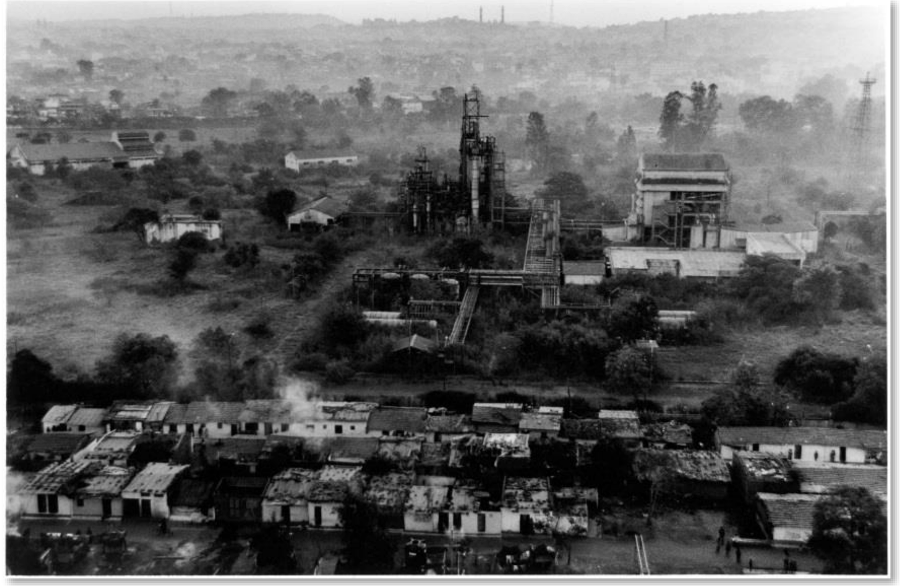
P2SAC - Pharmaceutical Related Research

Ray A. Mentzer
Visiting Professor & Associate Director,
Purdue Process Safety & Assurance Center (P2SAC)

Charles D. Davidson School of Chemical Engineering
Purdue University

August 30, 2019



Bhopal India – 1984; +2,000 fatalities

West Pharmaceuticals – 2003; 6 fatalities

Imperial Sugar, Georgia – 2008; 14 fatalities

Texas Tech University; Chemistry Lab – 2010

ATTENDEES – MAY 7, 2019 CONFERENCE

Sponsors

AMGEN
BP
Chevron
Dow
Fauske & Associates
GSK
Honeywell
Kenexis
Lilly
Phillips 66
Pfizer
Shell
3M

Guests

- Abbvie*
- aeSolutions
- Alkermes*
- American Chem Soc*
- Americas Styrenics*
- AMRI
- Biogen*
- CDC-NIOSH
- Cook Biotech*
- Corteva Agroscience
- Endress+Hauser
- Evonik
- FujiFilm Dimatix*
- Gexcon*
- ICASE
- Johnson Matthey*
- Merck*
- Occidental Oil & Gas
- Purdue GMP Center*
- Scale-Up Systems*
- Vertex Pharmaceuticals*

** denotes 1st meeting*

**Follow up conference planned for May '20*

On-going dialog with other Depts:
AAE, ABE, CHEM, IE, IPPH, ME & CV

MULTIPLE FACULTY ENGAGED IN PROCESS SAFETY RELATED RESEARCH
'19 / '20 PROGRAM




PhD

Sensing dust concentrations by imaging …

… Safer materials and processing design for next-generation printed electronics

New directions in prevention by catalyst design …

… Optimal placement of detectors and new directions driven by systems engineering approaches

Modeling and uncertainty analysis of dust explosions …

… Battery safety by materials design

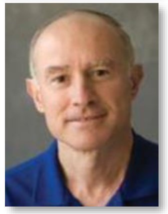
High throughput quantum chemical calculation of Benson group values for reliable thermodynamic calculations …

