Purdue Process Safety & Assurance Center (P2SAC)

Overview - Pharma

Ray A. Mentzer
Professor of Engineering Practice
Associate Director, P2SAC

Charles D. Davidson School of Chemical Engineering
Purdue University

May 8, 2024

PURDUE UNIVERSITY | Davidson School of Chemical Engineering

May 2024 Conference Registration

Sponsors

ACC – Am Chem Council
AcuTech
AMGEN
Chevron
Corteva
CountryMark
Curia Global
Dow
Endress+Hauser
Evonik
ExxonMobil
Fauske & Associates
GSK
Honeywell
Johnson Matthey
Kenexis
Lilly
Pfizer
PSRG
SABIC
Vertex

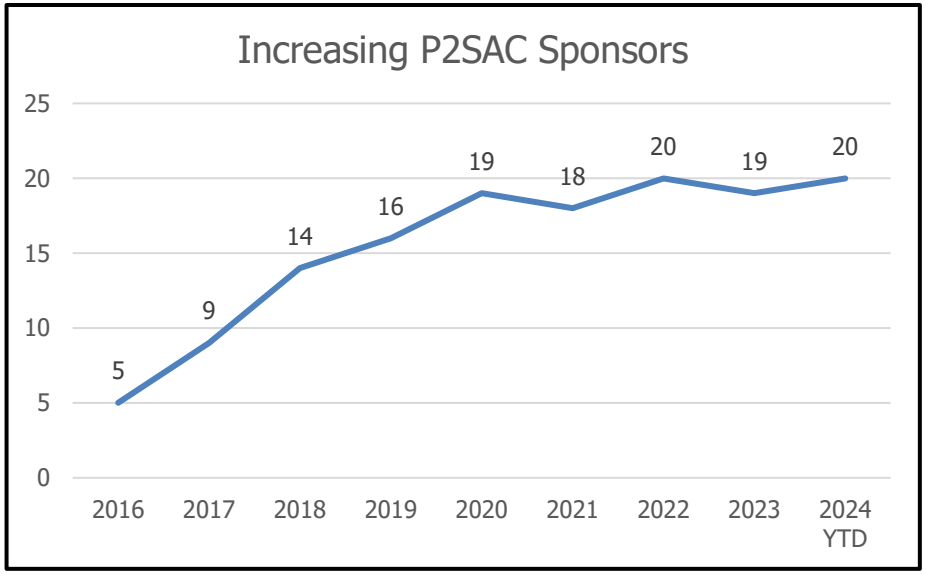
Guests

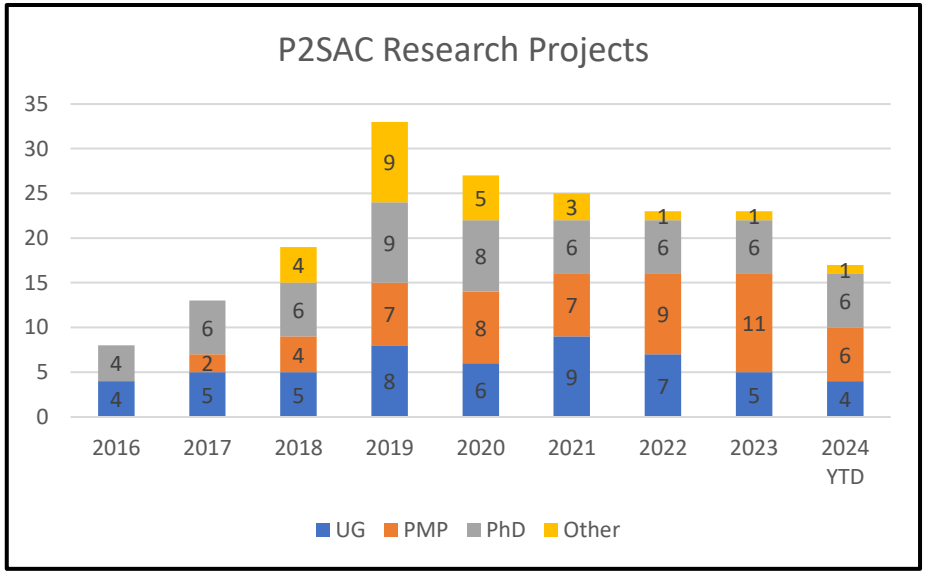
- Brystol Myers Squibb
- CCPS
- Gilead
- Grace
- Marathon Consulting*
- Merck
- Operational Sustainability*
- PHMS*
- Scitegrity*
- Spark Cognition*
- Thermal Hazard Tech*
- Toellner Consulting*

