

## Purdue Spring 2021 Conference

# Predicting the fire and explosion properties of early phase active pharmaceutical ingredients

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# What issues did this work set out to solve?



- Early phase pharmaceutical manufacture often occurs in the absence of powder fire and explosion test data.
  - Catch 22 – we have to make the powder to go away for testing to tell us what we needed to know to safely make the powder.
  - Competing priorities – with very little material in existence the patient need is often prioritised over sending material for testing.
- Yet...
- A process safety incident at 1-10kg scale can cause serious injury or death.
- Some pieces of equipment have restrictions on MIE,  $P_{max}/K_{st}$  or MIT/LIT – making it very hard to use the equipment when the parameters are unknown.
- Mitigating the lack of knowledge can involve complex precautions - making the process difficult for people to operate.

## Testing Is Always Best If Material Is Available

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- A methodology to predict powder fire and explosion properties:
    - Highlight 'materials of concern':
      - MIE <5mJ
      - $P_{max} > 10\text{bar(a)}$
      - ST3 ( $K_{st} > 300 \text{ bar.m/s}$ )
      - MIT/LIT into the T4, T5, T6 region
  - Success Criteria:
    - Use <1g of material.
    - Not require any additional equipment.
    - 'False positives' < 33% of the time.
    - 'False negatives' <3% of the time.