… Catalyst design and reactor runaway: selective oxidation of alcohols

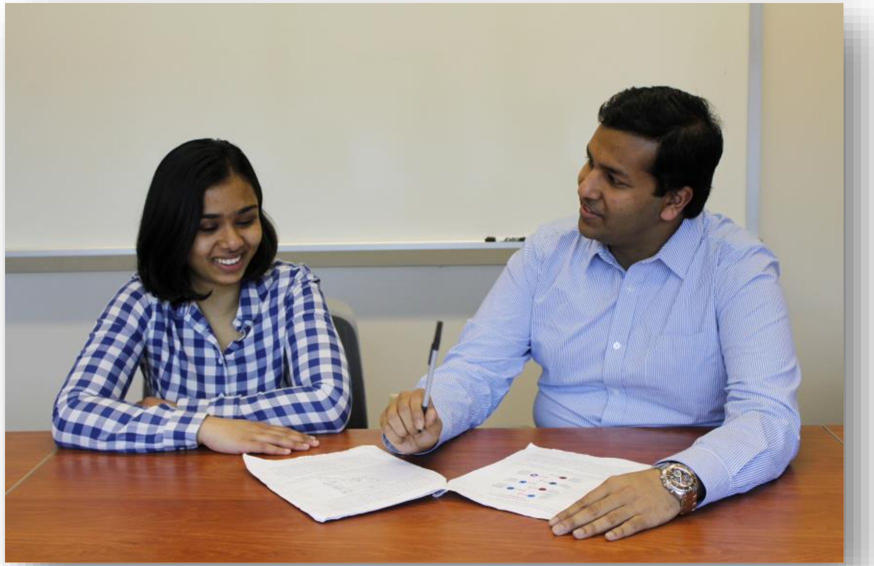
The role of chemical agents (surfactants) and electrostatics in coalescence …







CHE PROFESSIONAL MASTERS PROGRAM



- Grown from 9 students in ‘15 / ‘16 academic year to 55 fall ‘19
- 2017 Cohort: 34% female; 65% int’l; $69k avg starting salary, 100% placement

- Five areas of concentration:
  - Energy Systems Fundamentals & Processes
  - Kinetics, Catalysis, and Reaction Engineering
  - Biochemical Engineering,
  - Polymer Science and Engineering
  - Pharmaceutical Engineering

- Program scheduled for one year
  - Students take 2 core courses; 3 in area of concentration; 3 in Management; followed by summer research project
  - Additional semester required for those without BS in chemical engineering

- Summer research projects are typically suggested and led / mentored by industry
  - Students remain on campus with ~30 minute weekly call with industry mentor
  - Two students per projects noted above; +800 hrs of ‘free’ research’
  - Summer ‘19: Nine process safety related projects being pursued; ~50% of pgm
  - Companies participating: Air Liquide, AMGEN, Catalent, Chevron, Cook, CountryMark, Dow, Dow AgroScience, ExxonMobil, Fauske, Fresenius, Kenexis, Pioneer Oil, SP2, 3M

- Typical companies hiring graduates: 3M, Cook Pharmica, McKinsey, Nalco, Shire, etc

P2SAC RESEARCH PROGRAM – MS / UG

MS Projects – 2017-2019

2019

- Dimensional analysis and similitude for multiphase flows in pipe reactors (Chevron / DowAgro)
- Leveraging Data Science for Oil & Gas Asset Integrity Management (Chevron / DowAgro)
- Understanding Ignition Properties of Flammable Gas / Particulate Mixtures & Mitigation Through Inerting; (3M)
- Determination of Minimum Sufficient Dispersion Model Scenarios for Gas Detection Optimization (Kenexis)
- Improving Understanding of Hazards of Process Plants through PHA Gamification (Kenexis)
- Thermal Hazards in the Pharmaceutical Industry (AMGEN)
- Design and construct a prototype of a benchtop tool to be used to screen chemicals for reactivity (Fauske)
- Co-Processing Renewable Feedstock in a Distillate Hydrotreater (CountryMark)
- Optimization of Gasoline & Diesel Product Blending (CountryMark)

2018

- Quantification of toxicity effects of H_2S ingress into buildings / temporary refuge (Shell)
- Acoustically-induced vibration of piping systems (ExxonMobil)
- Develop a scheme for conducting process hazard analyses and develop guidance for automating (Kenexis)
- A systems engineering approach for managing changes in chemical process R&D labs (Dow AgroSciences)

2017

- Compilation of thermal hazard safety data for amide coupling reagents (Lilly)
- Validate large scale consequence modeling with Middle East propane release (Kenexis)