**denotes 1st meeting*

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

Growing Industry Participation & Projects in P2SAC





Pharma Related PMP / UG Projects .. examples

Survey of heats of reaction for some common reaction types in pharma industry & comparison with predictions – w / Amgen, Corteva, GSK, JP, Lilly, Merck, Pfizer, Vertex

Prediction of Gas Evolution in Common Reaction Solvents with ASPEN – GSK, Amgen, Lilly

Estimation of Decomposition Energies for Organometallic Materials – w / Johnson Matthey

Analysis of 73 global process safety incidents in the pharmaceutical industry - *published*

Thermal Hazards in the Pharmaceutical Industry – w / Amgen

Use of ARSST Calorimeter to Study Reagents Common to the Pharmaceutical Industry

Temperature at Which Time to Maximum Rate is 24 Hours – w / Amgen

Safety in Academic & Industrial Laboratories - *w / Corteva*

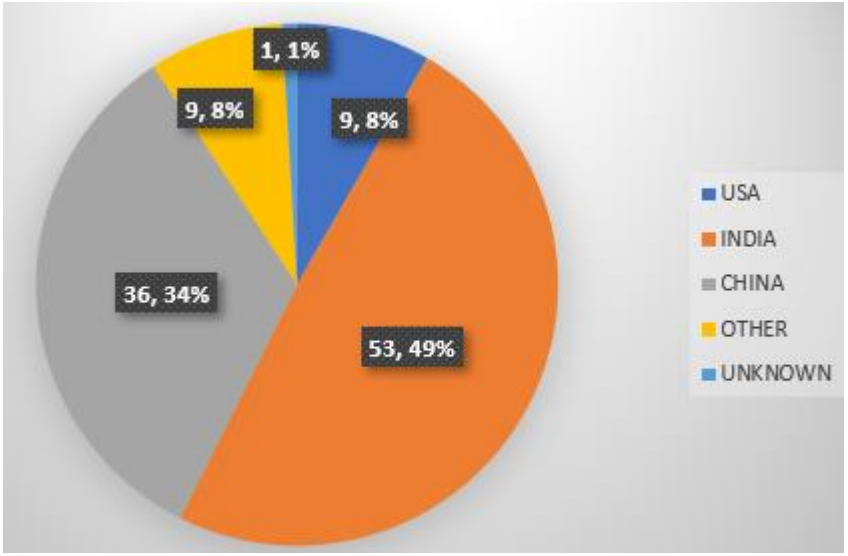
Heat transfer modeling in Accelerating Rate Calorimeter – w / Dow

Analysis of process safety incidents across 14 industries & comparison of root causes – *published*

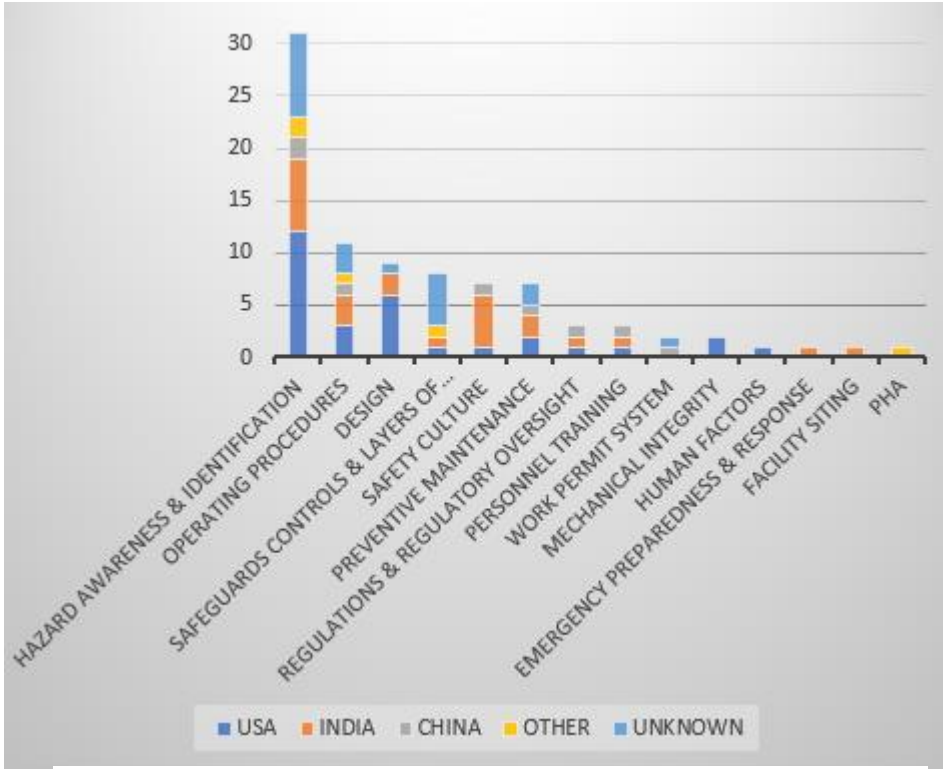
Review of Stoessel Classification Methodology and Potential Inclusion of Pressure

