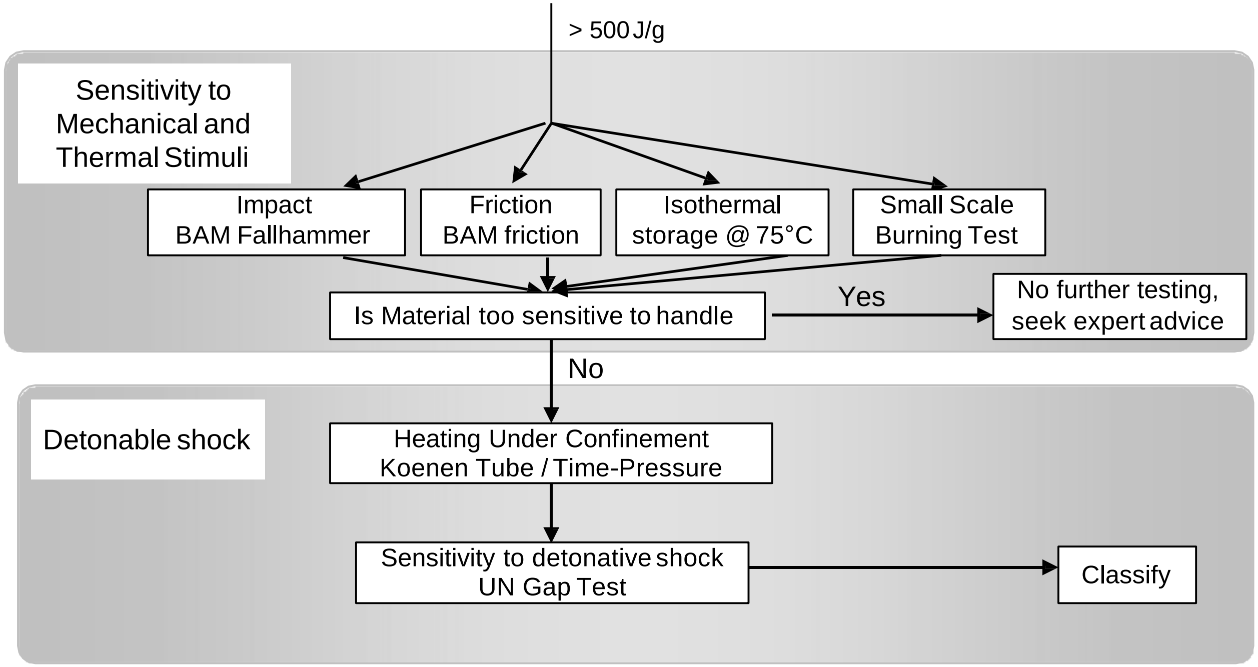
Strategy for Assessing Explosivity



Desk Screening / Literature Review

- Desk screening can be conducted through:
  - ➔Examination of functional groups, combined with (if appropriate)
    - ☞Oxygen balance calculations
    - ☞CHETAH calculations / Hess's method calculations
  - ➔Analogy with similar materials
  - ➔Literature search through appropriate sources

- Desk screening should ideally be performed before any new synthesis is conducted in a laboratory

ENERGETIC FUNCTIONAL GROUPS

Name / Structure	Range of decomposition energies (kJ.mol^{-1})
Alkenes ($R_2C=CR_2$)	50 → 90
Alkynes / acetylenes ($R\text{-}C\equiv C\text{-}R$)	120 → 170
Epoxides	70 → 100
Organic / inorganic peroxides / hydroperoxides (R-O-O-R / R-O-O-H)	230 → 360
Organic sulphoxides ($R_2S=O$)	40 → 70
Organic sulphonyl chlorides ($R\text{-}SO_2Cl$)	50 → 70
Hydrazines (R-NH-NH-R)	70 → 90
Diazo / Diazonium ($R\text{-}N=N\text{-}R$ / $R\text{-}N\equiv N^+$)	100 → 180
Azides ($R\text{-}N_3$)	200 → 240
Oxime ($R_2C=NOH$)	110 → 140
N-Oxides ($R_2N{:}O$)	100 → 130
Nitroso ($R_2C\text{-}N=O$)	150 → 290
Isocyanate (R-N=C=O)	50 → 75
Nitro ($R_3C\text{-}NO_2$)	310 → 360
N-nitro ($R_2N\text{-}NO_2$)	400 → 430
Acyl nitrates ($\text{-}O\text{-}NO_2$)	400 → 480

(R, in most cases, represents an organic fragment)

OXYGEN BALANCE

- A measure of the oxygen required for complete combustion to carbon dioxide and water. Units are grams of addition oxygen required for complete combustion of 100 g of substance.

- $C_XH_YO_Z$: Oxygen balance = -1600.(2X + Y/2 -Z) / mol. wt.

- Only useful when oxygen is bound in energetic groups (such as nitro, nitrate, peroxy, chlorate, etc).

- > -200 considered to be potentially hazardous

Nitrobenzene	-162	$C_7H_7O_2N$	-181
Nitrobenzoic acid	-119	$C_5H_{10}O_2$	-203
Nitropropane	-134	$C_2H_4O_2$	????
Ethanol	-208		

Oxygen Balance: Calculation - Example

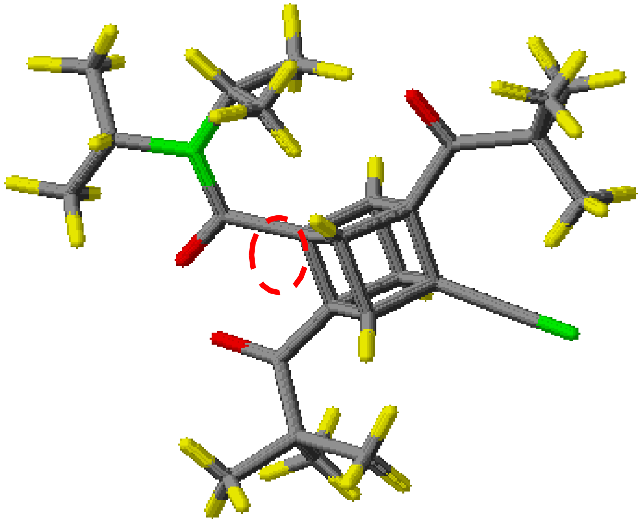
- Determine oxygen balance for $C_2H_4O_2$

- Calculation
- C = 12
- H = 1
- O = 16
- $C_2H_4O_2$ = 60
- Oxygen balance = - 1600 . (4+2-2)/60
- Oxygen balance = - 106

APPLYING THE OXYGEN BALANCE

- $C_{26}H_{35}N_2O_3$
- Dipivaloylcubane
- Shows activity against HIV
- Oxygen balance = -251.5

- **SAFE?**



Computational Methods

- CHETAH

→ Chemical Thermodynamic and Energy Release Evaluation
ASTM Sub committee E27.07 1974

- CHETAH uses Bensons method of Group Contributions

→ Prediction of reactivity hazards base on structure
→ Hazard rating
→ Heat of reaction
→ Other thermodynamic properties
→ ΔHf, ΔHc, Cp at temperatures of 298 K - 1000 K

- Basically, an enhancement of Hesses method of heat summation NB Never intended to replace physical testing.

HAZARDOUS situations could arise if this were the sole determinant in the safety case

CHETAH 9.0

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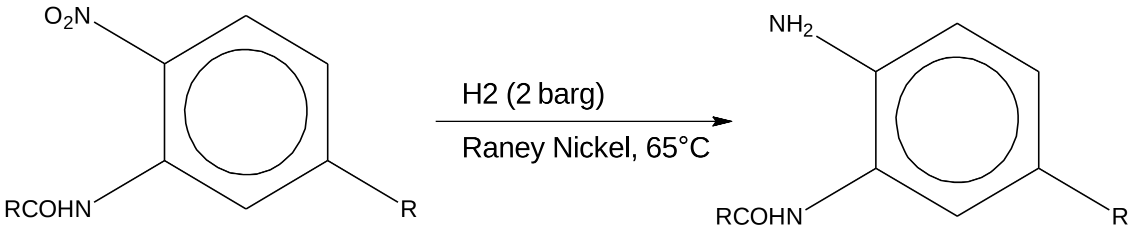
- Additional features:
- Adiabatic temperature rise calculations for decomposition reactions
- Database for Ideal Gas Benson Groups expanded. The database now
- contains 965 groups and is the largest Benson Group database
  - 77 groups were added since 8.0 of CHETAH
- New database of liquid and Solid Benson Groups included for condensed phase thermodynamic property predictions and reactions
- Highest calculation temperature raised from 1500 K to 4000 K
- Images for all ideal gas Benson Group ring corrections included for convenience

CHETAH CALCULATIONS FOR PROCESS SAFETY



- Example :
  - Hazard assessment of a synthesis reaction and thermal stability assessment of process materials.
- Use CHETAH to estimate:
  - predicted heat of reaction
  - energy release evaluation and hazard assessment of starting material and product

CHETAH CALCULATIONS FOR PROCESS SAFETY

- Predicted heat of reaction = -468 kJ.mol^{-1}
    - measured value = -540 kJ.mol^{-1}
- Energy Release Evaluation
    - Starting material
        - ➢Maximum decomposition energy : -3766 J.g^{-1}
        - ➢Overall energy release potential : HIGH
        - ➢Oxygen balance : -143
    - Product material

➢Maximum decomposition energy :-1960 J.g^{-1}

➢Overall energy release potential : LOW

➢Oxygen balance : -193

Useful Literature

- Sax, N. I., **Dangerous Properties of Industrial Materials**. Reinhold Publishing Corporation, New York, 9th ed., 1996.
- Kirk-Othmer, **Encyclopedia of Chemical Technology**. Wiley-Interscience, New York, 3rd ed., 1978 and 4th ed., 1992.
- Bretherick's **Handbook of Reactive Chemical Hazards**, 5th ed. Butterworth-Heinemann, Oxford, 1995.
- Hardy, J. K., **Hazardous Chemical Database**. University of Akron, Ohio, 1997. URLsite: http://odin.chemistry.uakron.edu/erd/
- Lewis, R. J., **Hazardous Chemicals Desk Reference**, 3rd ed. Van Nostrand Reinhold, New York, 1993.
- Davis, D. J. and Davis, J. A., **Hazardous Materials Reference Book**. Van Nostrand Reinhold, New York, 1996.
- Carson, P.A. and Mumford, C. J., **Hazardous Chemicals Handbook**. Butterworth-Heinemann, Oxford, 1994.
- **Chemical Reactivity Worksheet**, NOAA (US DoC and EPA) (http://response.restoration.noaa.gov/)
- **IChemE Hazards Symposium**, conference proceedings.
- **Material Safety Data Sheets**
- **The Internet**

Testing for Explosive Properties

- START SMALL!!!
- Synthesis must be carefully planned to avoid excessive temperatures or high energies
- Plan to collect, initially, only mg quantities.
- Use copious solvent

