Process Safety in Pharmaceutical Industry

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Safety in Chemical Industry…!!!

"During the ten year period more than 600,000 chemical incidents occurred in the United States. Approximately 10,000 of those incidents were associated with at least one death or injury, and on average 256 people die each year as a result of known chemical incidents"

"Many chemical incidents that occurred over those last years have gone unreported. The actual number of chemical incidents may be much higher

Dr Paul L. Hill Jr

Chairman of US Chemical Safety and Hazard Investigation Board

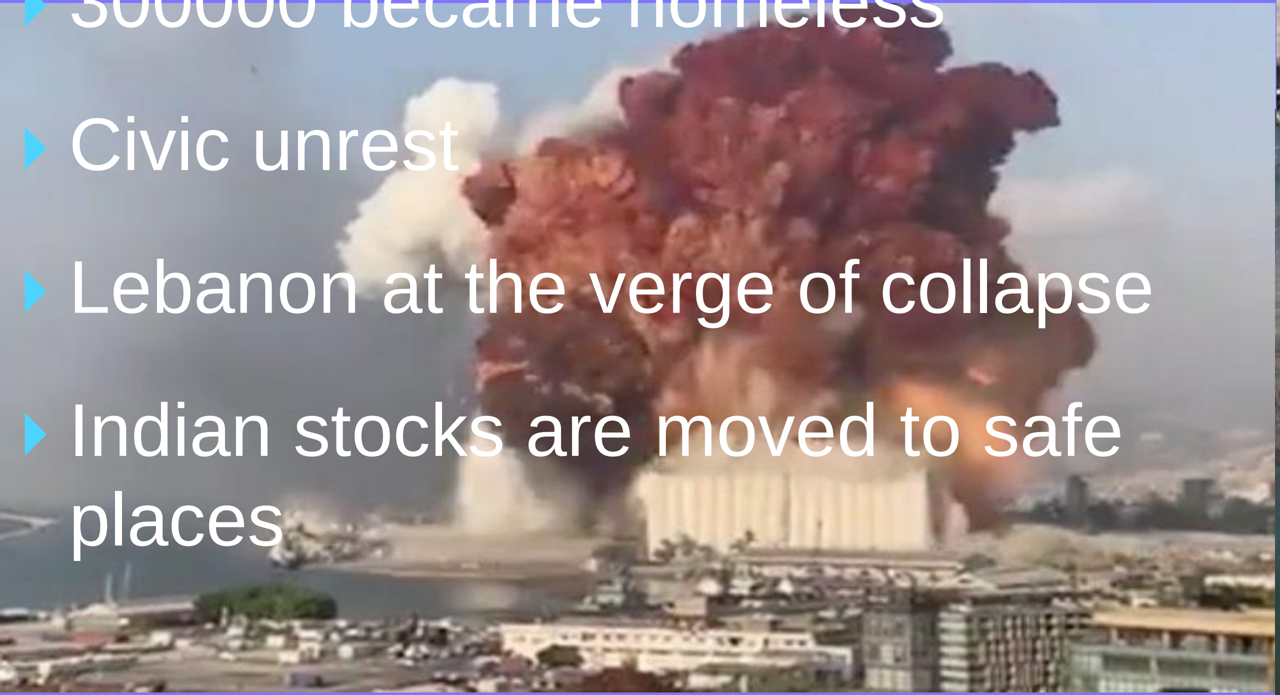
Accidents in Chemical Plants

- **Sheharbano Sangji (Sherri):** UCLA – 29th Dec 2008 while handling t-Butyl lithium
- ………… (Bollaram, 12th December 2020)
- ………….. (2016)
- … 2012
- …………….: Vizag Reactor blast – July 14th 2020
- …………………… Vizag: 29th June, 2020 gas leak
- …………………… – Haryana: 11th June 2019
- ....Mumbai – March, 2013
- ....Gujarat – August, 2012

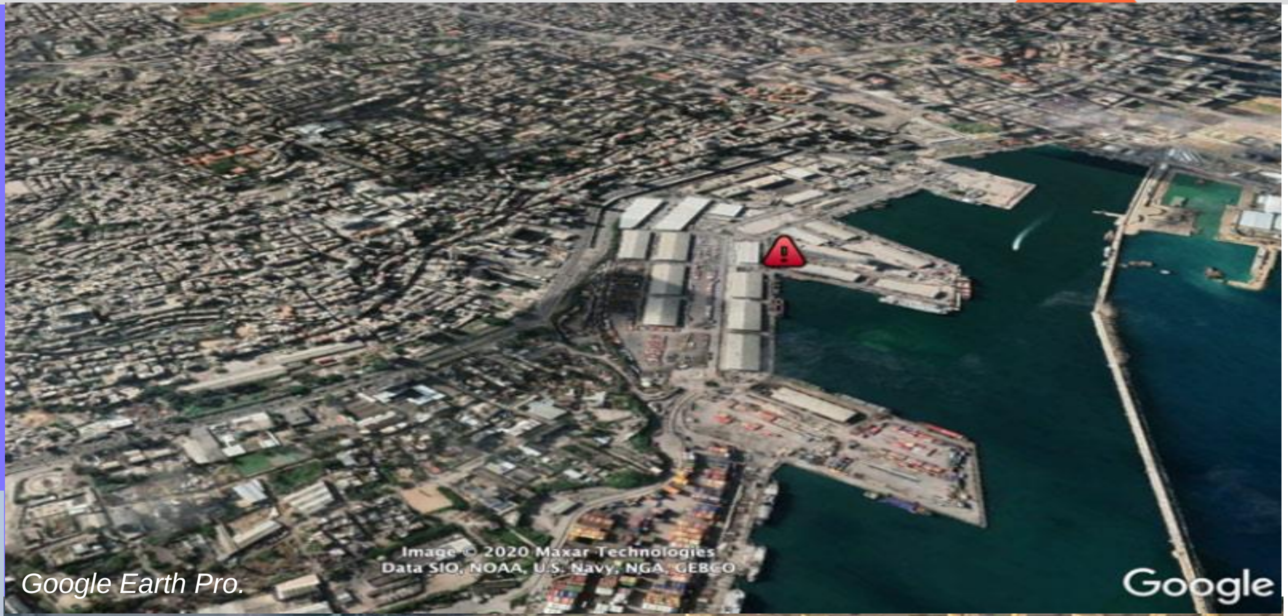
https://www.expresspharma.in/management-pharma/accident-analysis/

Beirut Explosion- 4th Aug 2020: No Lessons Learned

- 2700 tons of ammonium nitrate
- 180 people died
- 6000 injured
- 300000 became homeless
- Civic unrest
- Lebanon at the verge of collapse
- Indian stocks are moved to safe places



https://splash247.com/cypriot-police-interview-russian-at-centre-of-beirut-blast/



Google Earth Pro.