Global Process Safety Incidents in the Pharmaceutical Industry – PMP / UG

- Analyzed 73 process safety incidents; 108 fatalities between 1985-19
- Identified and summarized trends between the number of incidents, number of fatalities, location, and contributing factors
- Highest reported fatalities occurred in 2018 & 2019, 26 & 16, respectively
- 83% of fatalities occurred in China and India
- Explosions associated with 71% of incidents, resulting in 89% of fatalities
- Published: *J Loss Prevention in Process Industries*, 68, Nov (2020)



Number of Fatalities and Corresponding %



Number of Incidents vs. Contributing Factors

Thermal Safety - TMRad and TD24

- 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 hours.

- 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.

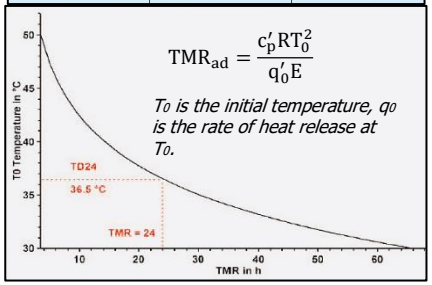
- Commonly used calorimetric techniques: DSC (most common), ARC, Dewar, TAM, ARSST, VSP2, DARC (more recent).

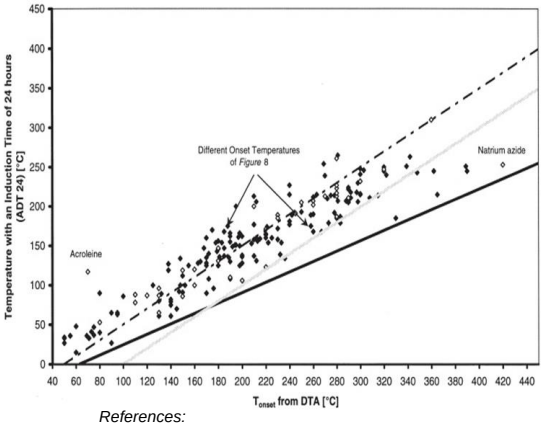
- Analysis of Calorimeter Data: Kinetics Evaluation, Correction for Thermal Inertia and TMR-TD24 estimation. Standard Approach Vs Expert Approach

- Software: AKTS Thermal Safety and CISP Thermal Safety Series

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

Risk / Factor	ΔT_{ad} in K	TMR in h
High	>200	<8
Medium	50 < ΔT_{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.

Benson Group Research

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 to various molecules

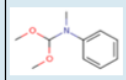
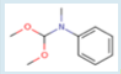
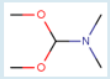
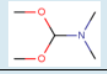
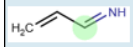
Process

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

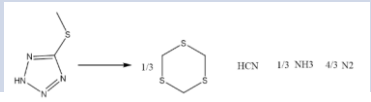
- Determined 13 new Benson groups; 6 based on molecules & 7 single group molecules
- Molecular modeling to be used to supplement when ΔH_f data missing

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)	O-(2C)	N-(2C,Cb)	CH3-(N)	Cb-(N)	Cb-(H)		 [6]	CH-(N,2O)	Experimental free energy change & entropy value
		-10.08	-23	26.2	-10.08	-0.5	3.3		-53.94	-19.9	
		CH3-(O)	O-(2C)	CH3-(N)	N-(3C) [10]				[17] 	CH-(N,2O)	Macro- Incrementing & Calorimetrically
		-10.08	-23	-10.08	24.6654				-94.4	-32.7454	
=CimH-(=C) 		=CimH-(Cb) [12]	=Cim-(2Cb) [12]	Cb-(C) [1]	.=Cim-(Cb,C) [12]	C-(=Cim)	C-(=C)	C-(Cb,=C) [2]		=CimH-(=C)	6-31G* (Gaussian)
		15.014	21.927	5.51	21.52	16.01	-5.51			10.5	