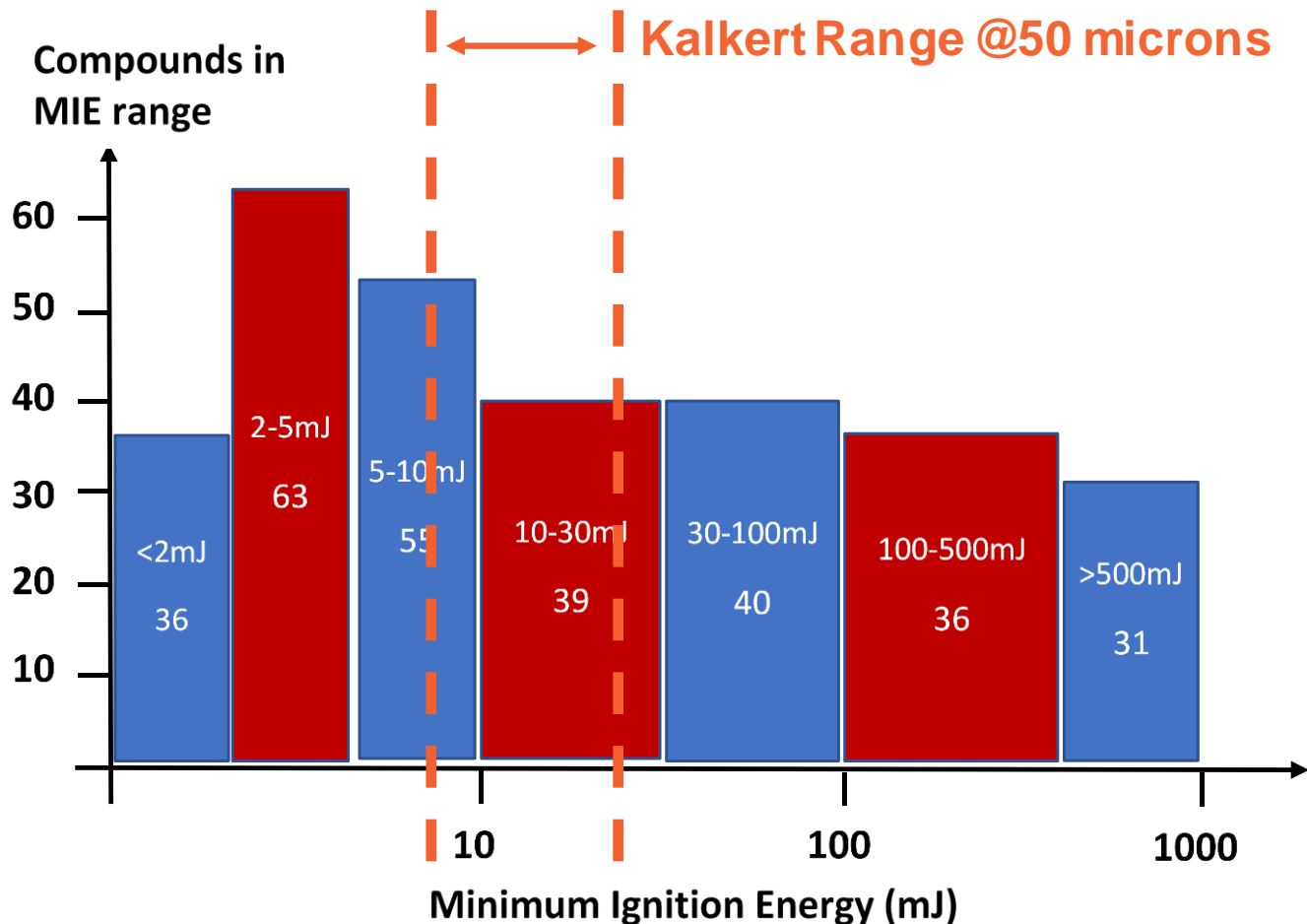
# Minimum Ignition Energy

- The Kalkert (1979) equation predicts the MIE (in Joules) of powder particle.

$$\text{MIE} = (4\pi\chi)^{3/2} \rho_g \cdot \text{Cp}_g \left[ \frac{\text{Ln}.2}{12} \cdot \frac{\rho_s \cdot \text{Cp}_s}{k_g} \right]^{3/2} T_{\text{max}} \cdot D_p^3$$

- Where:
  - $\rho_g$  = Gas (air) density in kg/m<sup>3</sup>
  - $\text{Cp}_g$  = Gas (air) specific heat in J/kg.K
  - $K_g$  = Gas (air) thermal conductivity in W/m.K
  - $\chi = K_g / (\rho_g \cdot \text{Cp}_g)$
  - $\rho_s$  = Powder density in kg/m<sup>3</sup>
  - $\text{Cp}_s$  = Powder specific heat in J/kg.K
  - $T_{\text{max}}$  = The air temperature around the particle. As per Kalkert (1979) taken as 1300K
  - $D_p$  = Particle diameter ( $d_{50}$ ) in m
- It can be solved for typical powder density and specific heat (at 50 micron particle size) – with an allowance for spark generation inefficiency – to give a prediction of circa 9 -26mJ.