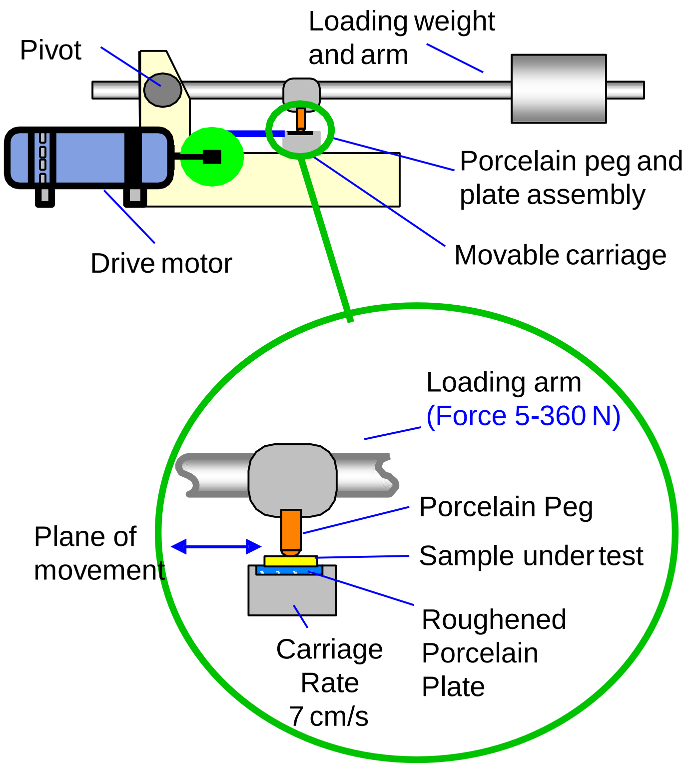
Differential Scanning Calorimetry

- Uses very small quantities of materials (up to 10 mg)
- Criteria for application proposed by UK HSE:

—> 300 J/g - may undergo dangerous self-heating
—> 500 J/g - may have some explosive properties
—> 800 J/g - may have some detonable properties

Substance	Onset (°C)	ΔH_{DEC} (J/g)
Ammonium nitrate	284	961
Ammonium perchlorate	389	Out of range
Azodicarbonamide	194	1105
AZDN	101	1301

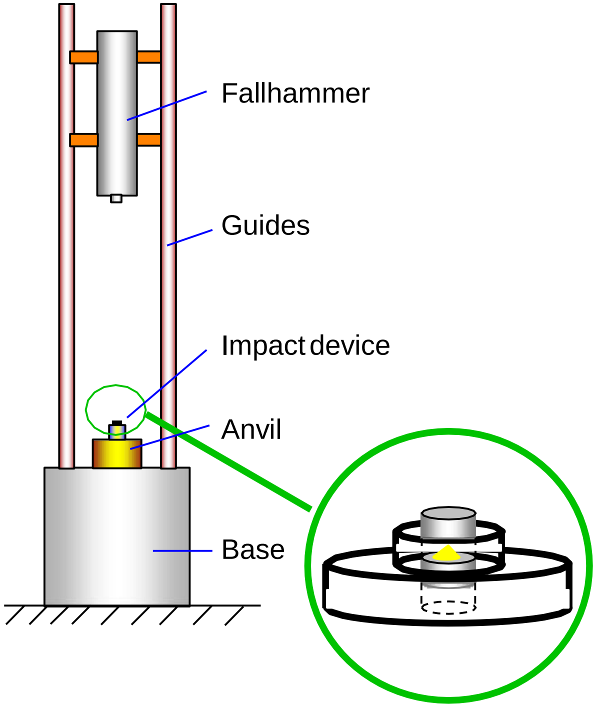
Explosivity Testing Friction Sensitivity Test



- Test specified in most regulatory test methods (UN test series 3, EC, etc)
- A substance is too sensitive for transport if LIMITING LOAD is 80 N or less
- Examples:

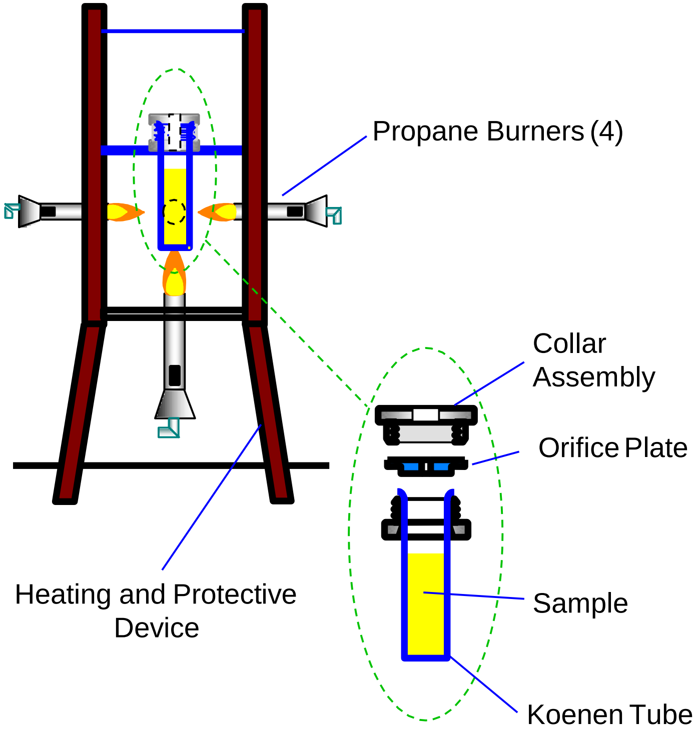
– Ammonium nitrate	>360 N
– Ammonium perchlorate	>360 N
– Lead azide	>10 N

Explosivity Testing Impact Sensitivity Test



- Test specified in most regulatory test methods (UN test series 3, EC, etc)
- A substance is too sensitive for transport if LIMITING IMPACT ENERGY is 2J or less
- Examples:
  - Ammonium nitrate 50 J
  - Ammonium perchlorate 5 J
  - Nitroglycerin 1 J
  - Lead azide ~2 J

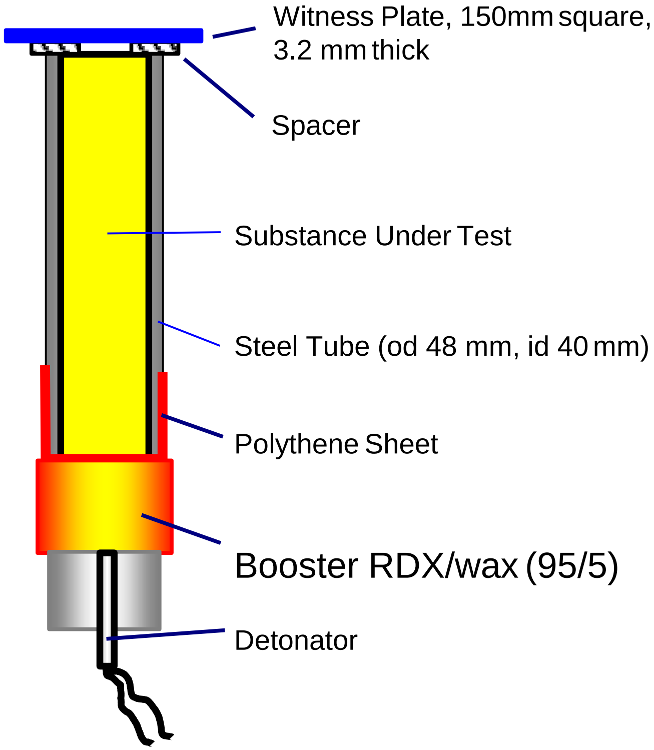
Explosivity Testing: Koenen Confined Heating Test



- UN Test series 1 and 2 (plus EC, etc) recommended method
- A substance exhibits "Thermally explosive properties" if the limiting diameter of the orifice

  is ≥ **1 mm**
- A substance is "Thermally Sensitive" if the Limiting Diameter of the orifice is ≥ **2 mm**
- DSC or other small scale screening method should be used to assess thermal sensitivity.
- Examples :
  - Ammonium nitrate 1.0 mm
  - Ammonium perchlorate 3.0 mm

Explosivity Testing
Shock Sensitivity Test (UN Gap Test)



- UN Standard method
- A substance is liable to propagate a detonation if:
  - The tube is fragmented completely
  - A hole is punched in the witness plate
- Further, larger scale tests can be required for detailed classification / declassification

Explosive Classification

- Explosivity is the only UN class in which results and method are scale dependent.

- Testing procedure (UN and good practice!) involves:
  - Conduct sensitivity tests (Test Series 3)

➢ Impact sensitivity	(< 2 J)
➢ Friction sensitivity	(< 80 N)
➢ Thermal stability at 75°C	(No ignition or explosion for 48 hr)
➢ Small scale burning test	(Explosion occurs)

  - Conduct severity tests (Test Series 1 and 2)

➢ Koenen Tube (Confined Heating) Test	(≥ 2 mm limiting diameter)
➢ Time / Pressure Test	(60 kPa 2070 kPa < 30 millisec)
➢ UN Gap Test	(Fragmentation/Hole in Wit. Plate)

  - Accept / reject as candidate for Class 1
    - ➢ If accepted, further tests required for sub-classification (UN Divisions 1.1 to 1.6)

Summary

- Examine structures and groups prior to synthesis
- Conduct predictive calculations
- Conduct small scale thermal screening and then sensitivity tests (impact / friction)
- UN test strategy generally considered to be the most complete and coherent
- Special precautions are required for handing explosive compounds (for chemical processing, generally try to handle in diluted / phlegmatised state throughout)

Questions

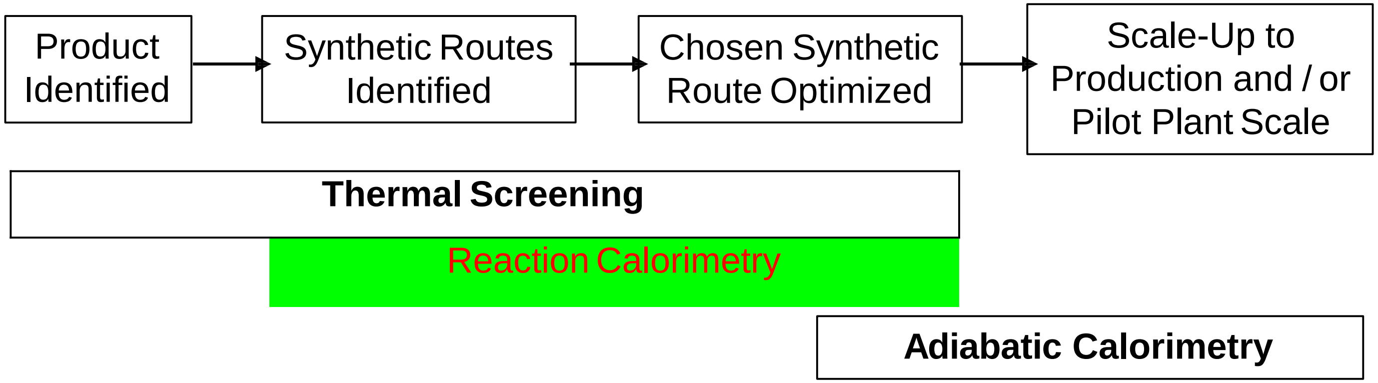
1. The oxygen balance will always highlight potentially explosive compounds. True / False
2. CHETAH predictions are as accurate as reaction calorimetry? True / False
3. CHETAH predictions are based on liquid phase heat of formation data? True / False

Reaction Characterization through Calorimetry
(A Fundamental Ingredient for Safe Processing)

Contents

- Applications of reaction calorimetry
- Techniques available for characterizing the normal process
- Overview of data that can be attained
- Interpretation of data
- An example

Where Does Reaction Calorimetry Feature in Assessing Process Safety?