Indian Express.com

LG Polymers: India (7th May 2020)

- Styrene gas leaked from the storage tanks
- 11 people died
- 1000 people got impacted
- Auto polymerization
- Cooling systems failed
- Adequate reaction terminators were not available
- Timely intervention of experts and Govt agencies

https://www.huffingtonpost.in/entry/lg-polymers-vizag-gas-leak-investigation_in_5eb3dafcc5b652c5647334e2

Bhopal (India – 1984): Accident waiting to happen

- The world's worst chemical incident occurred on the night of 2–3 December
- **Cause** : water ingress into a large storage vessel of Methyl isocyanate (MIC). Resulting reaction caused heat/pressurisation and release of 41,000 kg MIC and its reaction products.
- **Result** : immediate death of ~4,000 and subsequent death of over 16,000, with life long injuries suffered by over 200,000.
- Site designated for commercial use & not hazardous industries. A Govt Official had ordered the removal of the MIC storage. The company held out until the official was transferred (and never moved the storage)!
- **Plant design/modification – Cost saving:** Allowed water ingress to MIC storage. There was no early warning systems, insufficient water deluge system, and scrubber design was inadequate/inoperable to cope with such a significant MIC release

https://www.worldofchemicals.com/72/chemistry-articles/bhopal-gas-disaster-dark-day-in-the-chemical-industry-history.html

Process Safety - Overview

What makes a chemical process dangerous ?

Chemical Reaction Hazards

- Uncontrolled exothermic reactions
- Thermal instability
- Uncontrolled gas generation

Operational Hazards

- Static electricity
- Dust cloud explosions
- Flammability

Actual Plant situation

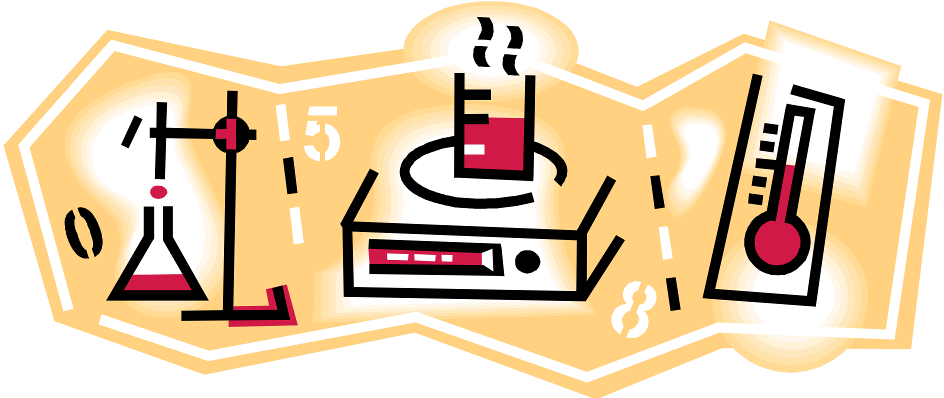
- Faulty equipment
- Improper SOP's
- Improperly trained personal

Runaway reactions, Fire and Explosions

Introduction to chemical reaction hazards

Major Causes for accidents

- Lack of understanding of Process Chemistry and Thermodynamics.
- Inadequate engineering design for heat transfer.
- Inadequate control and safety back-up systems.
- Inadequate operational procedures, including training.



Chemical Reaction Hazards: Runaway reactions

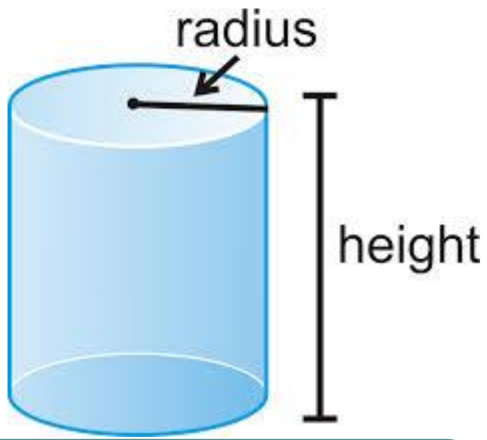
- **Run away reactions** result from uncontrolled chemical reactions.
- Heat generated by the reaction is >> the heat removed to the surroundings.
- Results in an **increase** in **temperature & the rate of reaction**
- **Increases** in the **rate** of heat generation
- Runaway reactions starts **slowly** but **accelerates**, results in **explosion**.

Why Accidents happen: Conti

Effect of Scale-Up: Heat Transfer

Heat production = f (volume) = f (r^3)

Heat removal = f (surface area) = f (r^2)



Volume= $\pi r^2 h$

<u>10 x scale-up:</u>

- Surface area : volume ratio reduced to 1/2
- Heat removal capability halved

Effect of Scale-Up: Heat Losses:(Liquids & No Active Cooling)

Typical time for batch at 60 °C to fall by 1 °C:

100 ml	15 seconds
50 liter	10 minutes
5,000 liter	1 hour
25,000 liter	> 4 hours

Chemical Reaction Hazards

- **Heat of Reaction** (Desired and decomposition reaction)
  - How much, how fast and whether the plant vessel can handle the rate.
- **Gas evolution** (Desired, decomposition reaction)
  - How much and how fast and whether the plant vessel can handle.
  - Vent Sizing, rupture discs, dump tanks
- **Thermal stability:**
  - Reagents, intermediates, reaction masses, distillation masses, waste streams, products.
  - At what temperature the above can decomposes.
- **Explosive screening:** Some of the compounds produced can have explosive properties.

Major causes of incidents & Accidents

Mischarging (21%)
- Addition of wrong materials
- Addition in wrong order
- Addition at wrong rate
- Addition of incorrect weight

Thermochemistry (20%)
- Poor appreciation of the Heat of Reaction
- Unknown thermal instability

Temperature Control (19%)
- Failure to maintain temperature
- Misreading the temperature
- Thermocouple incorrectly positioned
- Coolant failure

Maintenance (15%)
- Build-up of still residues
- Blockages
- Leaks
- Unauthorised modifications

Reactant Specification (9%)
- Variable raw material Specification
- Contamination

Other Factors (6%)
- Mainly human errors
- Not following procedures

Explosives

Explosibility: Definitions

- **Explosion:** The tendency of a chemical system to undergo violent decomposition
- **Deflagrating Explosion:** Propagation of a reaction at a velocity slower than the speed of sound
- **Detonating Explosion:** propagation of a reaction at a velocity faster than the speed of sound
  - Sound speed 343m/sec or 1235Km/hr
  - Measured in Mac
    - Eg: Rafale Fighter air craft speed is 1.8Mac (2222Km/hr)

Consequence of a Detonation

- Dangerous even in small quantities
  - **1 gram**: Serious injury to a person holding the explosive
  - **10 gram**: Very serious injury or may lead to death
  - **100 gram**: Almost certain death of persons in close proximity (e.g. holding the material)

Hazardous Chemicals Handbook by P. Carson & C. Mumford (pub.: Butterworth-Heinemann)

Hazard assessment

Scope:

- Stability of compound and mixtures
- Process as written
- Process under fault conditions (Eg: ‘What If studies’)

Steps:

- Desktop screening – literature, Oxygen Balance & expert knowledge
- Thermal screening
  - DSC, Carious Tube, Fall Hammer
- Reaction Calorimetry
- Adiabatic Calorimetry