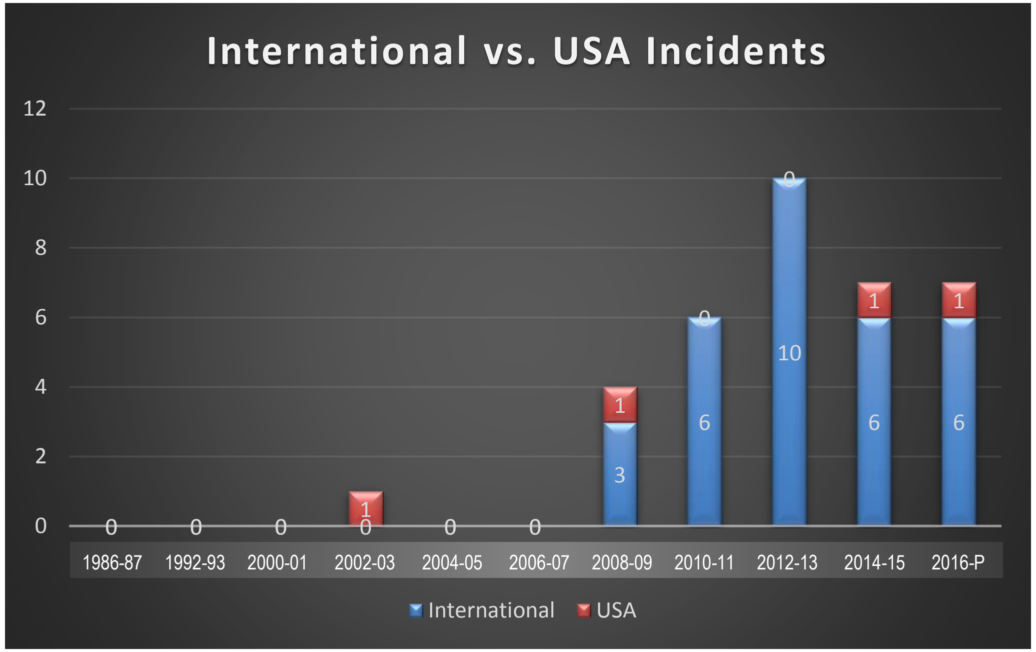
UG Projects – 2017-2019

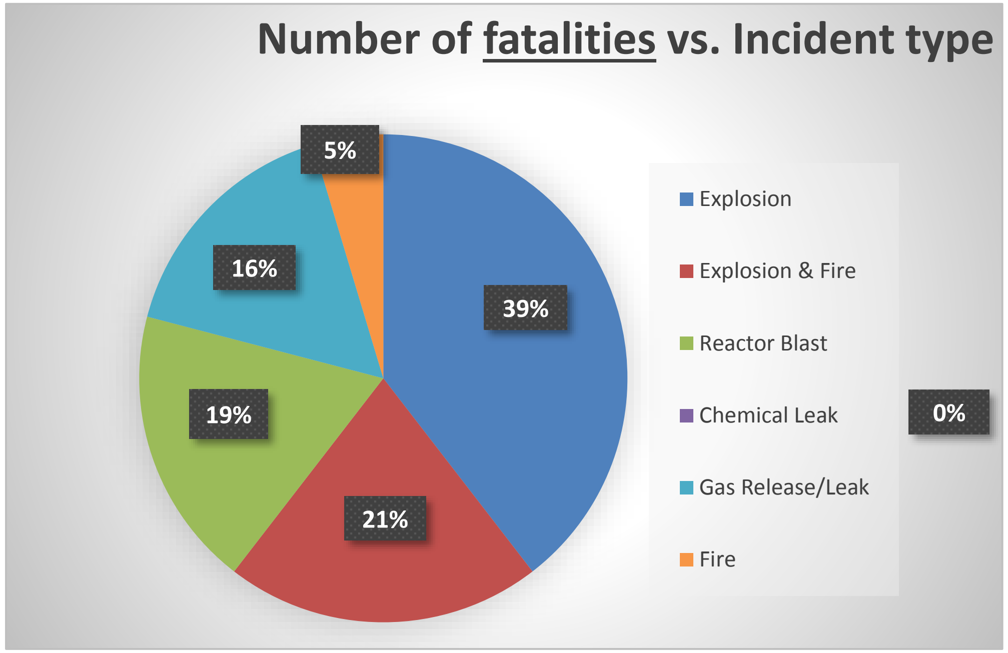
- Calorimetric study of pharmaceutical reagents by ARSST - *ongoing*
- Extend Benson group database for thermo property prediction – *evolved to PhD*
- Determine and predict temperature at which time to max rate of reaction is 24 hr
- Develop guidance on energy released during testing vs. volume of sample for pharma industry
- Risk and reliability of aged natural gas pipelines
- Develop database of MIEs of dusts with focus on pharma / mixtures – *evolved to PhD*
- Compilation of process safety related software commercially available
- Analysis of process safety incidents in the pharmaceutical industry - *update*
- Experience with corrosion under insulation; detection & mitigation
- Experience with LNG metallurgy failures
- Comparison of global process safety regulations