Product Identified → Synthetic Routes Identified → Chosen Synthetic Route Optimized → Scale-Up to Production and / or Pilot Plant Scale

Thermal Screening

Reaction Calorimetry

Adiabatic Calorimetry

Reaction calorimetry data should be available before large scale processing is conducted. It provides the essential baseline heat flow data to establish safe (normal) processing conditions.

Applications of Reaction Calorimetry

- Reaction calorimetry is designed to characterize the thermodynamics (and kinetics) of a chemical reaction under conditions that are to be used during normal processing.

- Generally, this entails :
  - Semi-batch reactions (although batch and continuous reactions can be studied).
  - Mobile reaction solutions (heterogeneous reactions can be assessed but not solids / highly viscous media).
  - Predominantly safety related but is used extensively for process development / optimization.

Techniques Available for Reaction Calorimetry

- Available techniques include :
  - Secondary Heat Transfer / Heat Flow Calorimetry
  - Power Compensation Calorimetry

- Applicable to batch and semi-batch reactions. Processes may be operated under the following conditions:
  - Isothermal (constant reaction mass temperature)
  - Isoperibolic (constant coolant temperature)
  - Adiabatic (no forced heat removal)
    - ➢not discussed further in this presentation.

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Heat Flow Calorimetry

- Commercially available methods include :
  - Mettler Toledo RC1 reaction calorimeter
  - ChemiSens range of calorimeters
  - HEL Simular
  - Setaram DRC (Differential Reaction Calorimeter)
  - Others…

- Measurement based on basic equation $Q = U.A.\Delta T$.

Mettler Toledo RC1

Thermostatic Jacket Fluid

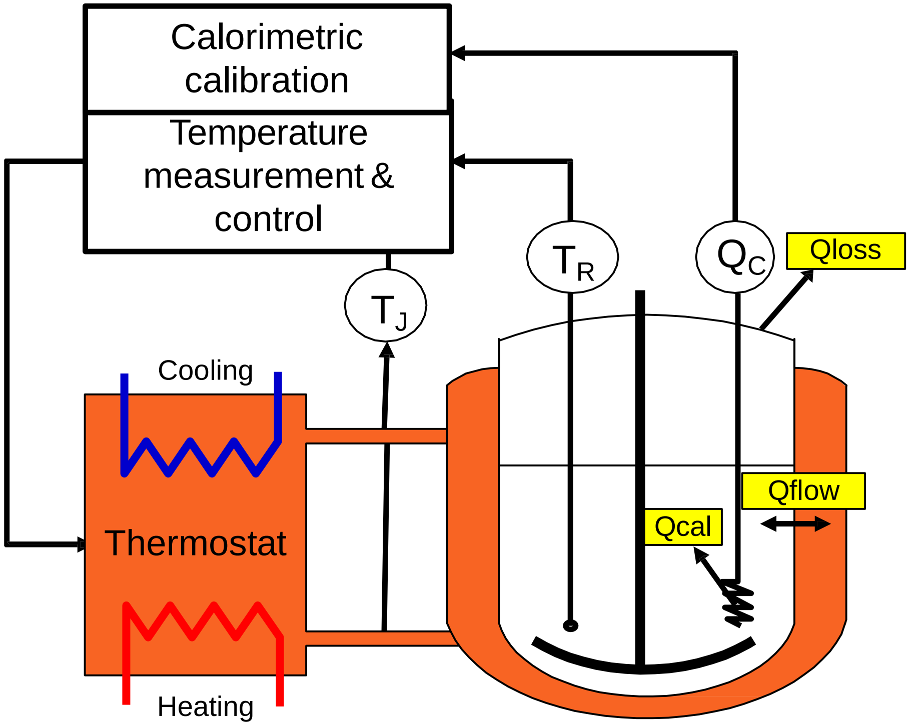
Reflux Calorimeter (optional)

Jacketed reactor

Dosing balances and controllers

Photo reproduced courtesy of Mettler Toledo Ltd.

Heat Flow Calorimetry



$$Q_r = Q_f + Q_a + Q_d + Q_l$$

Where:

Q_f = Reaction heat flow

Q_d = Heat flow through dosing

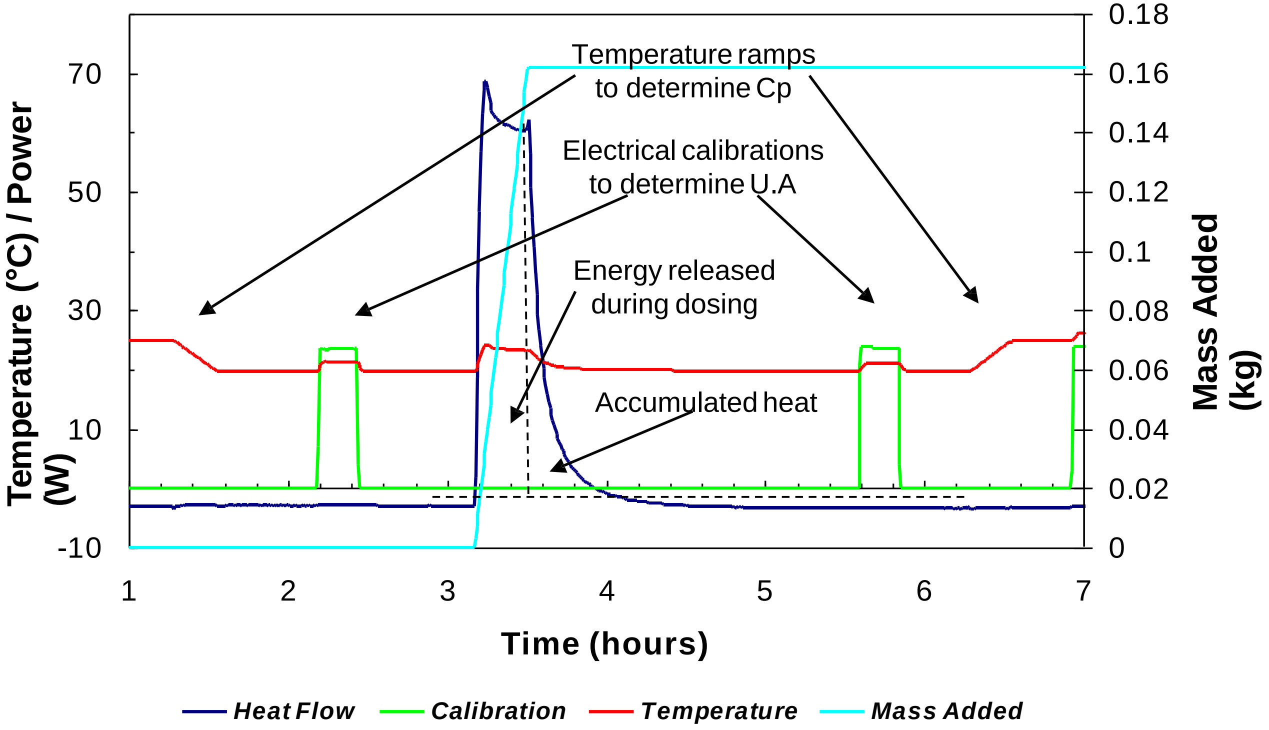
Q_l = Heat Losses

Q_a = Accumulated heat

Method of Heat Flow Calorimetry

- Conduct initial and final electrical calibrations
  - enables determination of U.A before and after reaction
- Conduct initial and final temperature ramps
  - allows determination of heat capacity before and after reaction
- Conduct batch or semi-batch addition according to prescribed process conditions.

Data Analysis
Acid Catalyzed Methanol / Acetic Anhydride Reaction



Data Obtained from Reaction Calorimetry

Reactant Name	Mass Used (g)	Mol. Wt (g.mol^{-1})	Moles used (mol)
Methanol	396	32.0	12.38
Acetic anhydride	162	102	1.588

Version of WINRC used for evaluation	6.20	
Type of baseline	Integral	
Calculated Cp during reaction	2252	J.kg^{-1}.K^{-1}
Calculated U value at start of reaction (1st calibration)	119	W.m^{-2}.K^{-1}
Calculated U value at end of reaction (2nd calibration)	112	W.m^{-2}.K^{-1}
Calculated Δ H	101.8	kJ
Total mass of reactants	0.563	kg
Heat of reaction	64.1	kJ.mol^{-1} (of acetic anhydride)
Calculated Δ H after addition	26.0	kJ
Extent of accumulation	25.5	%
Adiabatic temperature rise	80.3	K
Peak heat flow	122.6	W.kg^{-1}

What can we say about the reaction?

- Sufficient heat generated to reach boiling conditions
  - process controls or pressure relief required

- Predominantly feed rate controlled although accumulation equates to 25%.

- No significant change in viscosity (U values similar before and after reaction R_{int})

- No dramatic changes in heat flow during addition.

Interpretation of Data

- Kinetic data can be defined simplistically or formally
  - using secondary software / analysis packages
  - BatchCad™, Batch Reactor, CISP software, etc.

- Main data generated :
  - heat of reaction (ΔHr)
  - extent of reactant accumulation
  - adiabatic temperature rise (ignoring side reactions)
  - power output (for defining cooling requirements)
  - changes in physical characteristics (viscosity, etc)
  - gas generation (using ancillary equipment)
  - species formation / disappearance (using ancillary equipment – FTIR, etc.).

What do you do with the data?

- Safety decisions can be made regarding the potential for reaction mass to reach:
  - ☞boiling conditions
  - ☞decomposition / secondary reaction conditions

- Define cooling requirements for plant

- Accumulation must be minimized. If necessary, investigate the use of :
  - ☞higher temperatures,
  - ☞catalysts,
  - ☞longer feed duration, etc.

- Yields / productivity can be optimized.

Recent Advances In Reaction Calorimetry

- More advanced in-situ monitoring equipment
  - in process FTIR / Raman IR spectroscopy

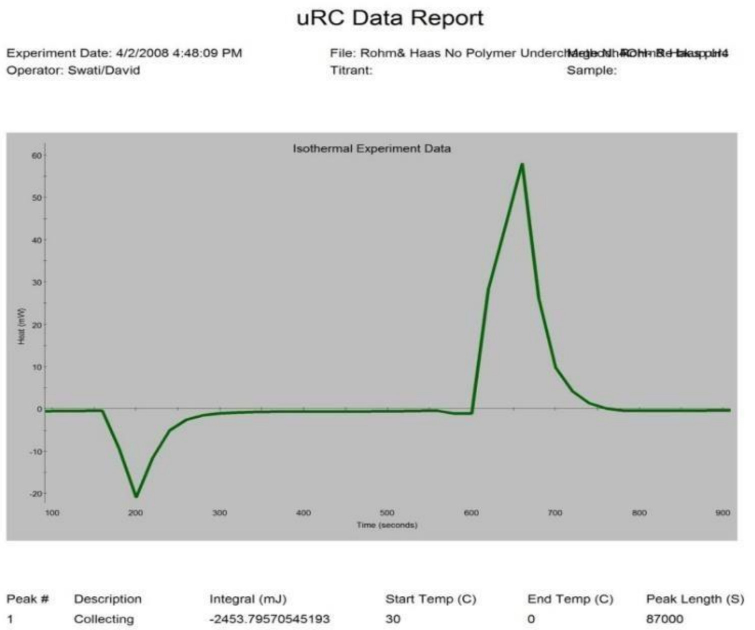
- Improvements in accuracy
  - development of Real Time Calibration (RTCal) for continuous U.A determination (Mettler RC1).
  - QuickCal options for rapid combined Cp and U.A determination (Mettler RC1).