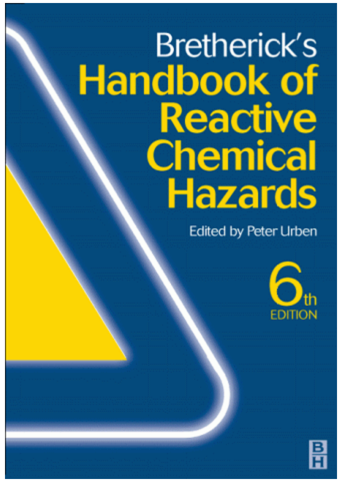
Chemical Screening Tests

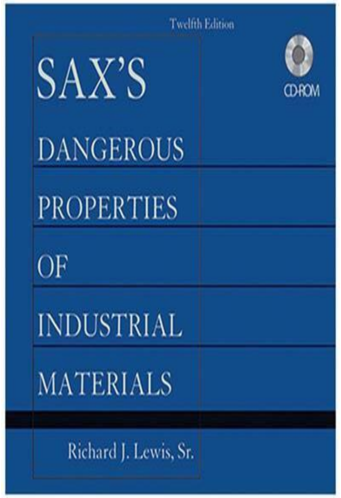
Thermal Stability Screening	Isothermal Calorimeter	Adiabatic Calorimeter	Potential Explosives	Gas Evolution
Carious Tube C80 DSC TSU Grewer Oven	Simular RC1 TAM II CPA	ARC Dewar Phi Tec II	DSC HR Carious Tube Fall Hammer Mini Autoclave	U Tube MKS Flow Controller MKS Flow Reader

There is no standard procedure that can be followed for all the reactions. The aim is to obtain sufficient data to assess the risks adequately.

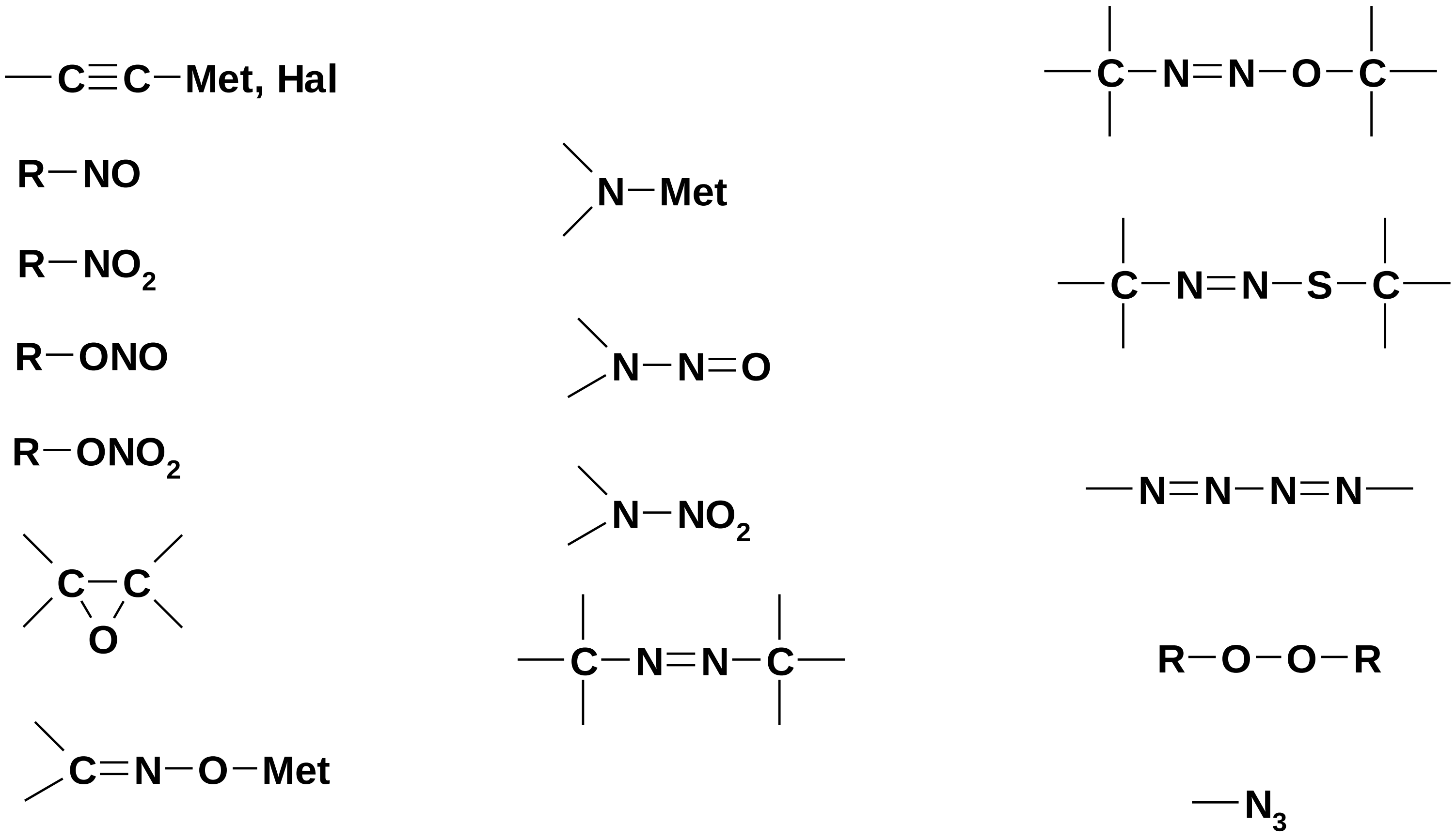
Desktop Screening: Literature

- **Bretherick's: Handbook**
  - **Handbook of Reactive Chemical Hazards**
- **Other sources:**
  - Chemical literature
  - Previous Incident/accident history
  - Chemists past experiences
  - Safety Data Sheets
  - Sax's Dangerous Properties of Industrial Materials
- Checking the enthalpies of the reactions in balanced reaction (ΔH)





Desktop Screening: Hazard Functional Groups



Desktop Screening: The Oxygen Balance

- Guide to the behaviour of an organic compound to decompose, deflagrate or detonate
- Compounds containing groups such as nitro, nitrate, chlorate or peroxy
- Almost all recognised detonation substances have an OB between +40 and -100

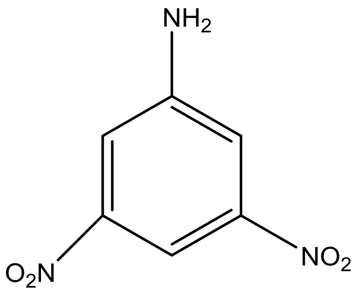
$C_XH_YO_Z$:

$$OB = \frac{-1600 \cdot (2x + y/2 - z)}{\text{molecular mass}}$$

Oxygen-Balance	Hazard Ranking
More positive than +160	Low
+160 to +80	Medium
+80 to -120	High
-120 to -240	Medium
More negative than -240	Low