# Kalkert Model versus GSK API Test Data

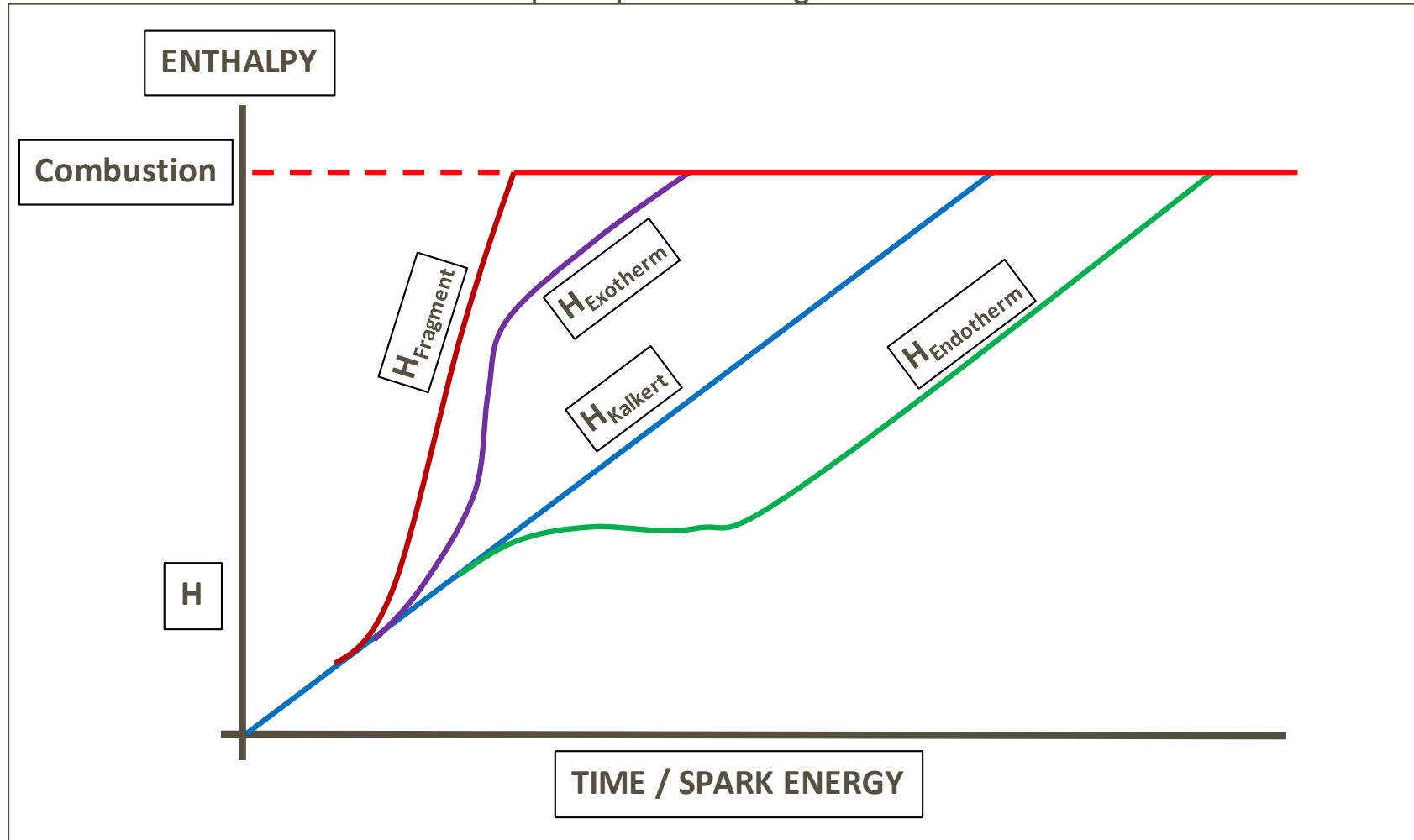


# Understanding the Model versus Reality Gap



## Thermodynamics

- Kalkert model is based on simple  $C_p \cdot dT$  heating



# Model Currently Used...



...How it will develop further

$$\text{MIE} = 2 \times \text{MIE}_{\text{Kalkert}} \left[ \frac{200}{100 + \Sigma F \cdot \Delta H_{\text{DSC}}} \right] \left[ \text{Inter Molecular Stability} \right] \left[ \text{Molecular Stability} \right]$$

- ‘2’ represents greater understanding of spark energy efficiency since Kalkert model developed.
- ‘F’ factor covering the shape of the DSC exotherm(s) and peak temperature.
- $\Delta H_{\text{DSC}}$  the size in J/g of DSC exotherm(s).
- Inter Molecular Stability – represents the strength of the crystal lattice and is based on the melt temperature and melt endotherm (from DSC).
- Molecular Stability – represents the structural integrity (or not) of the molecule and is based on:
  - Bond energies
  - Chemistry knowledge
  - Thermogravimetric analysis (TGA) to assess cleavage pathways
- **Future** – factor to represent particle shape and agglomeration/flow properties.



# Examples of the factors

All empirically derived – and subject to change



Exotherm Shape	Value of 'F'		
	Temperature at Exotherm Peak		
	< 200°C	200°C to 300°C	> 300°C
Sharp peak	1.5	Linear interpolation	0.5
Sharp bell curve	1.25	Linear interpolation	0.35
Classic bell curve	1	Linear interpolation	0.25
Shallow bell curve	0.75	Linear interpolation	0.1
Shallow curve	0.5	Linear interpolation	0
No exotherm	0	Linear interpolation	0

MS Guidance	0.1	Long side chains that includes a weak bond that would cleave a highly flammable molecule
	0.1	Weakness (unstable, high energy group) that would cleave a highly flammable molecule
	0.2	Molecule vulnerable to cleaving and liberating a flammable molecule
	0.2	Salts of highly flammable molecules (SCS) - propionate, valerate, olamine.
	0.3	Salts of flammable molecules (CS-C6) - maleate, glutarate, furoate, besylate.
	0.4-0.6	Salt of molecule with limited flammability (SC6) - salicylate, mesylate
	0.4-0.6	Side chain with potential weakness to liberate a moderately flammable molecule
	0.7-0.9	Side chains or high energy groups causing no obvious structural weakness
	0.9	Salt of molecule with very limited flammability - succinate
	0.8-1	Molecule could cleave to form two stable molecules of limited flammability
	1	Molecule has short side chains and no obvious weaknesses
	1.5	Tightly bound molecule with short side chains.
	2	Tightly bound molecule with no side chains.