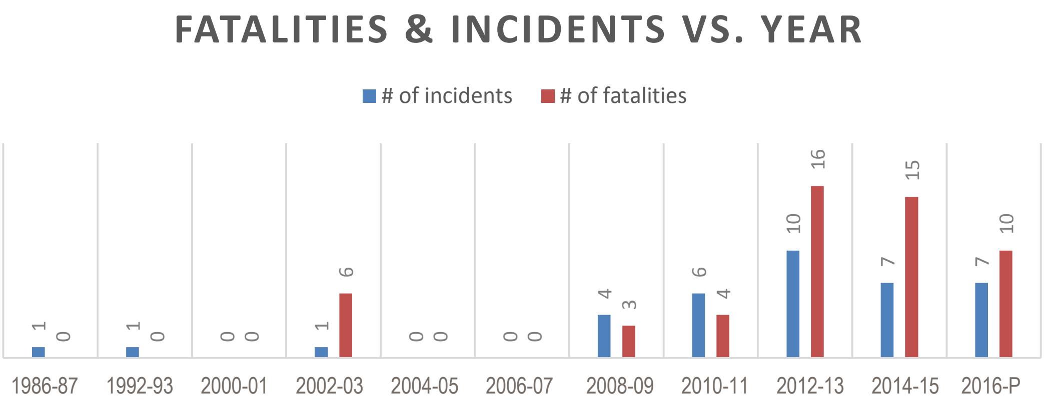
Joint NSF Funded Projects with CISTAR – 2018-2019

- *Safety in Academic & Industrial Laboratories*
- *Inherently Safe & Secure Cyber Physical Systems*

Process Safety Incidents in Pharmaceutical Industry - *UG Research, '16 & '19*





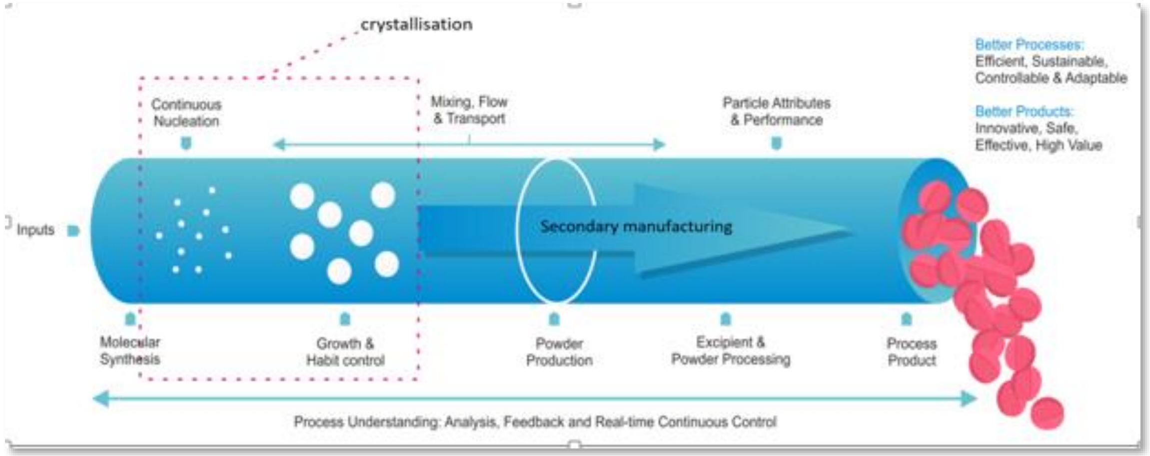


Updated database will include incidents like:

- July 12, 2018 explosion and fire at Yibin Hengda Science & Technology in China; pharma & food manufacturer; facility 3 years old
    - 19 fatalities … ~60 to be punished, per gov
    - Construction & production without approval; addition of wrong chemicals in production facility; safety culture

**per some accounts there have been 154 explosions at worksites in China, since 2015 Tianjin explosion*

WORKING TOWARDS FAULT-TOLERANT REAL-TIME RELEASE CONTROL IN PHARMACEUTICAL CONTINUOUS MANUFACTURING - *PHD RESEARCH*



- Dusts are a serious hazard with 281 dust fires & explosions in the US between 1980 - 2005 resulting in 119 fatalities.
- Pharmaceutical continuous manufacturing faces challenges in developing a real-time release control strategy complying with administrative regulations, upon which consistent and conforming immediate and final products are continuously manufactured.
- A risk-based and fault-tolerant control for the plant-wide continuous manufacturing process is of great potential in achieving a real-time release control strategy.
- **Research interests**: continuous crystallization (MSMPR, COBC, etc.), continuous feeding and blending, dry granulation or direct compaction for pharmaceutical solid dosage manufacturing.
- **Research strategies**: system identification, real-time process optimization and control, advanced model-based control design and analysis, risk management, process monitoring and fault diagnosis, data reconciliation and state estimation, process analytical technologies (PAT), quality by design, etc.
- **Research Goal:** Fault handling utilizes an integrated process understanding in process risks, assessment, and planning to allow a fault-tolerant real-time release control.