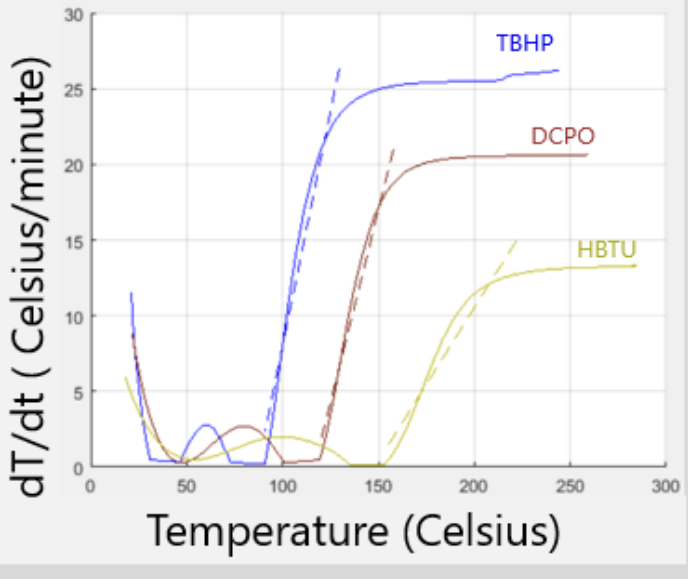
Resources: Purdue Online Libraries: access to research papers, CHETAH 10, Reaxy: molecule modeling software finds published data of molecules containing specified groups

Predicting Heats of Reactions Common In Pharma Industry – UG / PMP

- Project uses experimental reaction data from pharmaceutical companies, including Amgen, Corteva, GSK, JM, Lilly, Merck, Pfizer, and Vertex to compare with predictions of:
  - CHETAH – widely used, licensed by ASTM since 1974, based on Benson groups
  - TCIT – novel Purdue methodology, combines quantum chemistry & G4 data
  - YARP – new Purdue methodology, generates potential decomposition products without any user provided reaction data
- Programs calculate the heat of rxn when given the molecular structures in SMILES string format, generated through ChemDraw
- Study included: decomposition reactions for various tetrazole based compounds in TCIT and CHETAH, 1H-tetrazole and methyl tetrazole decompositions in YARP
  - CHETAH cannot handle SMILES string for any tetrazole compound, tetrazoles modeled manually using Benson groups
  - 8 different Tetrazoles studied
- Sample reactions shown below
- **CONCLUSIONS**: TCIT calculations have an average 20 % error; Overall TCIT results were better than CHETAH heat of reaction results; neither method can currently handle ionic and free-radical groups. YARP successfully predicted expected products for 1H tetrazole and methyl tetrazole
- **NEXT STEPS**: continue with TCIT & CHETAH comparison for different reactions, use of YARP to predict decomposition products

Reaction	Measured ΔHrxn (kJ/mol)	CHETAH ΔHrxn (kJ/mol)	TCIT ΔHrxn (kJ/mol)	% DIFF CHETAH	% DIFF TCIT
1H-tetrazole -> HCN + 1/3 NH3 + 4/3N2	-160.5	-232.98	-208.91	45.16	30.16
Methyl Tetrazole -> CH3CN + 1/3NH3 + 4/3 N2	-242.07	-228.59	-201.24	5.56	16.87
5- (methylthio)-IH tetrazole 	-156.33	-217.35	-187.9	39.03	20.19

Thermal Analysis Using ARSST Calorimeter – UG Research



- Dicumyl peroxide: DCPO
- Peroxide: TBHP
- (2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate: HBTU

Chemical Sample	Test Sample Composition	Phi Factor ϕ	Adiabatic Temperature Rise (K)	Heat of Reaction (J/g)	Activation Energy (kJ/mol)
DCPO	39.98% weight solution in ethylbenzene	1.08	126.1	< -635.3	142.6
TBHP	70% weight solution in water	1.05	140.0	< -353.0	154.6
HBTU	14.29% solution weight in DMSO	1.07	100.5	< -533.4	207.6

Benefits from Being P2SAC Sponsor

- Direct engagement in suggesting & selecting process safety research projects at all levels – PhD, PMP and UG.
- Priority in serving as mentor for process safety related Professional Masters Project 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