Oxygen Balance

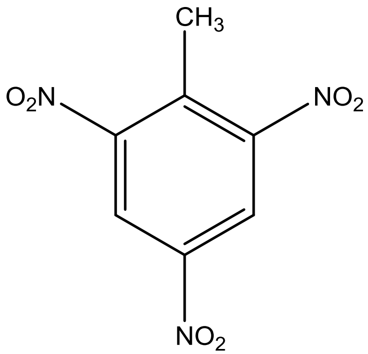
Dinitro Aniline - $C_6H_5N_3O_4$



$$OB = -1600 \frac{[(2 \times 6) + ½ (5) - 4]}{183} = -91.8$$

Oxygen-Balance	Hazard Ranking
More positive than +160	Low
+160 to +80	Medium
+80 to -120	High
-120 to -240	Medium
More negative than -240	Low

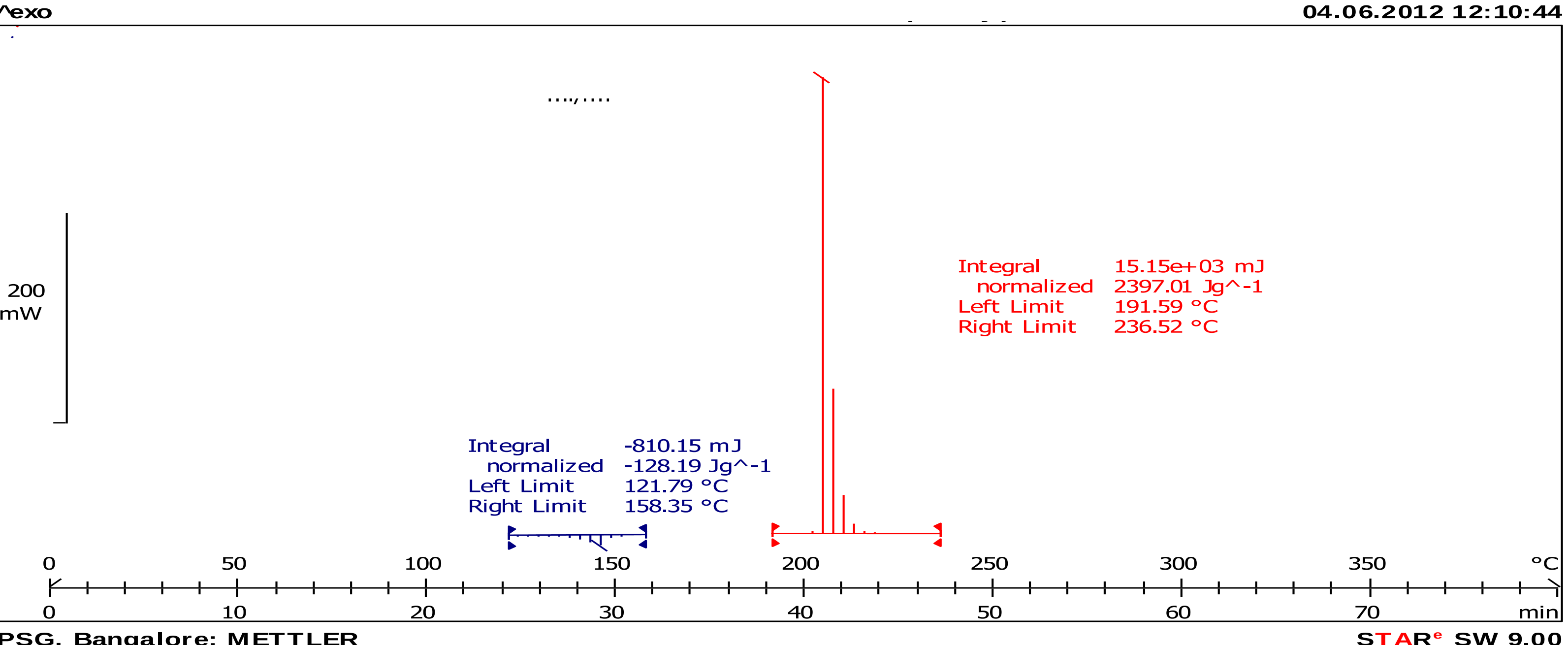
Tri-Nitro Toluene (TNT) - $C_7H_5N_3O_6$



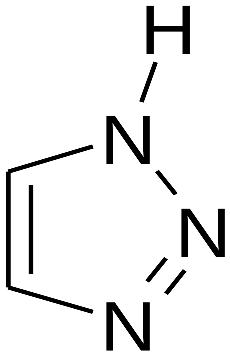
$$OB = -1600 \frac{[(2 \times 7) + ½ (5) - 6]}{227} = -74$$

Laboratory screening- DSC

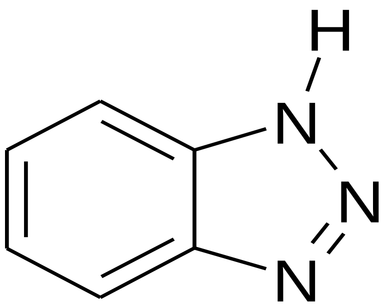
- Gold crucibles
- 10mg sample
- Heating rate 5 ^{0}C min-
- Temperature range: 25 – 350 ^{0}C
- Interpretation of Data