- Commercially available power compensation calorimetry

- Increased range of conditions
  - High pressure reactors (up to 400 bar)
  - Low / High temperature systems (-70 to +300°C)

Micro-Reaction Calorimeter (μRC)

- Purpose: To determine thermodynamics and kinetics of reaction when conducted under isothermal conditions.
- Data: Heat flow vs time, energy of reaction.
- Sample Size: 1- 100 milligrams , μL
- Test Cell: Glass vials.
- Temperature Range: -10 to 200°C
- Pressure Range: No pressure data
- Notes:
  - Agitation rate up to 400 rpm
  - Shot additions of liquids at predetermined rate
  - Heat capacity measurement
  - Rapid results (ΔHr and Cp available)
  - Safe and easy to operate



uRC Data Report

Experiment Date: 4/2/2008 4:48:09 PM
Operator: Swati/David

File: Rohm& Haas No Polymer Underc[illegible]
Titrant:
Sample:

Peak #	Description	Integral (mJ)	Start Temp (C)	End Temp (C)	Peak Length (S)
1	Collecting	-2453.79570545193	30	0	87000

Conclusions

- Understanding the “normal” process is a crucial stage of assessing the overall hazards of a chemical process.

- Reaction calorimetry should be conducted for EVERY process step involving a chemical reaction.

- Reaction calorimetry can be employed for “what if” studies, optimization and kinetic modeling studies.

- Many commercial units are available although simple DIY calorimeters can be developed at relatively low cost (e.g.. Dewar methods, isoperibolic calorimeters, etc).

Some Questions

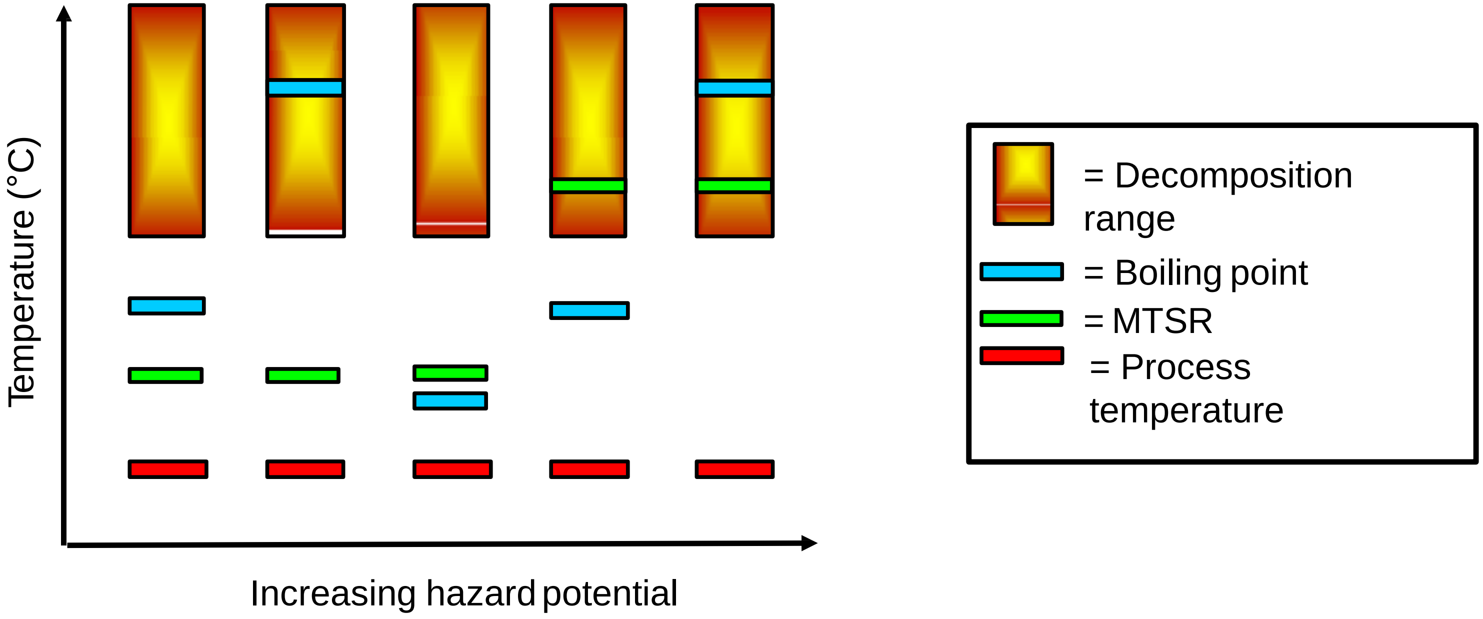
1. Isothermal calorimetry data can be used for vent sizing calculations. True / False
2. The U value for a production vessel will typically be higher than for an RC1 calorimeter. True / False
3. If a reaction mixture becomes more viscous, the U value of the vessel will go – Up or Down?
4. You can measure kinetic parameters from reaction calorimetry data True / False
5. Accumulation is caused by:
   - Process temperature too high? Yes / No
   - Inhibiting species present? Yes / No
   - Feeding reagent too fast? Yes / No
6. Catalysts reduce the heat of reaction True / False

Characterization of Thermal Runaway Reactions using Adiabatic Calorimetry

When is Adiabatic Calorimetry Required?

- Adiabatic calorimetry is required when:
  - Batch processing techniques are used
  - The consequence of a process deviation is unknown (but expected to be significant) and cannot easily be determined through modeling
  - Reaction characterization indicates significant accumulation
  - Vent sizing data is required for a runaway reaction (or specification of other protection systems)

Potential Scenarios Applicable To Batch And Semi-Batch Processes



▨ = Decomposition range
🟦 = Boiling point
🟩 = MTSR
🟥 = Process temperature

Adiabatic Calorimetry

- Used to assess the runaway reaction kinetics in terms of temperature, pressure and time.

- Test apparatus is designed to be :

  →Low Phi Factor (close to 1.00)

  →Low Heat loss (adiabatic environment)

- Data used for :

  →calculating cooling rates required to control runaway at any temperature

  →calculating time to maximum rate data

  →assessing thermal stability during high temperature storage and different sizes of vessels/storage containers

  →collecting data for vent sizing

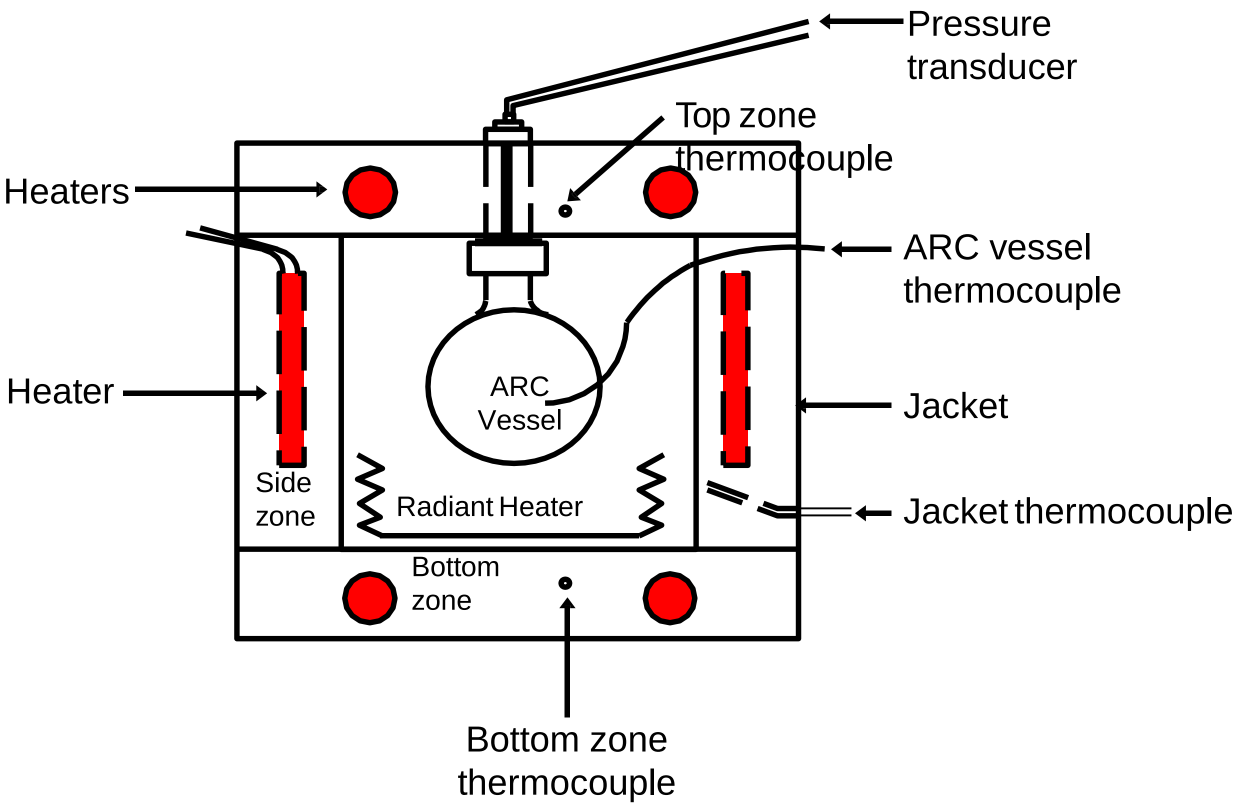
Types of Adiabatic Calorimeter

- Pressure Resistant Adiabatic Calorimeters
  - Accelerating Rate Calorimetry (ARC)
  - Adiabatic Pressure Dewar Calorimetry (ADC II)
- Pressure Compensated Adiabatic Calorimeters
  - Vent Sizing Package (VSP II)
  - Advanced Pressure Tracking Adiabatic Calorimeter (APTAC)
  - Phi Tec II
- Reaction calorimeters used in adiabatic mode
  - Mettler Toledo RC1 calorimeter