Propionate, C<sub>3</sub>H<sub>5</sub>O<sub>2</sub>, from propionic acid, BP 140°C  
 Valerate, C<sub>5</sub>H<sub>9</sub>O<sub>2</sub>, from valeric acid, BP 186°C  
 Furoate, from furoic acid (C<sub>5</sub>H<sub>4</sub>O<sub>3</sub>), BP 230°C  
 Maleate, from maleic acid (C<sub>4</sub>H<sub>2</sub>O<sub>4</sub>), BP 202°C  
 Glutarate, from glutaric acid (C<sub>5</sub>H<sub>8</sub>O<sub>4</sub>), BP 200°C  
 Mesylate, methanesulfonyl acid (CH<sub>3</sub>SO<sub>3</sub>H), BP 167°C  
 Salicylate, from salicylic acid (C<sub>7</sub>H<sub>6</sub>O<sub>3</sub>), BP 211°C

BP 190°C  
 BP 222°C  
 BP 170°C  
 BP 235°C, FP 206°C

## IMS Guidance

0.25	Minimum value
0.5	London forces, melting point <100°C, melting endotherm < 30J/g
1	Mainly London Forces with some polar bonding, melting point 100-120°C, melting endotherm 30-50J/g
2	Some polar bonding, melting point circa 150°C, melting endotherm circa 50-70J/g
4	Hydrogen bonding, melting point 180-200°C, melting endotherm circa 70-100J/g
6	Significant hydrogen bonding, melting point >200°C, melting endotherm > 100J/g
10	Ionic bonding, melting point >300°C or no melting during DSC test
16	Maximum value

As formula Factor = ((Melt temp (°C) - 75)/50) + (Melt endotherm/50) - 0.3

Maximum values if no melting

Polar bonding - Factor = 9

Ionic bonding - Factor = 16

# Results to date for API predictions prior to test data



There are no 'false negatives' to date

Prediction Accuracy	Compound	Predicted MIE (mJ)	Test MIE (mJ)
Correct prediction of 'material of concern' <5mJ	AA	2 to 4	2 to 3
	BB	1 to 3	<3
False positives – predicted 'material of concern' but not	CC	2 to 4	6 to 7
	DD	4 to 11	7 to 8
Correct prediction that NOT a 'material of concern' (≥5mJ) & Prediction broadly correct	EE	35 to 43	35 to 40
	FF	7 to 15	10 to 13
	GG	5 to 9	16 to 19
	HH	30 to 45	60 to 70
	II	8 to 17	25 to 30
	JJ	7 to 28	10 to 13
	KK	70 to 130	200 to 300
	LL	15 to 37	15 to 18
	MM	10 to 20	15 to 17
	NN	10 to 17	6 to 22 (two tests)
Prediction excessively 'safe side'	OO	25 to 46	400 to 500
	PP	8 to 12	100 to 200

# Issues with the model – particle size and the micronization anomaly



- Model works well for particles that are sized reduced to <75 microns for test.
- Model breaks down at small particle sizes (micronized or similar) as test results do not change uniformly with particle size.
- Hypothesis is that this is due to agglomeration.

Compound	Test Result Unmicronized	Test Result Micronized
1	8 to 10	2 to 3
2	25 to 30	9 to 10
3	35 to 40	60 to 70
4	5 to 10	4 to 5
5	200 to 300	200 to 300
6	7 to 8	9 to 10
7	40 to 50	60 to 70
8	4 to 5	40 to 45
9	100 to 200	300 to 400
10	30 to 35	100 to 200
11	3 to 4	45 to 50

- Well accepted by the business.
- Success Criteria:
  - Use <1g of material ☒
  - Not require any additional equipment ½ - TGA available before but not routinely used
  - 'False positives' < 33% of the time ✓ - Promising so far but small data set
  - 'False negatives' < 3% of the time ✓ - Promising so far but small data set

# Dust Explosion Characteristics

$P_{max}$   
 $K_{st}$

- 
- Not as advanced as MIE prediction.
  - Still one factor to work on,
    - Which may explain a phenomenon in our test data set.
-

# Hypothesis



Follows on from the MIE work...