Impact of Crucible Selection



- Aluminium crucibles: ΔH ~125 J/g
- High Pressure crucibles: ΔH ~2600 J/g



- Aluminium crucibles: ΔH ~600 J/g
- High Pressure crucibles: ΔH ~1600 J/g

Tetrahedron Letters 48 (2007) 1233

Bench-Scale Reaction calorimetry

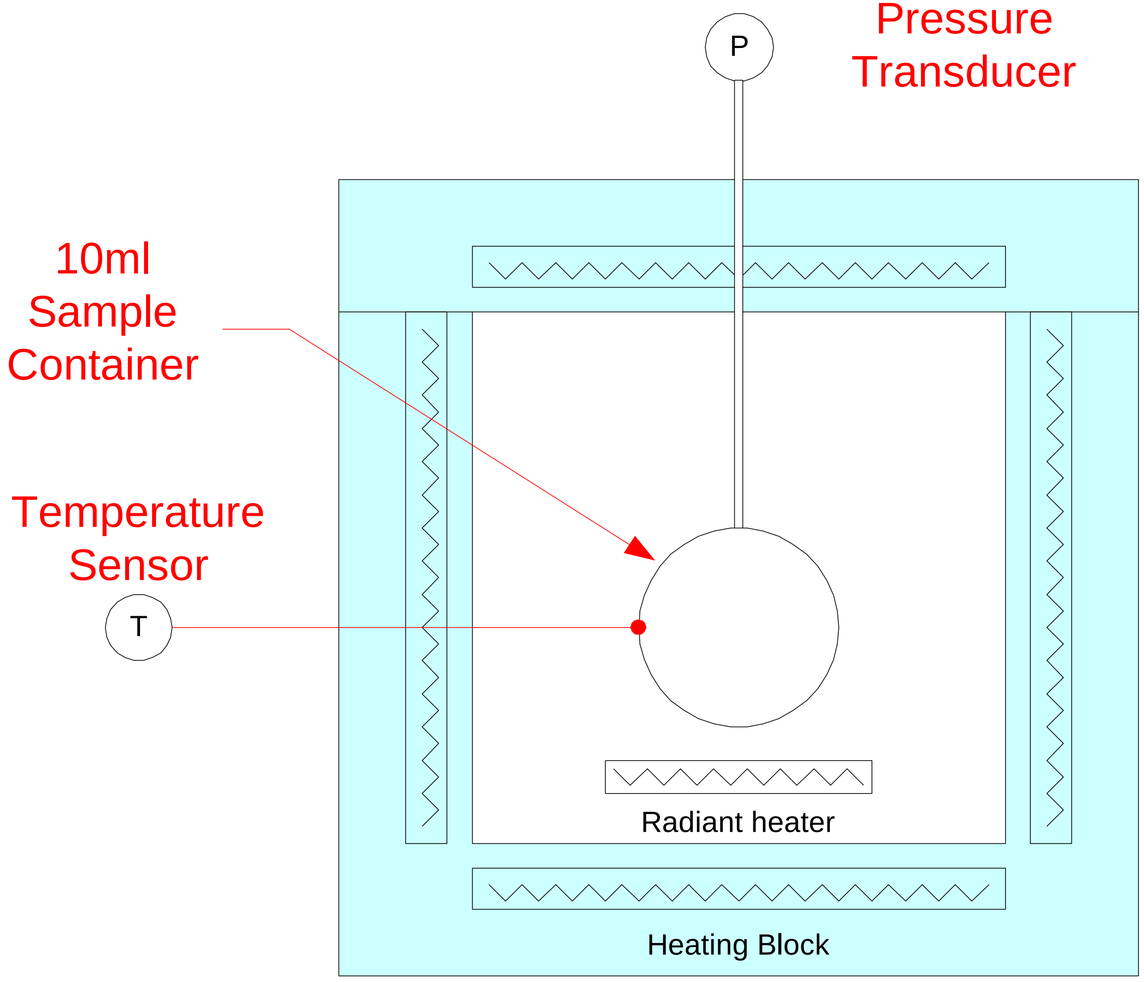
Focus: Primary reaction

- Mimics the process as written as close as possible
- Heat of reaction
- Volume & Rate of gas evolution
- Detection of a delayed onset (e.g. Grignard reaction)
- **Limitations**
  - Can't operate at (or near) boiling point
  - Not good for long reactions (>1 day)

https://d3pcsg2wjq9izr.cloudfront.net/files/2317/download/468606/91RC1e_Process_Safety_Workstation_Brochure.pdf

Accelerated Reaction Calorimetry (ARC)

- Thermal stability test (2-5g)
- Adiabatic Conditions
- Near plant conditions
- Used after DSC screen
  - Pressure screening capability
  - All in one reactions.
  - Storage conditions
  - Self Accelerated Decom Temp (SADT) calculation

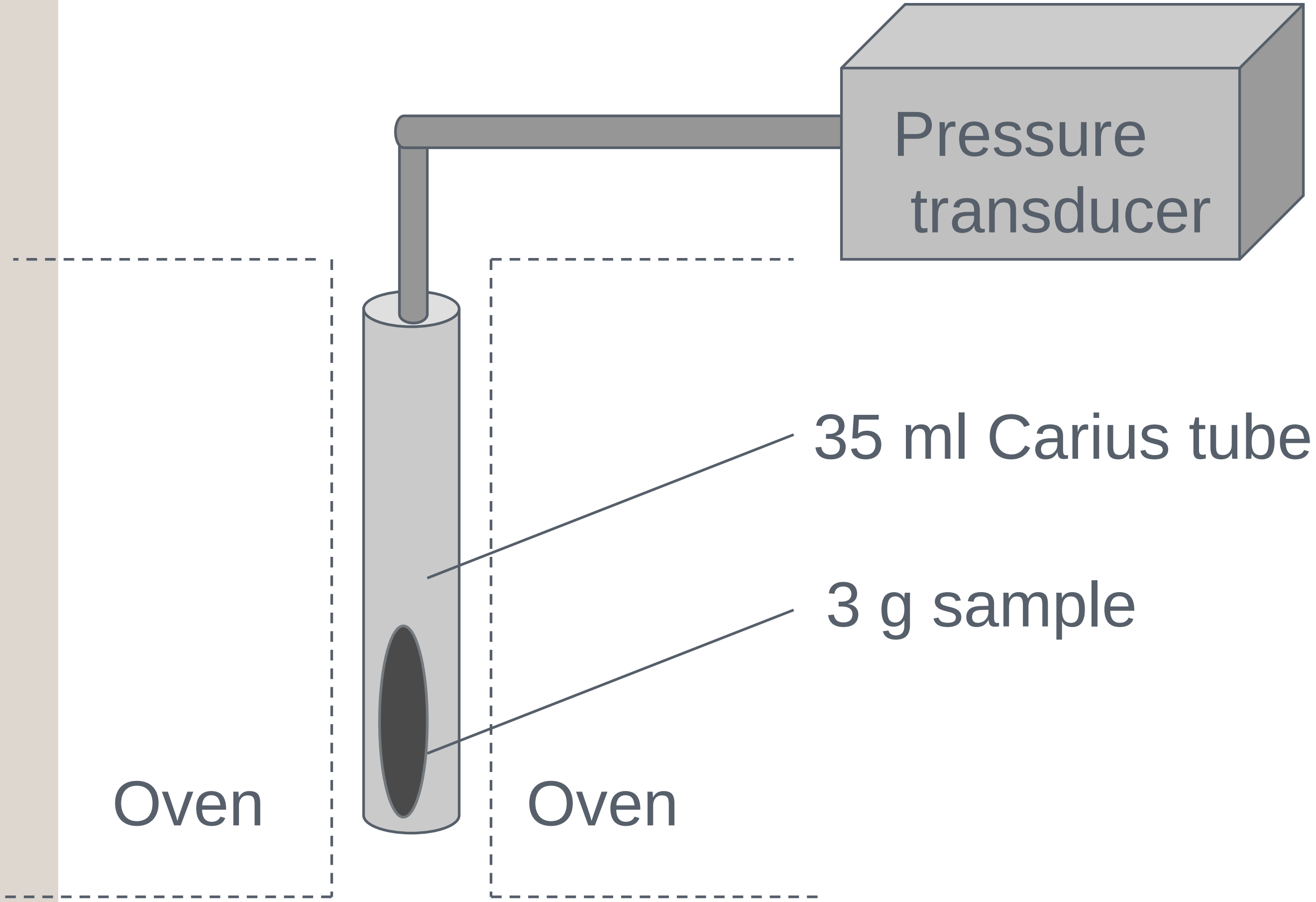


Carious Tube test / TSU

- To find the onset for gas liberation
- Thermal stability of raw materials/reaction mixtures.
- Gas evolution and explosivity
- Interpreting the data
  - Onset for exotherm (T_d)
  - Gas liberation