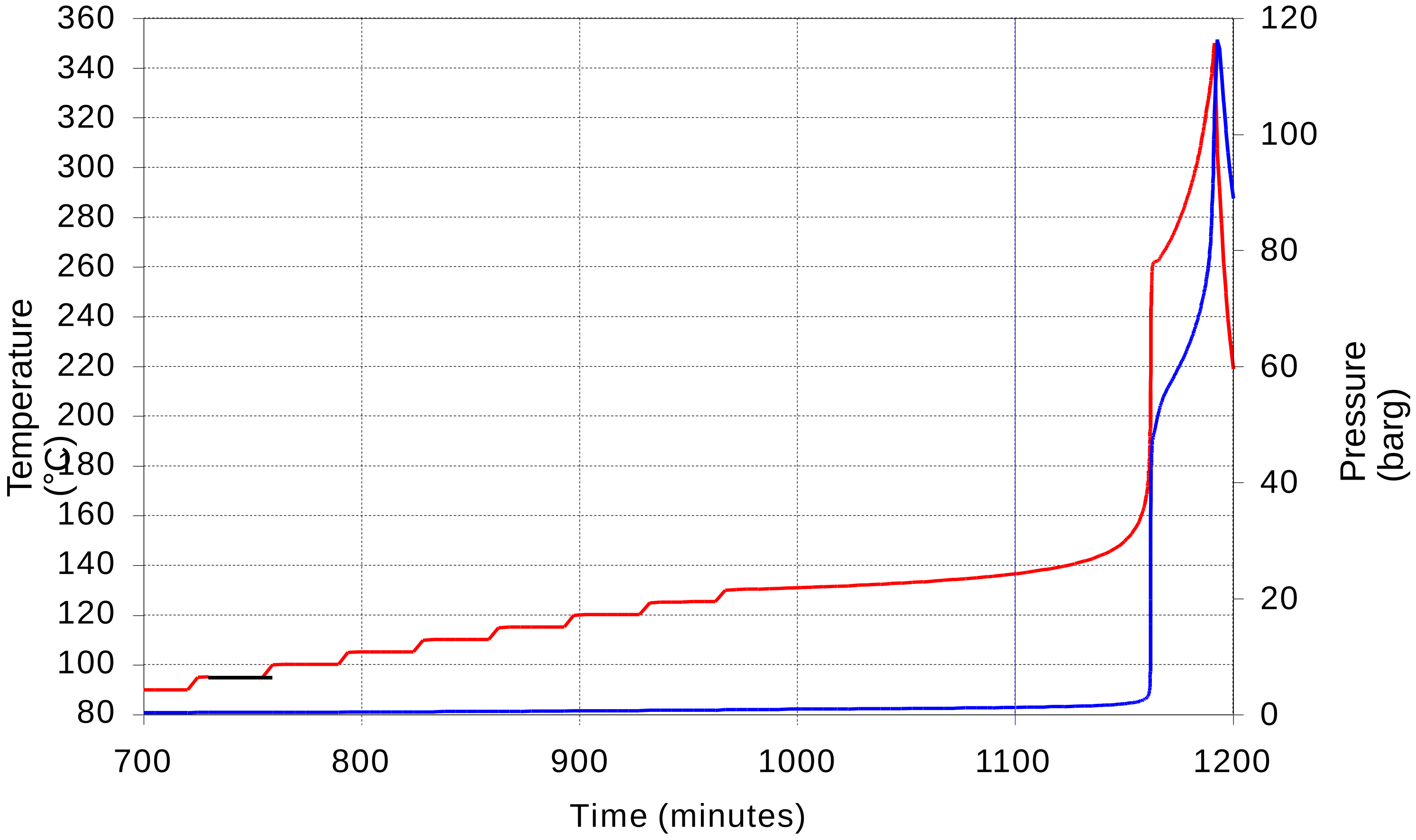
Accelerating Rate Calorimeter (ARC)

Photo reproduced courtesy of TIAX Inc.

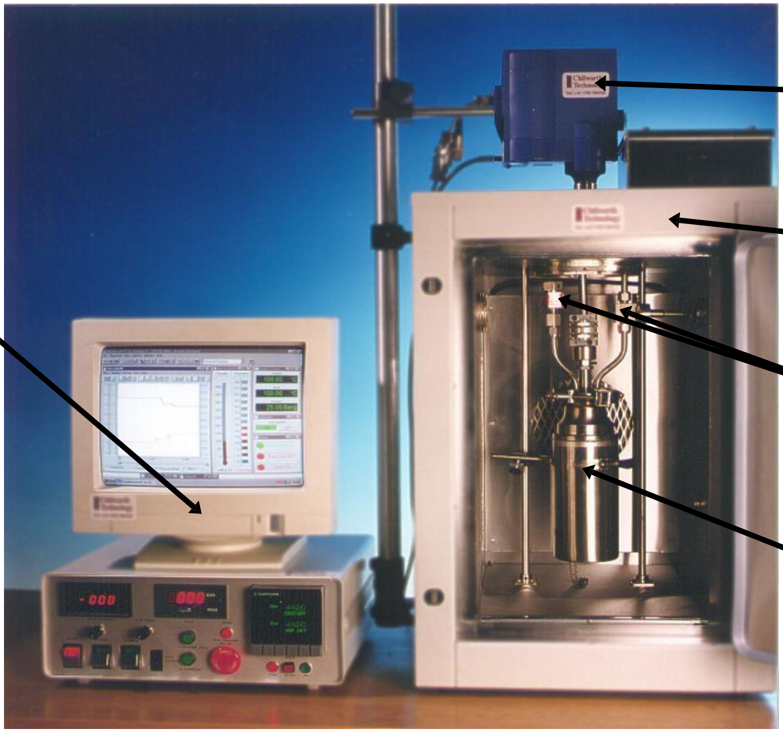
Accelerating Rate Calorimeter



ARC DATA
Sulfonoxy Ester Derivative



Adiabatic Dewar Calorimeter (ADC II)