ADVANCED REACTIVE SYSTEM SCREENING TOOL (ARSST) PROJECT – UG RESEARCH, '18 & '19

- Used to study the decomposition of Dimethyl Sulfoxide (DMSO)
- The ARSST records temperature and pressure data over time
- Calculated the ΔH_R, E_a, and the Pre-Exponential Factor from the DMSO decomposition reaction
- Compared the thermochemical properties of the DMSO decomposition under acidic conditions by mixing DMSO with acids of varying pKa's
- Obtained a Linear Free Energy Relationship between the onset T of the DMSO decomposition reaction and the pKa of acid added to the system
- Analyzed the change in Linear Free Energy Relationship under different concentrations of acid with DMSO

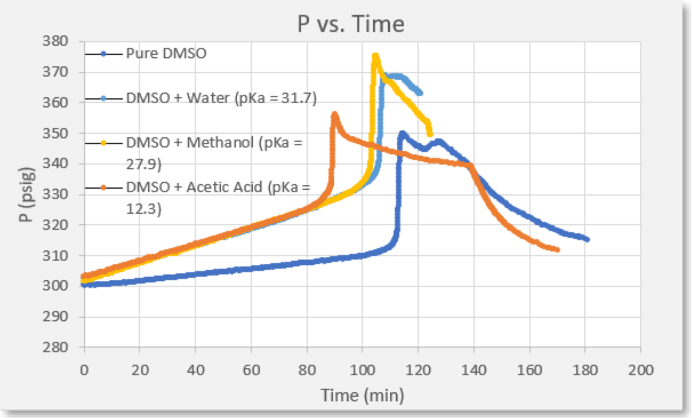


Figure 1: Plots illustrating pressure generation over time

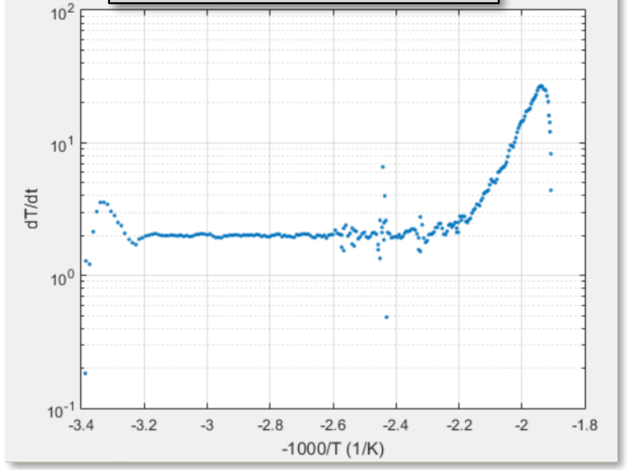


Figure 2: Slope of linear portion on the right is proportional to E_a

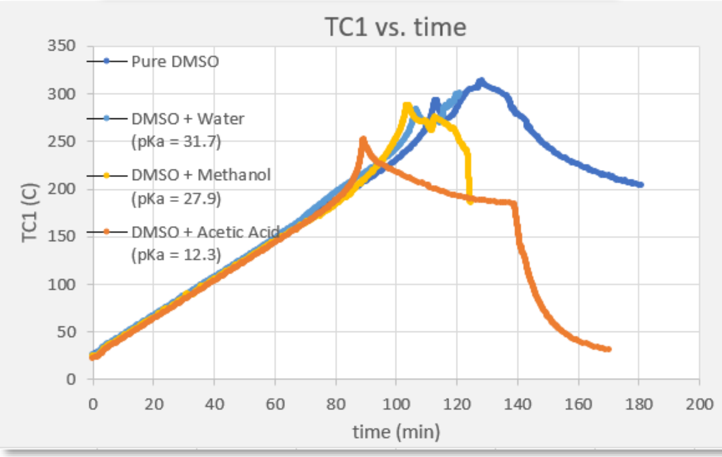


Figure 3: Plots illustrating the change in T_{onset} with different acid strengths

THERMAL SAFETY – TIME TO MAXIMUM SELF-HEATING RATE (TMRAD) AND TD24 – PMP RESEARCH

- Objective: Literature Review of TD24, Calorimetric Techniques available, Comparison of model based estimation of TD24 with ADT 24 obtained from adiabatic storage tests and the 100K-50K rules, Mathematical Methods for the Analysis of Calorimetric Data, Commercially Available Software.

- The probability for a 'runaway' scenario can be described by the time to maximum self-heat rate under adiabatic conditions, i.e., the **TMRad**. The adiabatic temperature rise ΔTad describes the severity in a 'runaway' scenario. **TD24** is the process temperature which will lead to a runaway in 24 hrs.

- For temperatures above 200K, the temperature under adiabatic conditions rises sharply with time. For TMR less than 8 hours (1 shift), the probability of occurrence is very high.