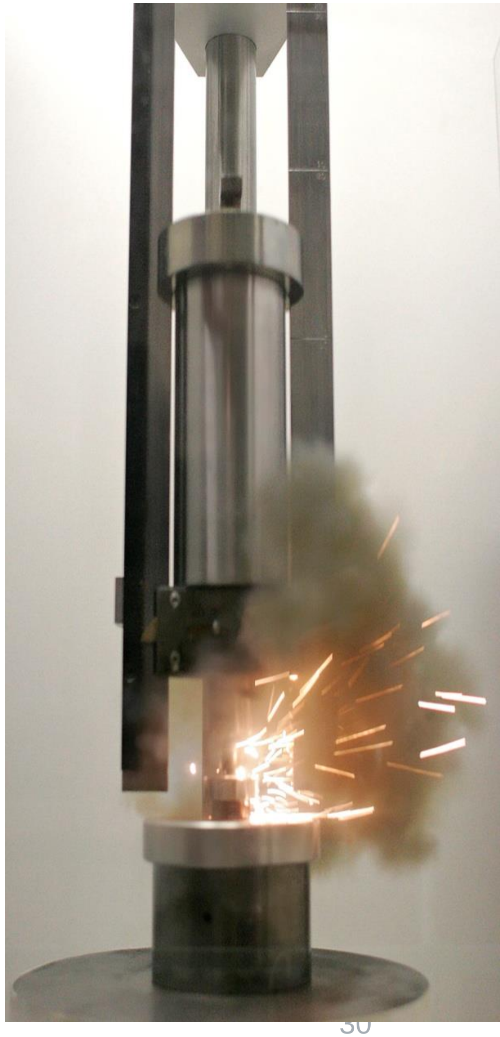
High Rate Carious Tube test (HRCT test)

- 35 ml tube
- Sample mass 3 g
- Heating rate 2 ^{0}C/min
- 200 to 400 psi < 100ms – Potential explosive
  - 14 to 28 bar



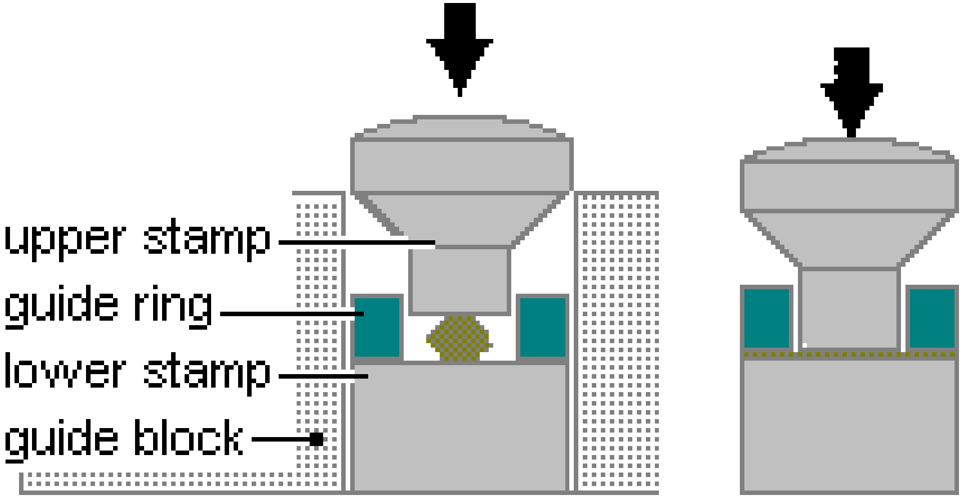
Explosive screening: Fall Hammer Test

- Impact sensitivity test.
- Solids, Pastes and Gels etc.
- Standard hammer weights to fall on a confined quantity of sample
- Height required to decompose or detonate the charge.
- UN Transport of Dangerous Goods Manual of Tests and Criteria
- Classification, Packaging and Labeling of Dangerous Substances in the EU Part 2- testing methods (latest editions).



Fall hammer

- Sample mass: 10x100 mg
- Drop weight: 5 kg (49 N)
- Drop height: 80 cm
- Impact energy: 39.2 Nm

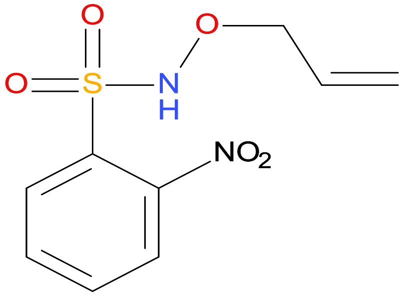


Hazard assessment

- Check the functional group for Plosophores/Explosophores
- Calculate the oxygen balance
- Obtain the DSC to find decomposition energy.
- Reaction Calorimetry studies
- ARC studies
- Confirm potential explosive nature by HRCT
- Impact sensitivity by Fall Hammer Test.