- The dust explosion properties are dominated by the most readily flammable portion of the molecule.
  - Sometimes this is the whole molecule.
  - Sometimes this is a flammable fragment that has cleaved from the parent.
  - Example (data from test):

Compound	MIE (mJ)	Pmax (Bar)	Kst (bar.m/s)
XXX	80 to 90	8.8	153
XXX.salicylate	10 to 15	8.2	212
Salicylic acid	4 to 5	8	270

- Pmax – estimated via thermodynamic combustion of the flammable parts,
  - Plus whole molecule as a safeguard.
- Kst – as a pseudo rate based on MIE, % of molecule that burns, adiabatic flame temperature, heat of combustion and a dispersion factor TBD.

# Maximum Explosion Pressure (Pmax)



- This follows the published methodology developed by Michael Toth of Merck & Co.
- The difference is that it is based on the cleaved flammable part(s) of the molecule if TGA suggests a partial cleave rather than the whole molecule disintegrating.

Compound	Test Pmax (bar)	Predicted Pmax (bar)
YYY	9.3	8.8
Iso-butene cleave	N/A	9.3

- Heat of combustion from CHETAH or published data.



# Example combustion calculation to estimate Pmax



Grid reference (e.g. Row 1, No. 1)

Row 1, Number 3

## Pmax Simulation

Substance **Iso-butene**

Flammable fragment most likely to come of

## Experimental values

Source (e.g. MHD)

MHD

MIE

mJ

Pmax

Bar

Kst

Bar.m/s

Formula

$C_4H_8$

Carbons

4

48

Hydrogen

8

8

Oxygen

0

Molecular mass

56

kg/kmol

Reactants		
Solid	Oxygen	Balance of air

Products		
Gas products	Balance of air	

Combustion (kmols)

$C_4H_8$

+

6  $O_2$

+

22.6  $N_2$

=

4  $CO_2$

+

4.0  $H_2O$

+

22.6  $N_2$

Mass (kg) (one kmol)

56

192

632.0

176

72

632.0

Gas kmol reactants =

28.6

Gas kmol products =

30.6

Expansion =

1.07

Mass reactants (kg) =

880

Mass products (kg) =

880

Check it balances

Heat of combustion

Source (e.g. Chetah)

Eng. Toolbox

Hc =

-2708 kJ/mol

Hc =

-48357 kJ/kg

How much material does the 20L test use and how much heat is liberated?