- TMR-TD24 (based on reaction kinetics) is scientifically more accurate than the 50K and 100K rules (based on the onset temperature).

- An emergency cooling system must be effective within a time shorter than the TMR. Temperatures above the TD24 must be avoided.

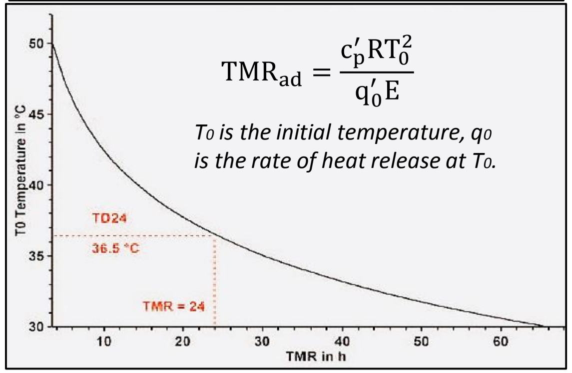
- Commonly used calorimetric techniques: DSC (most common), ARC, Dewar, TAM, ARSST, VSP2, DARC (more recent).

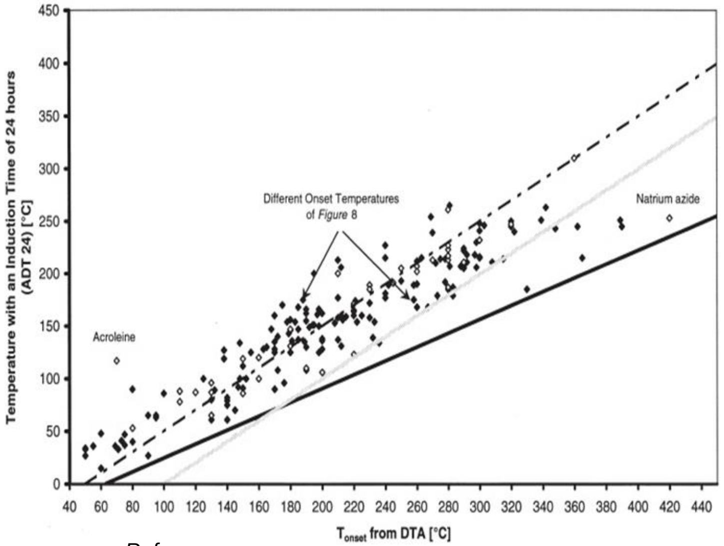
- Analysis of Calorimeter Data: Kinetics Evaluation, Correction for Thermal Inertia and TMR-TD24 estimation. Standard Approach vs. Expert Approach

- Software: AKTS Thermal Safety and CISP Thermal Safety Series

- Next Steps: Compare various methods of estimating the TD24 with experimental data to find the most accurate and efficient approach.

Risk / Factor	ΔT_{ad} in K	TMR in h
High	>200	<8
Medium	$50 < \Delta T_{ad} < 200$	8 < TMR <24
Low	<50 °	>24





References:
[1] Francis Stoessel, "Thermal Safety of Chemical Processes", Wiley-VCH, 2008.
[2] Jorg Pastre et.al (2000), "Comparison of different methods for estimating TMRad form dynamic DSC measurements with ADT 24 values obtained from adiabatic Dewar experiments", J. Loss Prev. Ind., 13, pp. 7-17.

ANALYSIS OF CALORIMETRIC DATA – PMP Capstone

OBTAIN EXPERIMENTAL DATA

- Undergraduate researcher had conducted temperature ramp experiments on the ARSST
- 9 different sets of data were available to us

ANALYZE DATA

- Using mathematical methods available in literature estimate the TMR_{ad} and T_{D24}
- 4 different methods were chosen