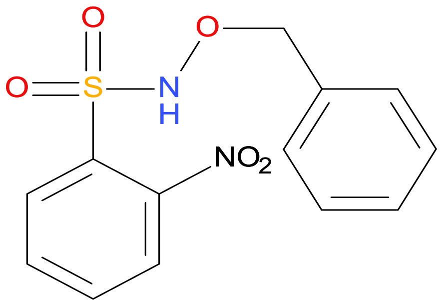
Case study – intermediates

Explosive screening has been carried out for the two energetic intermediates



O.B: -111

Allylnosylate



O.B: -140

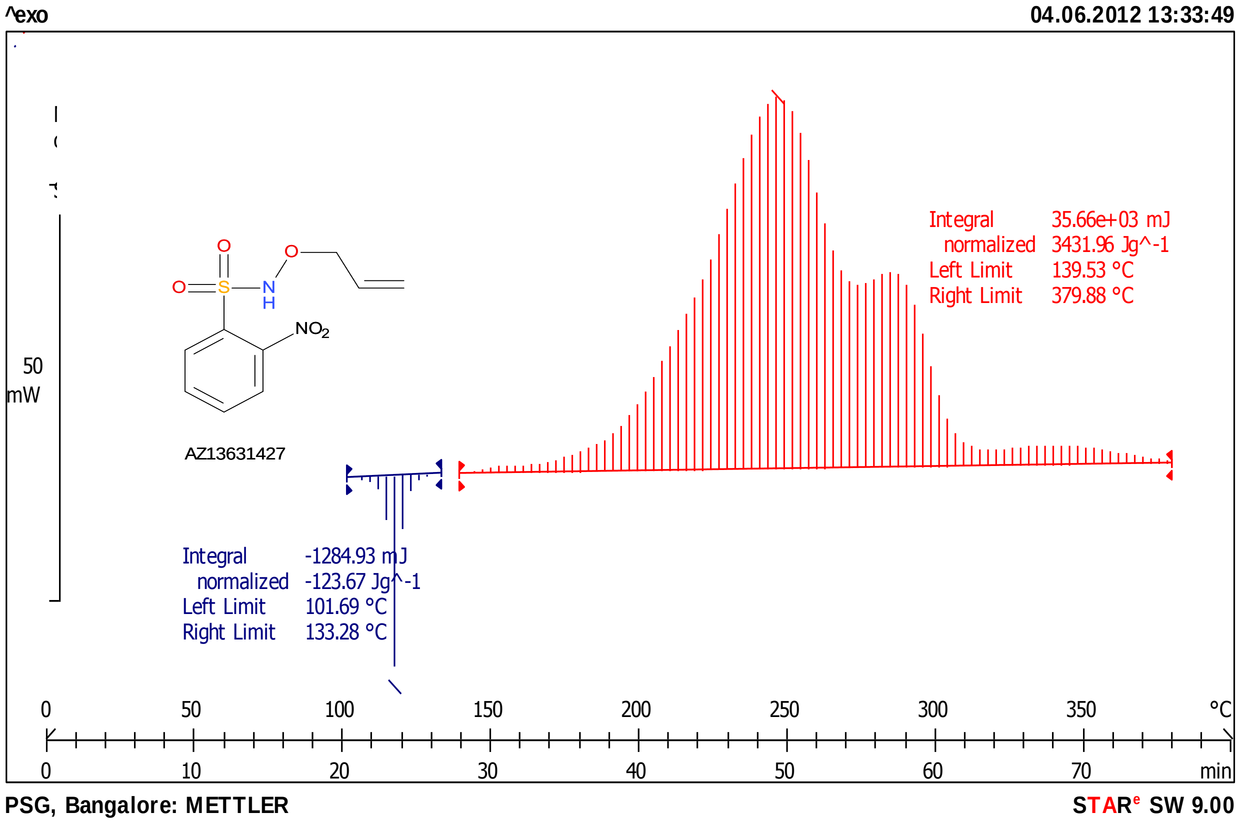
Benzylnosylate

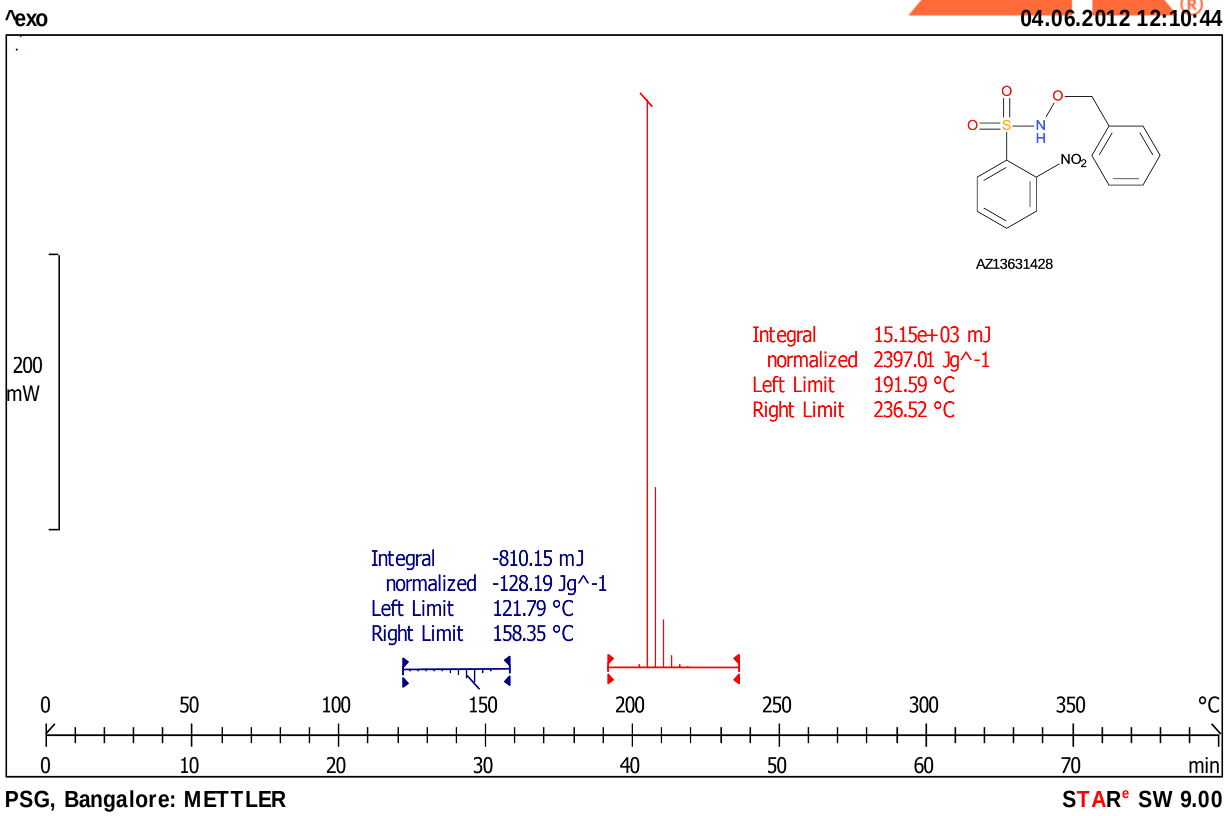
$C_XH_YO_Z$:

$$OB = \frac{-1600 \cdot (2x + y/2 - z)}{\text{molecular mass}}$$

Oxygen-Balance	Hazard Ranking
More positive than +160	Low
+160 to +80	Medium
+80 to -120	High
-120 to -240	Medium
More negative than -240	Low

DSC Thermograms





DSC AllylInosylate:
Endotherm (Presumably melting) detected from 101°C
Exotherm (-3432 J/g) detected from 139°C .

DSC of BenzylInosylate:
Endotherm (presumably melting) detected from 121°C
Exotherm (-2397 J/g) detected from 191°C .

Fall Hammer & Carious Tube Tests

Fall Hammer Test Results

Material/ Test	Limiting Impact Energy (J)	Result	Comments
Allylnosylate FH12012	>49	Number of tests performed 8 & All shots were negative	Not Sensitive to Impact
Benzylnosylate FH13013		Number of tests performed 8 & All shots were negative	Not Sensitive to Impact

Carious Tube Test Results

Material/ Test	Time from 200 – 400 PSIG	Comments
Allyl Nosylate CAR12042	9 ms	300-500psig: 5ms Max dP/dt: 3690 bar/sec Tube burst pressure: 40.0 barg
Benzylnosylate CAR12041	290 ms	300-500 psig: 134ms Tube burst pressure: 66.0 barg