Approx  $O_2$  mols in 20L sphere

0.175 mols

0.000175 kmols

Amount of starting material combusted =

2.92E-05 kmols

0.001633 kg

1.633333 g

Actual heat output =

-78.9833 kJ

First iteration to determine temperature rise

Specific heat assuming 2000K rise

Cp =

1.310 kJ/kg.K

Temperature rise from  $Q = m.Cp.dT$

Q =

2708000 kJ

m =

880 kg

Cp =

1.310 kJ/kg.K

Therefore,

dT =

2349 K

Based on 2000K rise

Water Cp =

2.458 kJ/kg.K

CO2 Cp =

1.247 kJ/kg.K

N2 Cp =

1.197 kJ/kg.K

Second iteration with adjusted Cp values

Cp =

1.332 kJ/kg.K

Temperature rise from  $Q = m.Cp.dT$

Q =

2708000 kJ

m =

880 kg

Cp =

1.332 kJ/kg.K

Therefore,

dT =

2310 K

Based on 2000K rise

Water Cp =

2.458 kJ/kg.K

CO2 Cp =

1.247 kJ/kg.K

N2 Cp =

1.197 kJ/kg.K

Based on 2400K rise

Water Cp =

2.548 kJ/kg.K

CO2 Cp =

1.272 kJ/kg.K

N2 Cp =

1.215 kJ/kg.K

Value used

2.536 kJ/kg.K

1.269 kJ/kg.K

1.213 kJ/kg.K

## Results

If  $T_0$  =

300 K

$T_c$  =

2610 K

Adiabatic flame temperature

$P_{max} = P_0 \times (n_p/n_r)^{\gamma} \times (T_c/T_0)$

$P_0$  =

1 bara

$P_{max}$  =

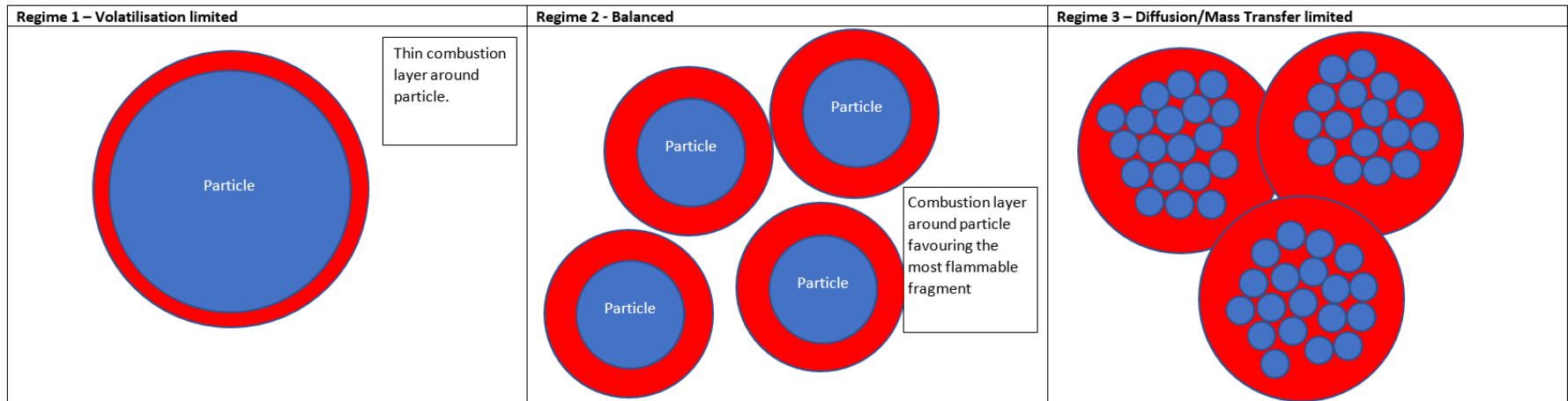
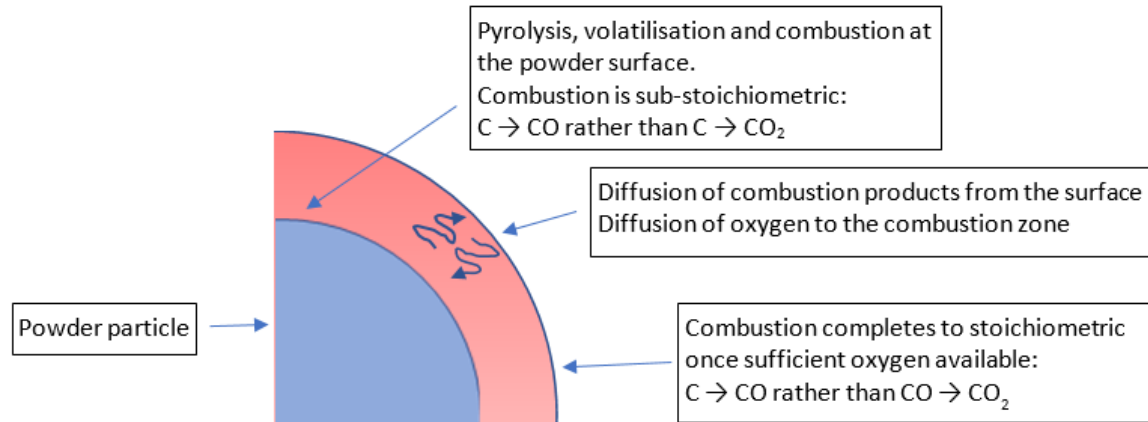
9.31 bara