PC Control and Data Logging System

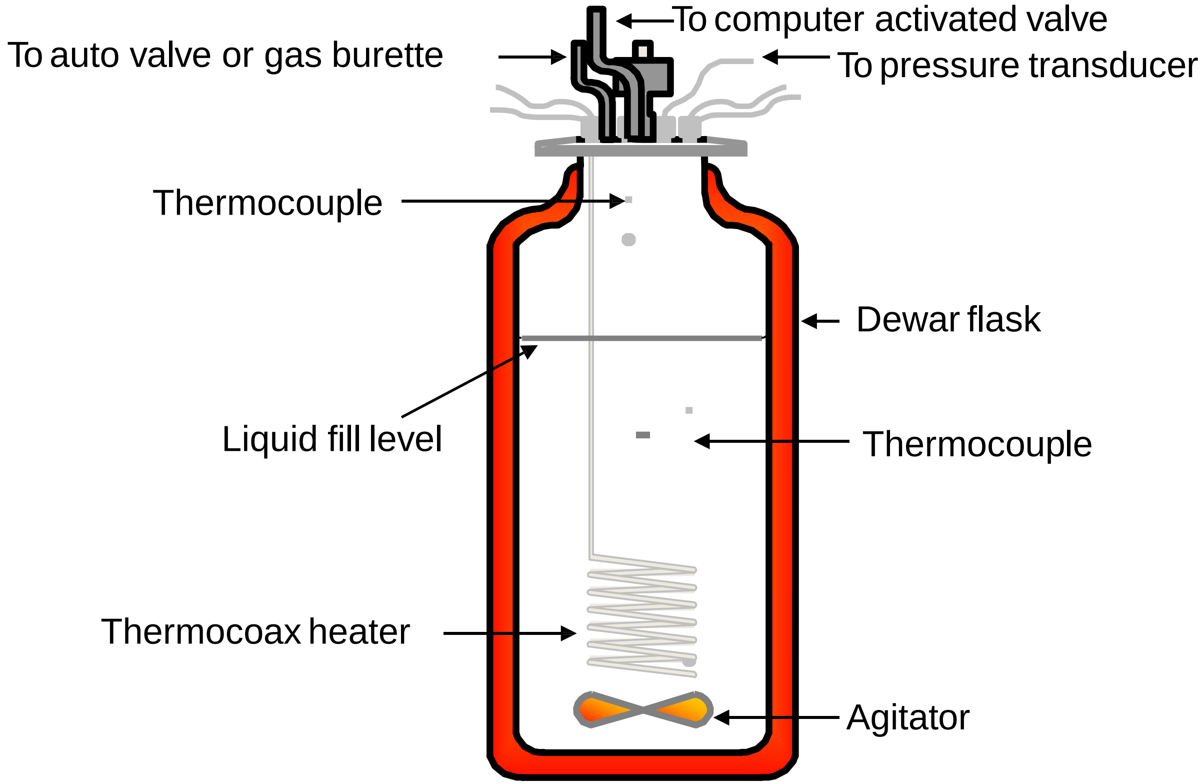
Stirrer Drive

Adiabatic Enclosure

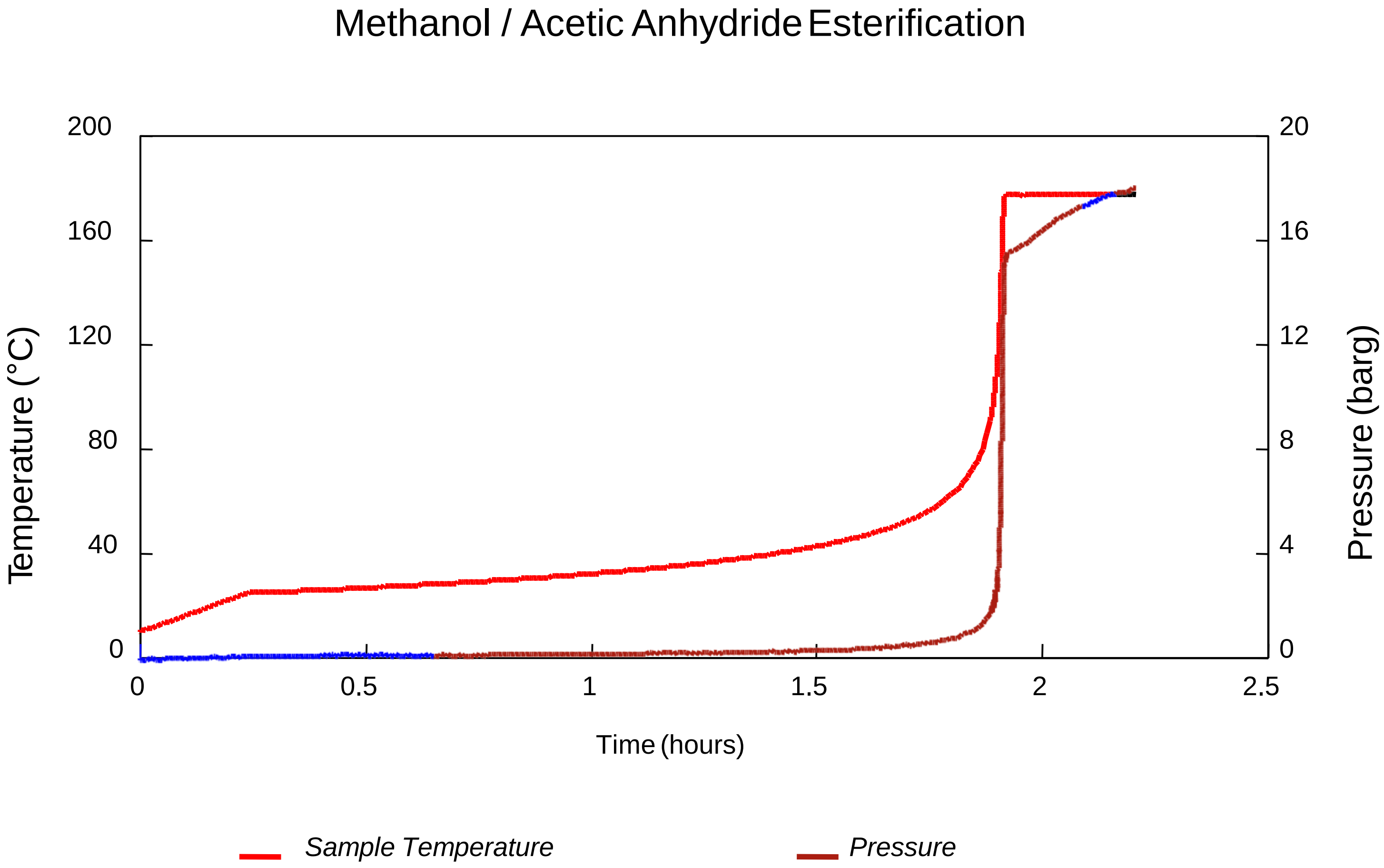
Safety Devices

Dewar Vessel

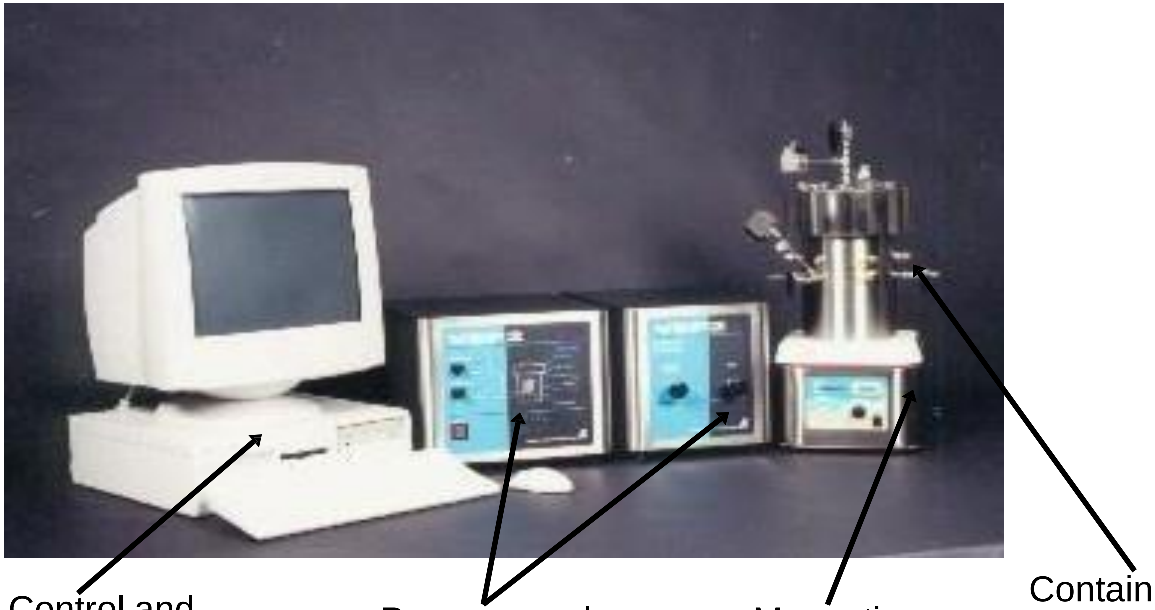
Adiabatic Dewar Calorimeter (ADC II)



Example Of Dewar Data



Pressure Compensated Adiabatic Calorimetry



PC Control and
Data Logging System

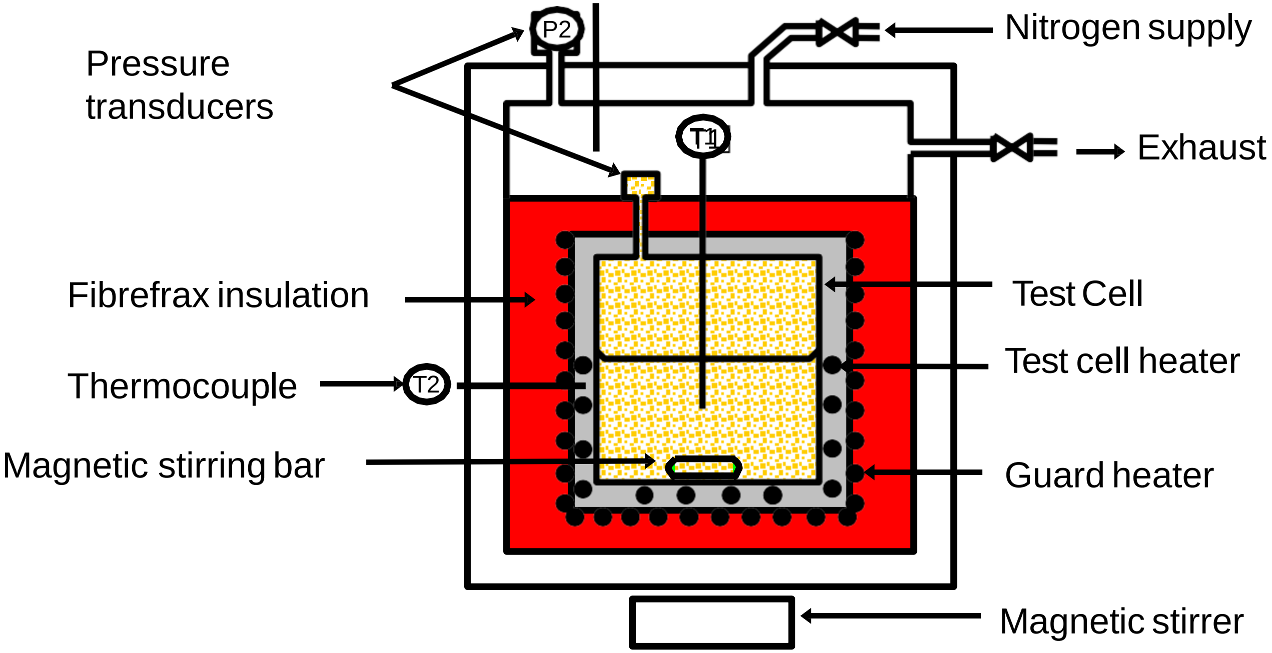
Pressure and
A/D controls

Magnetic
Stirrer drive

Containment
vessel

Photo reproduced courtesy of Fauske & Associates Inc.

Pressure Compensated Adiabatic Calorimetry



Examples include : Vent Sizing Package (VSP, VSPII), Phi-Tec II and APTAC

A Comparison Of Adiabatic Test Techniques

	Adiabatic Pressure Dewar Calorimeter	Pressure Compensated Calorimeters	Accelerating Rate Calorimeter
Minimum Phi	1.05	1.05	1.5
Energy Content	A	A	A
Onset Temperature	A	A	A
Time to Maximum Rate	A	A	B
Vessel Size	1000 ml	120 ml	10 ml
System and flow Characterization	A	A	X
Maximum Pressure	35 barg	140 barg	140 barg
Stirring	Mechanical	Magnetic (can be mechanical but increases phi)	None normally (magnetic possible)
Remote Addition	A	B	X

A = Good, B = Can be adapted, X = Not possible

Data derived from Tharmalingham, S, "Assessing Runaway Reactions and Sizing Vents", The Chemical Engineer (IChemE), August 1989.

Summary

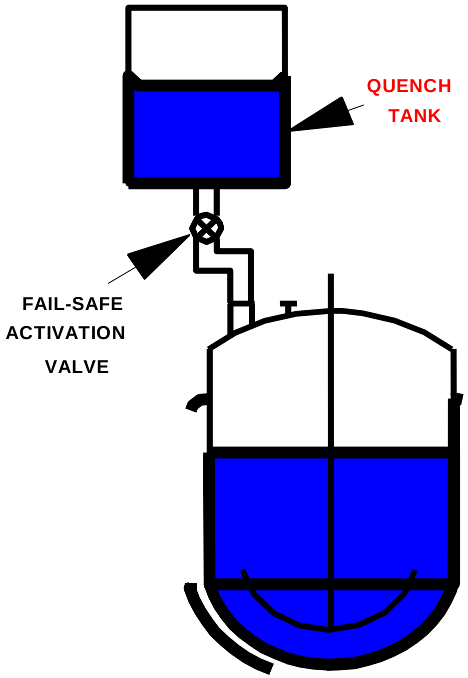
- **When interpreting laboratory data, the following aspects should be considered:**
  - Phi factor (i.e.. sample size)
  - Heat loss (is the test adiabatic)
  - Availability of air (important for powders)
  - Mode of test (ramped, heat-wait-search, isothermal storage)

The aim of the thermal analyst is to provide data and (more importantly) interpretation of such data to enable the specification of plant safety measures

Some Questions

1. You can measure heat of reaction in an adiabatic calorimeter True / False
2. A high boiling solvent is always safer than a low boiler True / False
3. ARC data can be used for vent sizing Sometimes / Always / Never
4. Runaway reaction vent sizing data should be obtained in adiabatic calorimeters Sometimes / Always / Never
5. Adiabatic calorimeters can have high atmospheric heat losses True / False

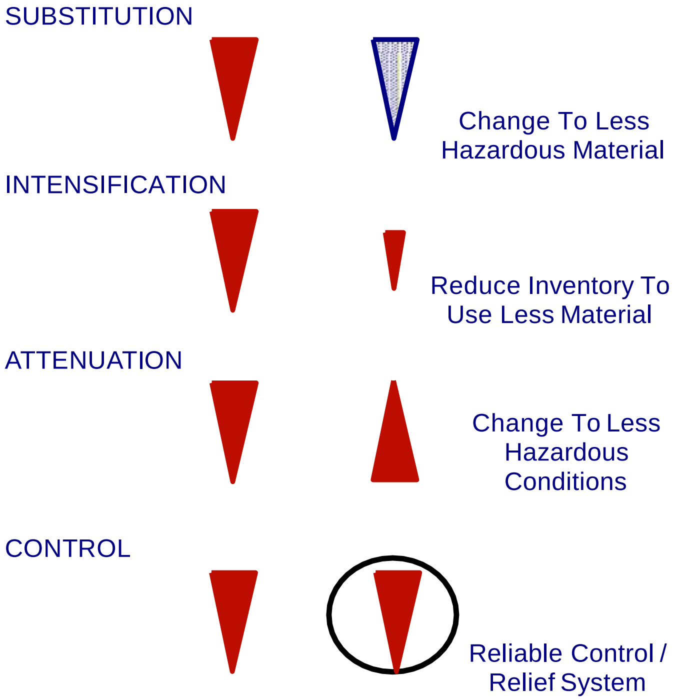
SAFETY MEASURE SELECTION



SAFETY MEASURE SELECTION

- **INHERENT SAFETY**
- **PROCESS CONTROL**
- Process Control plus **CONTAINMENT**
- Process Control plus **CRASH COOLING**
- Process Control plus **QUENCHING / DROWN- OUT / DUMPING**
- Process Control plus **REACTION INHIBITION**
- Process Control plus **REACTOR VENTING**

INHERENT SAFETY



SUBSTITUTION

Change To Less Hazardous Material

INTENSIFICATION

Reduce Inventory To Use Less Material

ATTENUATION

Change To Less Hazardous Conditions

CONTROL

Reliable Control / Relief System

INHERENT SAFETY

- “Selecting a process or synthetic route which, by virtue of its design, does not produce a hazard should a maloperation occur”

- TRADITIONAL APPROACH: Reduce Inventory or switch to non-flammable/non-hazardous substances

- PHYSICAL APPROACH: Total process control using suitable safety devices

- CHEMICAL APPROACH: Different synthetic routes considering thermal stability properties of intermediates, reactants, catalysts etc.