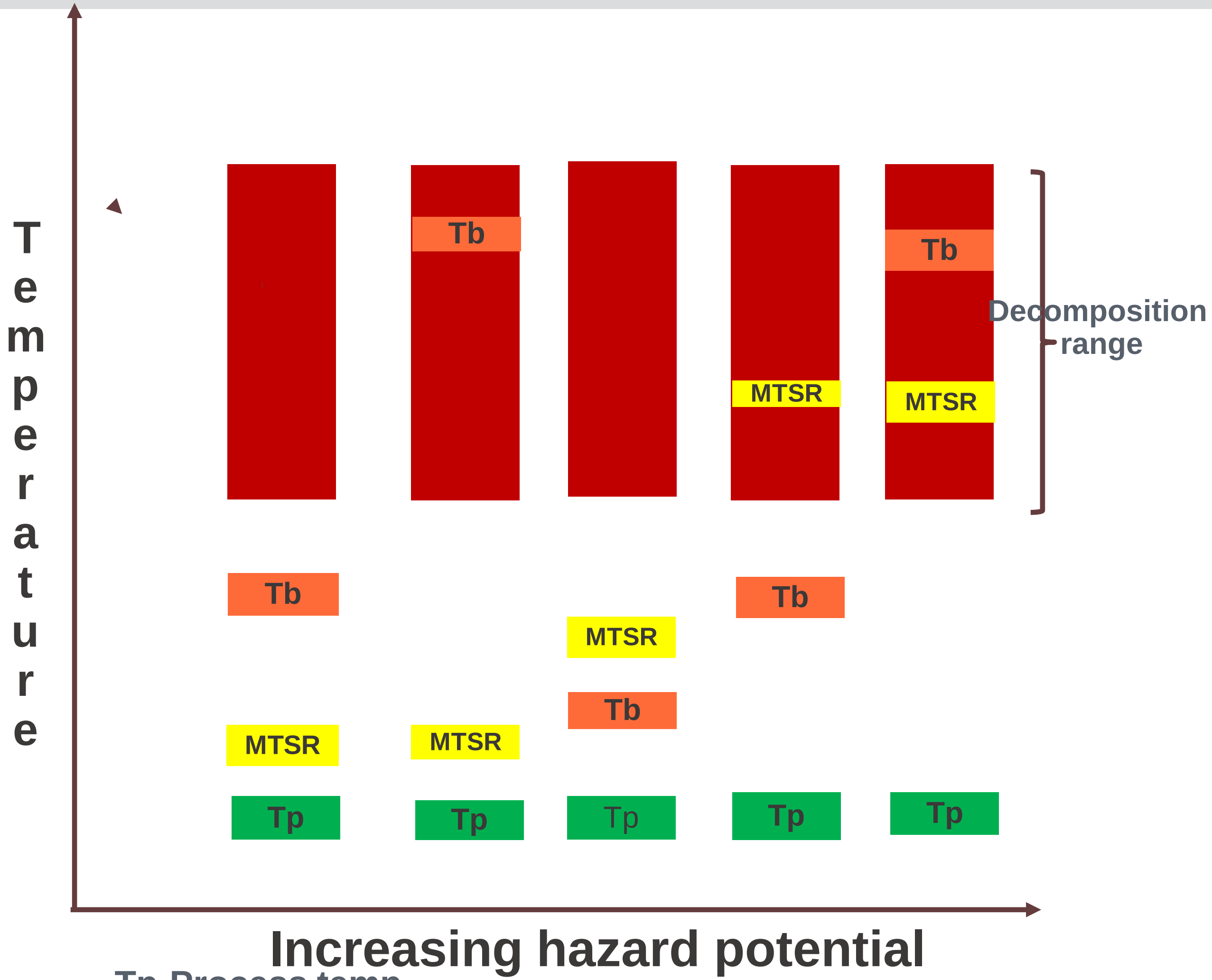
200 to 400 PSI < 100 ms is potential explosive

Recommendations

Material	OB	DSC	Carious Time from 200 – 400 PSIG	Fall Hammer	Conclusion
Allylnosylate	-111	MP: 101 0C Dec: 139 0C Exoth: - 3432 J/g	9 ms	Not Impact sensitive	Lab scale: Potential explosive Further studies needed: 1, 2 & 3
Benzylnosylate	-140	MP: 121 0C Dec: 191 0C Exoth: - 2397 J/g	290 ms	Not Impact sensitive	Lab Scale: Not highly explosive but adequate care to be taken Kilo lab: Further studies – 1, 2 & 3

1. Reaction Calorimetry
2. ARC
3. Other tests

Stoessel criticality class



Tp-Process temp

MTSR= Max Temp of synthesis rxn = Tp+ Ad Temp rise

Tb- Boiling Pt of solvent

Chem. Rev. 2006, 106, 7, 3002–3027

Class A: This is a thermally safe or intrinsically safe process

Class B: Decomposition onset is below solvent boiling point (bpt). Need to prevent overheating of the reaction mixture.

Class C: MTSR is above the solvent bpt. Over pressurisation or evaporation of all solvent a possibility. Reaction control essential.

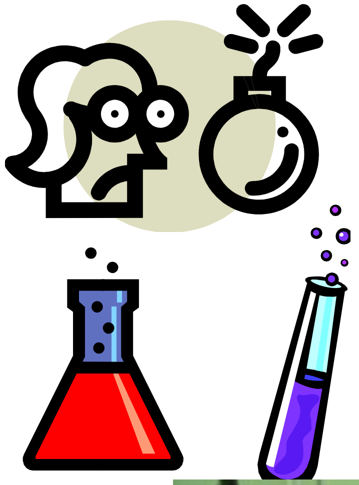
Class D: MTSR exceeds solvent bpt and will initiate decomposition. Reaction control must be applied, emergency relief venting required

Class E: Decomposition will occur below solvent boiling point. Reaction control required, protection to control required, protection to mitigate the consequences of decomposition required.

Ways of Working- Scale of Manufacture

Development Laboratory : Safety based on the following

- No Explosive Compounds
- Relatively small scale of operation
- Fume-cupboard/ Safety Screen protection
- If something goes wrong, then the fume-cupboard will contain the incident.
- Risk assessment
- The Basis of Safety is containment.



Ways of Working- Scale of Manufacture

Large Scale Laboratory : Safety can be based on the following:

- Limited scale-up
- Use of Self – Assessment Form
- Carefully judged level of hazard testing
- No Explosive Compounds
- DSC, RC-1, HRCT and Fall hammer
- Any other test as required
- Process Safety Report

Ways of Working-Scale of Manufacture

Plant Operation : Safety based on the following

- **At this scale of operation all processes are fully assessed and understood.**

- Experimental testing is carried out to determine:
  - Thermal stability of the starting materials, mixtures, products & waste streams etc.
  - The amount of heat and gas generated at any stage during the process.
  - Detailed Operational risk assessment is required

Basis of Safety

- All the chemical hazards testing has been performed
- The hazards of the process have been defined
- Measures need to be implemented to allow safe operation of the process on plant to be drawn
- These measures are known as the **Basis of Safety.**

Process Safety Report

- Reports are required as a good means of communication, archiving and building corporate knowledge.
- A Report should contain:
  - **Scope:** What the assessment includes and what it does not (Eg: Kilo lab vs Commercial scale
  - **Document history:** References to any previous assessments.
  - **Experimental details/results:** Detailed description of any testing performed.
  - **Discussion:** Explanation of the experimental results and the reasoning behind decisions.
  - **Basis of Safety**: Actions required to make the process safe.

Process Safety Methodology

- Identify the hazard
- Assess the risk
- Eliminate the risk if any
- Find a safe substitute
- Contain it
- Protect yourself
- Run……**Presence of mind is good but absence of body is better…..**

Thank You

Empowering a healthy tomorrow

Questions

Empowering a healthy tomorrow