Confidential

17

# Kst Hypothesis

Three regimes – Kst highest at Regime 2



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- This is taken as a rate and is assumed to follow an Arrhenius type relationship:
  - $K_{st} = (M_o/M_i)^3 \cdot A \cdot e^{(-E/RT)}$
  - Where:
    - $M_o$  = Gas mols post combustion
    - $M_i$  = Gas mols pre combustion
    - $A$  = Pre-exponential factor and is related to Minimum Ignition Energy (MIE) and the percentage of the molecule that burns
    - $-E/R$  = Activation energy divided by the Universal Gas Constant and is related to the heat of combustion of volatile fragment(s)
    - $T$  = Adiabatic flame temperature of the combusted fragment(s) (K)

# Factor Values at Present



All empirical and subject to change

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- At present
- $-E/R$  – Varies from -6,500 at a heat of combustion of  $\leq 10,000 \text{ kJ/kg}$  linearly to -4,800 at a heat of combustion of  $\geq 40,000 \text{ kJ/kg}$
- $A = A_F + A_I$
- $A_F$  = Relates to the fragmentation of the molecule.
  - $A_F$  = % fragmentation x 20, up to a maximum value of 1,000 (50% fragmentation)
  - $A_I$  = Relates to the MIE in mJ.  $A_I = -205.4 \ln(\text{MIE}) + 1600$ , down to a minimum of 500 (MIE 200mJ)
- These values are all best fit based on data for ST2 and ST3 compounds (API and late intermediates) from the GSK database of dust explosion test results

# Results to Date



Predictions done before results available

Predicted Pmax >9.5 and/or Kst > 275 bar.m/s flagged as materials of potential concern for Pmax > 10 bar and/or Kst >300 bar.m/s (ST3).

Several prediction far in excess of test values:

Prediction Quality	Compound	Predicted Pmax (bar)	Test Pmax (bar)	Predicted Kst (bar.m/s)	Test Kst (bar.m/s)
Material of concern (MoC) correctly flagged	QQ	8.8	8.6	316	309
	RR	8.8	8.6	286	319
False positive	SS	9.6	7.8	285	135
	TT	9.1	8.4	277	185
Not MoC and prediction broadly correct	UU	8.2	8.2	190	172
	VV	9.1	9.0	272	247
	WW	8.3	7.4	133	140
	XX	8.2	7.8	224	173
Prediction excessively 'safe side' but correct as not MoC	YY	9.1	7.8	219	91
	ZZ	8.6	7.4	108	90

# Missing Factor? Dispersion characteristic?



Can flow properties predict Regime 2 versus Regime 3?

- The model may be missing a factor that describes how well the powder disperses and whether reality is closer to Regime 3 than Regime 2.
- Models become:
  - $K_{st} = DF \cdot (M_o/M_i)^3 \cdot A \cdot e^{(-E/RT)}$ 
    - Where DF = Dispersion Factor
  - $P_{max} = DF \times P_{max(\text{thermodynamic})}$

Compound	Flow Properties	Pmax predicted Bar	Pmax Test Bar	Kst Predicted Bar.m/s	Kst Test Bar.m/s
RR	Easy flowing	8.8	8.6	286	320
SS	Cohesive	9.6	7.8	285	135
SS 25% blend	Easy flowing	N/A	8.1	N/A	219

- Well accepted by the business.
- Success Criteria:
  - Use <1g of material ☒
  - Not require any additional equipment  $\frac{1}{2}$  - Required CHETAH licence
  - 'False positives' < 33% of the time ☒ - Promising so far but small data set
  - 'False negatives' < 3% of the time ☒ - Promising so far but small data set