SOFTWARE PREDICTION

- Have the AKTS Thermal Safety Software predict the T_{D24} for comparison

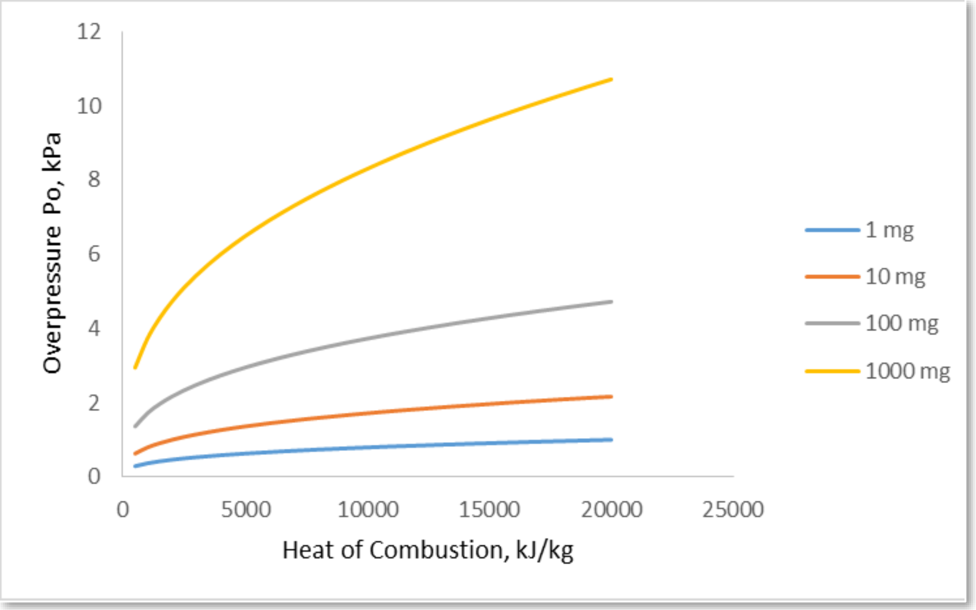
EXPERIMENTAL VALIDATION

- Conduct an adiabatic storage test using the ARSST to experimentally validate the results obtained by data analysis

PURDUE
UNIVERSITY

ENERGY RELEASE CALCULATIONS FROM ~SMALL SAMPLES: IMPACT CALCULATIONS – PMP RESEARCH

- Objective: To study the variation in peak overpressures with the mass of a potentially explosive substance using TNT analysis and to quantify the consequences of calculated overpressures using probit correlations.



- Equations Used:

$$m_{TNT} = \frac{\eta m_{hc} \Delta H_c}{E_{TNT}} \qquad z_e = \frac{r}{m_{TNT}^{1/3}}$$

$$\frac{p_o}{p_a} = \frac{1616\left[1 + \left(\frac{z_e}{4.5}\right)^2\right]}{\sqrt{1 + \left(\frac{z_e}{0.048}\right)^2}\sqrt{1 + \left(\frac{z_e}{0.32}\right)^2}\sqrt{1 + \left(\frac{z_e}{1.35}\right)^2}}$$

Po = Peak Overpressure, Pa = ambient pressure, η = Explosion Efficiency (assumed as 5%)

- Overpressure Vs Mass: The overpressure increases with an increase in heat of combustion and also increases with an increase in the mass of explosive substance.

- The resulting overpressures are in the range between 0.1 kPa and 11 kPa (an overpressure of 11 kPa corresponds to 99.8% Glass Breakage and 5% Structural Damage).

- Overpressure Vs Distance: While calculating the overpressures depicted in the figure, distance ‘r’ was assumed to be 1 m. For distances close to the site of explosion (0.1 cm), the calculated overpressures were very high (533 kPa for 10 mg TNT).

- Explosion Proof Fume Hoods: Designed to eliminate igniting spark potential of fume hood components, cannot contain an explosion.

BENSON GROUP RESEARCH – UG RESEARCH, EVOLVED TO PHD

CALCULATING HEATS OF FORMATION FOR UNKNOWN GROUPS

- CHETAH used to predict reactivity hazards
- Benson group method used, based on heat of formation, ΔH_f
- ΔH_f calculated by summing the ΔH_f of individual groups of atoms that make up molecule.
- Several unknown Benson groups identified, limiting application

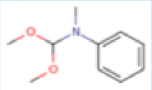
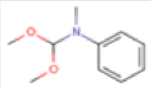
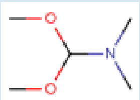
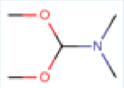
Process

1. Find ΔH_f of a molecule containing an unknown Benson group via literature search
2. Determine unknown group's value, based on known groups and ΔH_f of molecule

$$x_u = \frac{\Delta H_f - \sum_{i=1}^{N-1} n_i x_i}{n_u}$$

Results

- Determined 13 new Benson groups; 6 based on molecules & 7 single group molecules
- Molecular modeling to be used to supplement when ΔH_f data missing or suspect

Unknown Benson Group		Known Groups Contained [kcal/mol]	Known Groups Contained [kcal/mol]	Known Groups Contained [kcal/mol]	Known Groups Contained [kcal/mol]	Known Groups Contained [kcal/mol]	Known Groups Contained [kcal/mol]	Known Groups Contained [kcal/mol]	Molecule Observed [kcal/mol]	Est. heat of formation [kcal/mol]	Method
CH-(N,2O)		CH3-(O) -10.08	O-(2C) -23	N-(2C,Cb) 26.2	CH3-(N) -10.08	Cb-(N) -0.5	Cb-(H) 3.3		 [6] -53.94	CH-(N,2O) -19.9	Experimental free energy change & entropy value
		CH3-(O) -10.08	O-(2C) -23	CH3-(N) -10.08	N-(3C) [10] 24.6654				[17]  -94.4	CH-(N,2O) -32.7454	Macro- Incrementing & Calorimetrically
=CimH-(=C) 		=CimH-(Cb) [12] 15.014	=Cim-(2Cb) [12] 21.927	Cb-(C) [1] 5.51	.=Cim-(Cb,C) [12] 21.52	C-(=Cim) 16.01	C-(=C) -5.51	C-(Cb,=C) [2]		=CimH-(=C) 10.5	6-31G* (Gaussian)