INHERENT SAFETY- EXAMPLE

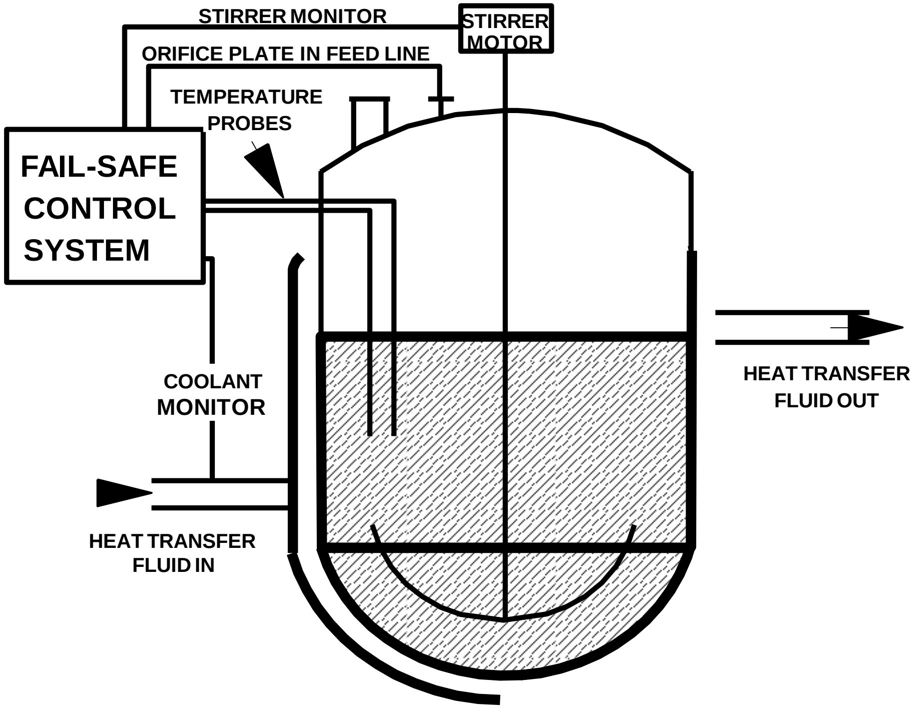
- Seveso
  - 300 °C steam was used to heat reaction mass up to 160 °C
  - incident happened when a batch was overheated initiating a decomposition that began at 185 °C
  - steam at <180 °C would have prevented this

PROCESS CONTROL

- Total process control is a situation whereby the process is controlled in such a manner that the conditions required for an uncontrollable exothermic event cannot be attained
- Information required
  - optimum process conditions
  - onset temperature of undesirable event
  - temperature below which reactant accumulation occurs

- Safety measures may include, among others
  - orifice plate in addition line
  - interlocks / cut-outs etc
  - fail-safe coolant supply

PROCESS CONTROL

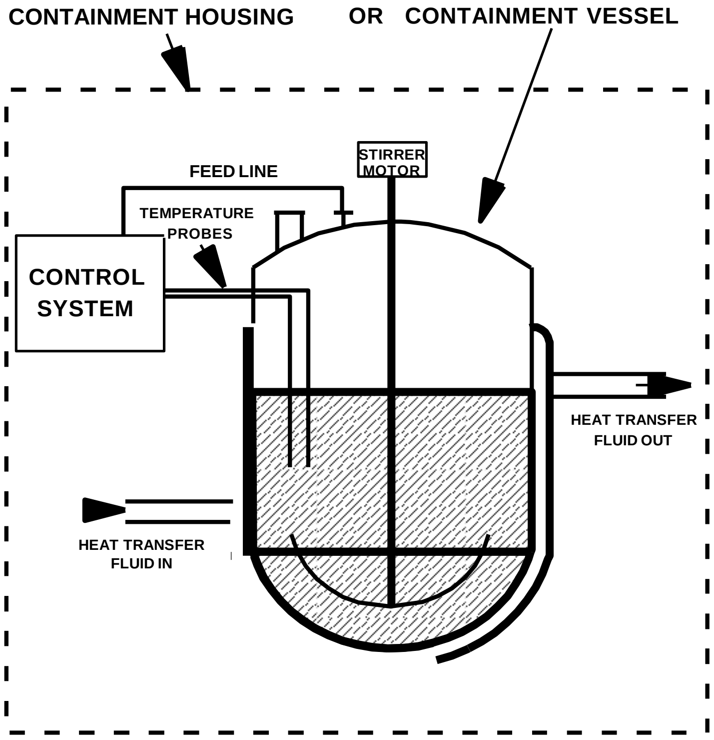


PROCESS CONTROL PLUS CONTAINMENT

- Process control is used to control the reaction under normal operating conditions
- Additionally, when a runaway reaction is initiated due to maloperation, the vessel is designed to withstand the peak pressure
- Experimentation
  - based on worst case scenario
  - accurate definition of maximum pressure
  - conducted under plant heat-loss conditions
- Safety measures
- build vessel with design pressure above the maximum runaway pressure

PSCI
PHARMACEUTICAL
SUPPLY CHAIN
INITIATIVE

PROCESS CONTROL PLUS CONTAINMENT



PROCESS CONTROL PLUS CRASH COOLING

Process control measures are used to control the reaction under normal operating conditions Additionally, when a runaway reaction is initiated due to a maloperation, the vessel is protected by emergency cooling facilities

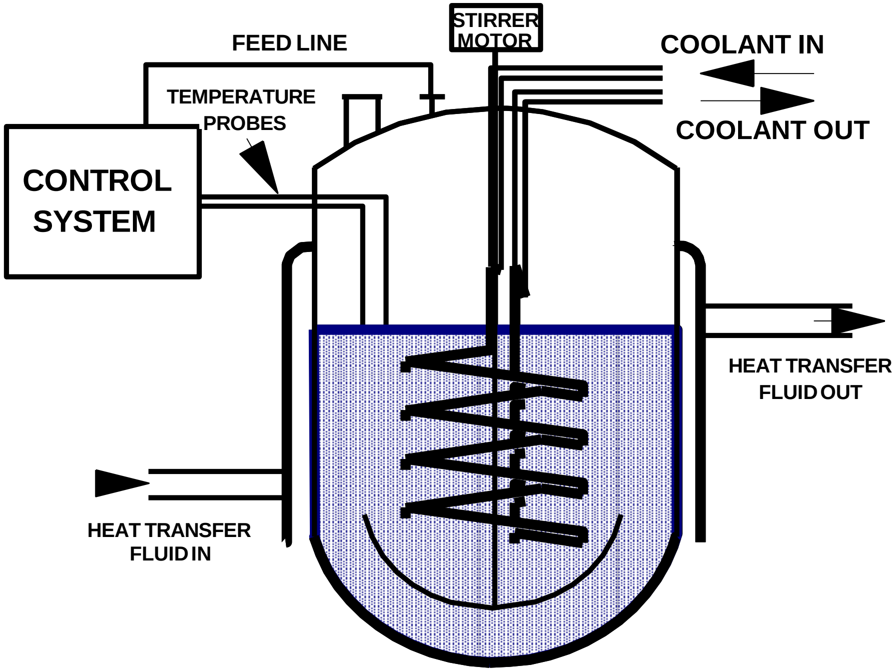
EXPERIMENTATION:

- based on ‘worst case scenario’
- accurate definition of power output profile
- conducted under plant heat-loss conditions
- defines the time to hazardous pressure
- used to calculate desired cooling rate

SAFETY MEASURES:

- select suitable cooling system (coils/jacket)
- select cooling medium (usually water)
- design runaway detection system that will activate the cooling system

PROCESS CONTROL PLUS CRASH COOLING



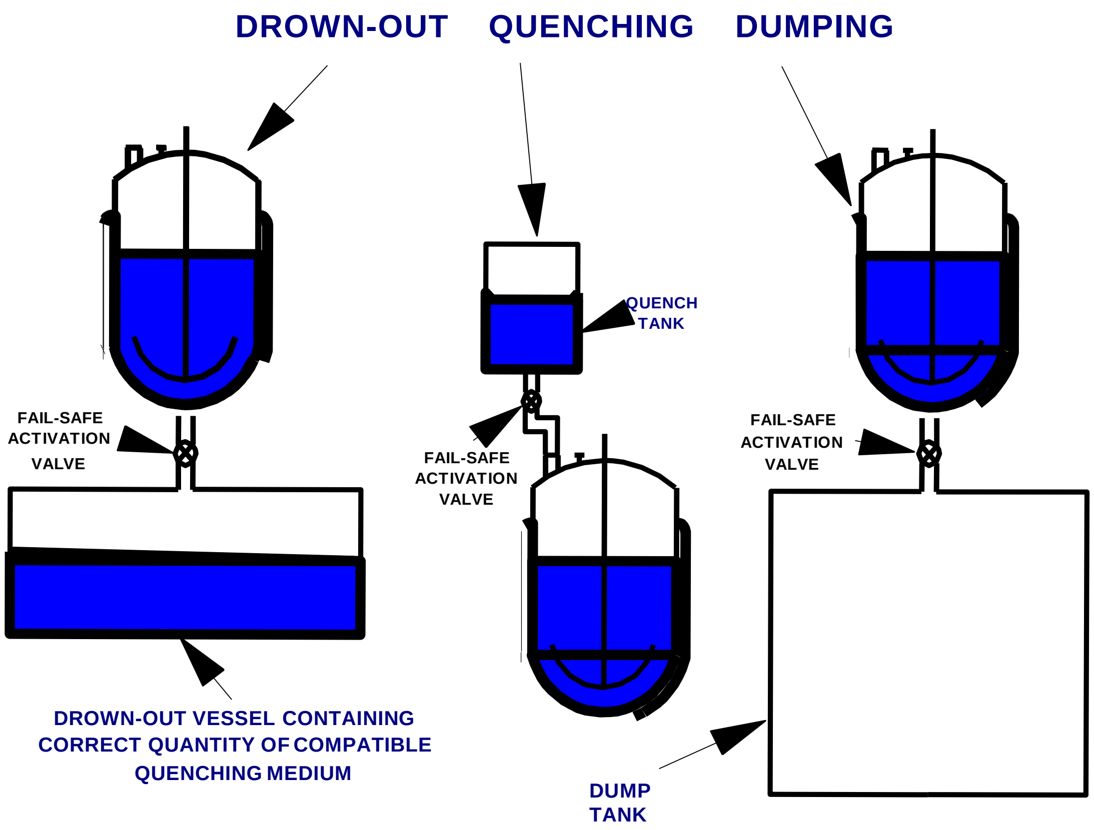
PROCESS CONTROL PLUS QUENCHING / DUMPING / DROWN-OUT

Process control measures are used to control the reaction under normal operating conditions

Additionally, when a runaway reaction is initiated due to a maloperation, the vessel is protected by emergency facilities capable of either

- QUENCHING the rapid reaction by the addition of cold diluent
- DROWNING-OUT the reaction by transferring to a vessel containing cold diluent
- DUMPING the reaction mass into a large vessel hence reducing the temperature and providing a large ullage space to reduce the pressure

PROCESS CONTROL PLUS QUENCHING / DUMPING / DROWN-OUT



DROWN-OUT

QUENCHING

DUMPING

QUENCH TANK

FAIL-SAFE ACTIVATION VALVE

FAIL-SAFE ACTIVATION VALVE

FAIL-SAFE ACTIVATION VALVE

DROWN-OUT VESSEL CONTAINING CORRECT QUANTITY OF COMPATIBLE QUENCHING MEDIUM

DUMP TANK

PROCESS CONTROL PLUS REACTION INHIBITION

Process control measures are used to control the reaction under normal operating conditions

Additionally, when a runaway reaction is initiated due to a maloperation, the vessel is protected by emergency inhibition 'bombs' which chemically quench the runaway reaction.