Resources: Purdue Online Libraries: access to research papers, CHETAH 10, Reaxy: molecule modeling software finds published data of molecules containing specified groups

Process Safety Incident Learnings Across Multiple Industries – UG & PMP Research

Process Safety Incidents Occur Across Many Industries

- Refining
- Chemical Plants
- Oil & Gas
- Storage Facilities
- Pharmaceuticals
- Agriculture
- Fertilizer
- Power Plants
- Pipelines
- Mining
- Manufacturing
- Food
- Fireworks
- Other – rail, air transport

Analysis of Incidents

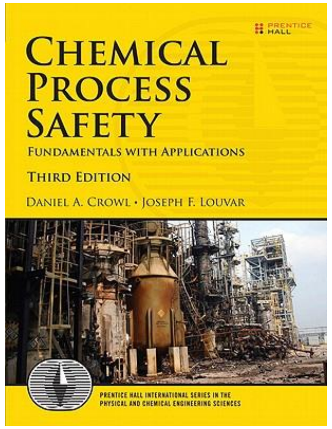
- 3 incidents that occurred in the past two decades, as well as other noteworthy incidents (ex, Bhopal) were chosen for each industrial sector.
- Root causes of these incidents were studied, focusing on those in common.
- Associated hazards across each industry also captured..

Are there common hazards and root causes across industries?

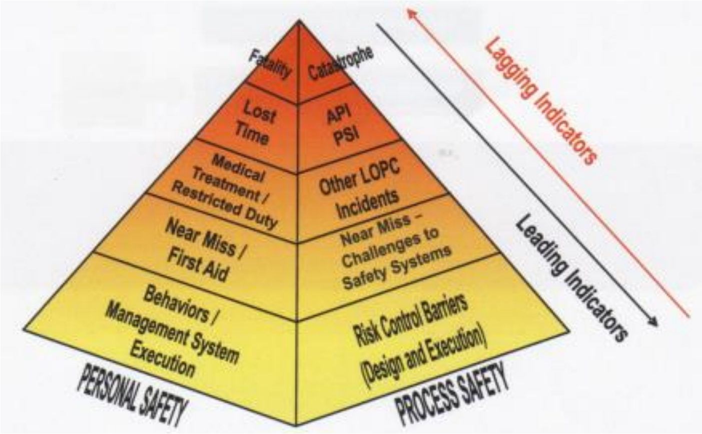
- After analyzing process safety incidents across ~ 14 industries, anticipate commonalities in the root causes & hazards.
- Analyze for most common hazards & root causes.

CHE 420 / 597 - CHEMICAL PROCESS SAFETY – CORE UG COURSE

- Personnel vs. Process Safety & Metrics
- Applicable regulations: OSHA PSM, EPA RMP, etc
- Source Term Modeling
- Toxicants & Industrial Hygiene
- Toxic/Flammable Gas Release
- Dispersion Modeling
- Fire & Explosion Protection
- Chemical Reactivity
- Relief System Design
- Hazards Identification (HAZOP, ..)
- Risk Assessment (Matrix, QRA, ..)
- Accident Investigations



Process Safety Metrics



Typical 4x4 Risk Matrix

		Likelihood			
		Frequent	Possible	Rare	Remote
Severity	Major	Very High	Very High	High	Moderate
	Serious	Very High	High	Moderate	Low
	Minor	High	Moderate	Low	Low
	Incidental	Moderate	Low	Low	Low

HAZOP

Node # _:
Design Intent:

Parameter	Guide Word	Deviation	Causes	Consequences	Recommendations

BENEFITS FROM JOINING P2SAC

- Direct engagement in suggesting & selecting process safety research projects at all levels – PhD, MS and UG.
- Priority in engaging with students by serving as mentor for process safety related Professional Masters Project(s) of your choice.
- Attendance at biannual meetings to review research progress and learn from outside expert presentations.
- Sharing among companies of process safety learnings and challenges.
- Contact with students as they develop process safety expertise and enhance the science.

P2SAC SPONSORS

Typical Sponsor agreement is $25k / year for 3 years