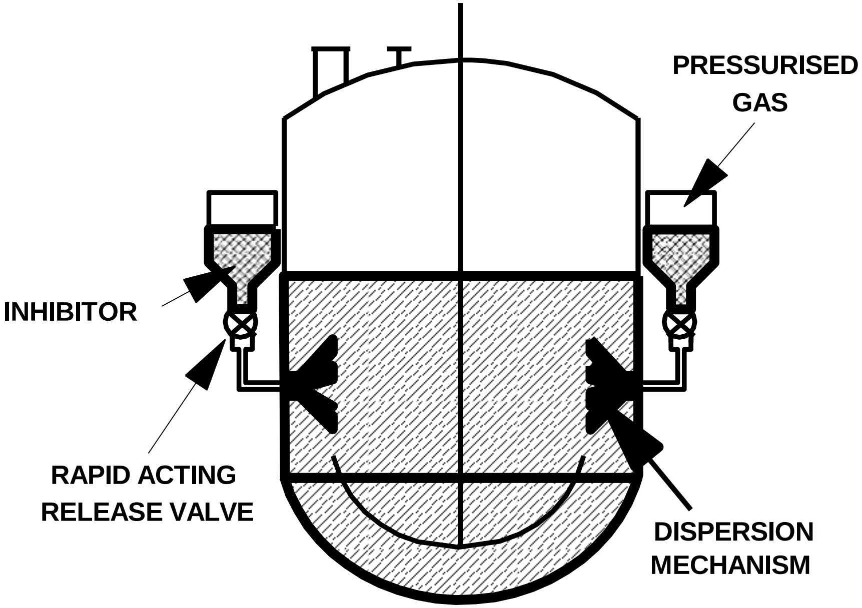
EXPERIMENTATION:

- based on 'worst case scenario'
- evaluates most efficient inhibitor
- conducted under plant heat-loss conditions
- evaluates optimum injection conditions
- determines point of injection

SAFETY MEASURES:

- design an inhibition system to give the required dispersion and install high integrity detection system which activate injection at the required rate.

PROCESS CONTROL PLUS REACTION INHIBITION



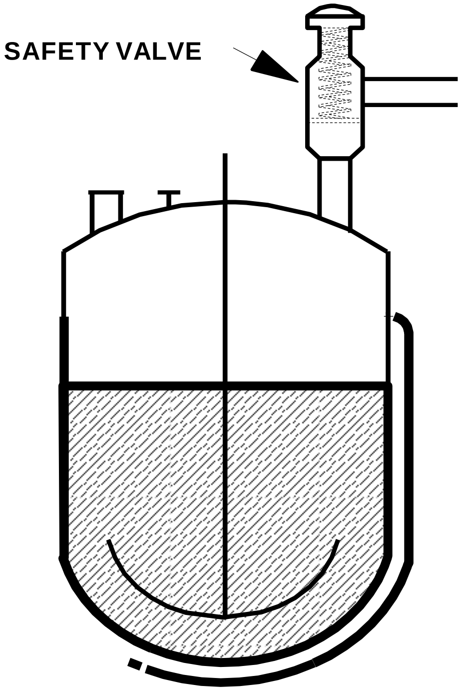
PROCESS CONTROL PLUS REACTOR VENTING

- Process control is used to control the reaction under normal operating conditions

- Additionally, when a runaway reaction is initiated due to a maloperation, the vessel is protected by an emergency relief vent

- Experimentation
  - based on worst case scenario
  - defines reaction kinetics and T-P relationship
  - conducted under plant heat-loss conditions
  - evaluates the discharge type (e.g. two phase)
  - provides data for sizing adequate vent

PROCESS CONTROL PLUS REACTOR VENTING



TECHNICAL CONSIDERATIONS

- Is engineering prohibitively difficult?
- Would maintenance cause prohibitively long shut-down periods?
- Is the system a feasible economic proposition?
- Will plant personnel understand the safety system and will they be able to take corrective actions safely without inadvertently impairing the operation of the system?
- Can modifications be made easily following modifications to the process?

Summary

In order to minimize the risk of an adverse reaction (thermal runaway reaction), ensure the following occur:

- Have a clear understanding of the chemistry by developing a balanced chemical equation for the product substrate and by products for the desired reaction(s). Quantify the heat of reaction for the desired reaction(s) and evolved gas rate.
- Develop a proper engineering design to allow for adequate heat transfer for the scaled-up up process.
- Ensure adequate control systems, safety back-up systems, and properly sized emergency relief systems including process vent capacity.
- The batch instructions must be comprehensive and easy to understand; the operators must be properly trained on the process.

Problems

Contact:

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Email: safety-usa@chilworthglobal.com
Website: www.chilworth.com

PROCESS SAFETY SOLUTION AREA

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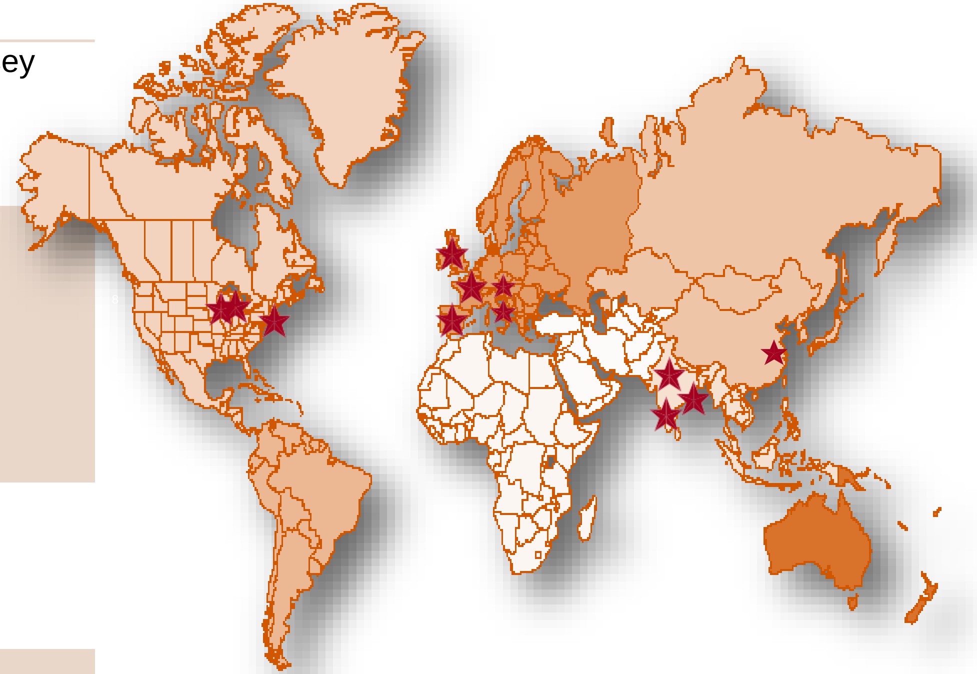
Phone 609 799 4449
Web www.Dekrainsight.Com

Legacy Chilworth Technology - *An Overview*

- Leading provider of **specialist process safety services** in the world - since 1986
- Over 150 staff including engineering professionals, scientists and laboratory technicians with specialist process safety expertise
- Objective, practical advice
- Chilworth Technology was acquired by **DEKRA SE** in July 2011

DEKRA Insight - Process Safety Centers of Excellence

North America	• Princeton, New Jersey
	• Chicago, Illinois
	• Forreston, Illinois
Europe	• United Kingdom
	• Spain
	• France
	• Italy
	• Netherlands
India	• New Delhi
	• Mumbai
	• Hyderabad
China	• Shanghai



Process Safety - Definition

- **Process Safety - ** The prevention and control of fires, explosions, and accidental chemical releases in chemical & process industries
- Such incidents may result in serious injury, property damage, lost production, and environmental impact

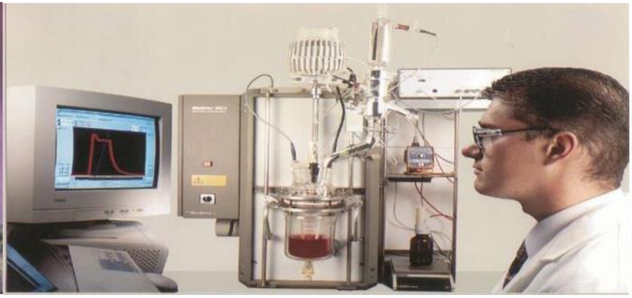
2015 - Warehouse Fire & Explosion, Tianjin, China
173 killed and 797 injured (*as of September 12th, 2015*)

2008 - Imperial Sugar, Georgia
14 Killed, > 40 injured

DEKRA Insight - Process Safety Business

- We help process industries avoid fire, explosion, and loss of containment events and improve performance.
- Combining specialist **process safety management (PSM)** and **process safety engineering** expertise, with generation and use of **process safety data** allows us to help our clients achieve the most **effective** and **practical** approaches to safe and **efficient** operations and processes, **globally**.

DEKRA Insight - Process Safety Portfolio


Consulting	Laboratory Testing	Competence Development
Process Safety Management - Program Implementation & Improvement - Gap Analysis - Process Hazard Analysis - Quantitative Risk Assessments - Consequence Modeling - Incident Investigations ***Process Safety Engineering*** - Dust Flash Fire & Explosion Hazards - Gas & Vapor Flammability Hazards - Electrostatic Hazards - Chemical Reaction Hazards	- Combustible Dust Fire & Explosion - Gas & Vapor Flammability - Thermal Instability - Chemical Reactivity - Static Electricity - DOT & UN Transportation of Hazardous Materials - Explosivity / Energetic Materials - Customized & Large-Scale Testing	- Courses Covering all Key Aspects of Process Safety - Continuing Education Units (CEU's) - Multiple Languages - Multimedia - Instructor-Led Content - Computer-Based Training

DEKRA Insight - Process Safety Client Industries

- Bulk & Fine Chemicals
- Agro-Chemical
- Energy / Power
- Food & Drink
- Flavor & Fragrance
- Machine/Equipment Mfg
- Government Agencies
- Engineering / Consultants
- Legal/Insurance/Risk

- Primary Metals & Machining
- Automotive & Aviation
- Personal & Household Products
- Oil & Petrochemical
- Pharmaceuticals
- Plastics & Rubber
- Pulp & Paper
- Wood / Forestry
- Consumer Electronics

Questions

THANK YOU