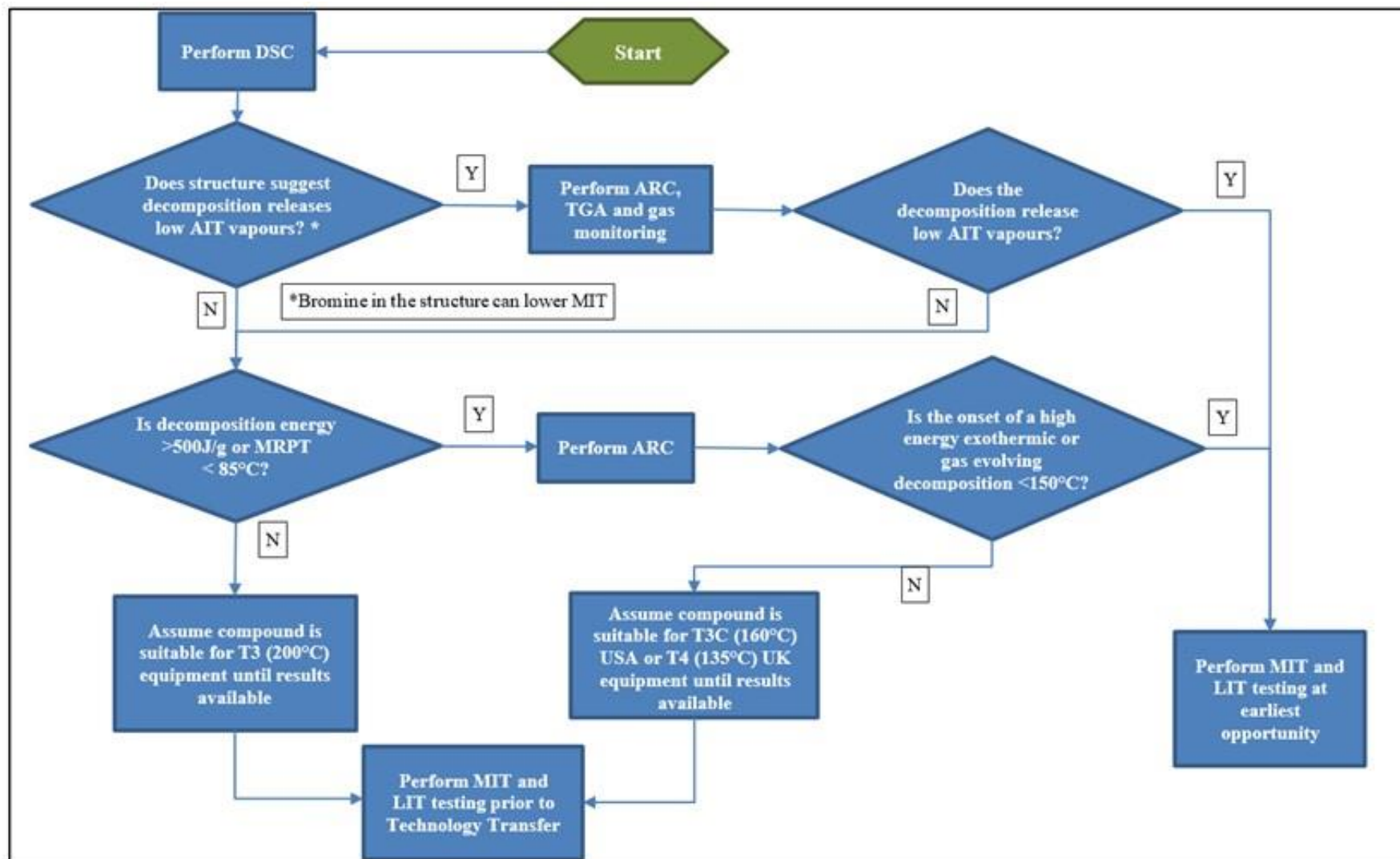
# Minimum and Layer Ignition Temperatures

MIT  
LIT



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- Equipment 'T' rating is the lower of LIT – 75°C or 2/3rds of the MIT (in °C).
  - Hazardous Area rated equipment generally has a 'T' rating – although not all pilot plant equipment has an external zone.
  - GSK has database of >1,000 MIT/LIT tests on API, intermediates, excipients and reagents.
  - As part of the work on MIE and dust explosions we have assessed the cleavage pathways of >100 compounds (mainly API) at temperature.
  - Empirically we have found that the following flow chart works and is 'safe side'.

# 'T' rating flowchart



- Well accepted by the business.
- Success Criteria:
  - Use <1g of material ☑ - Unless ARC testing required
  - Not require any additional equipment ☑ - DSC & ARC available and routinely used
  - 'False positives' < 33% of the time ☑ - Large data set
  - 'False negatives' <3% of the time ☑ - Large data set, no false negatives

# Conclusion

# Conclusions



## Testing is best if material quantities allow

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- Versus Success Criteria:
  - Reliably predicting 'Materials of Concern'.
  - Meeting success criteria.
  - Working ongoing to establish 'dispersion factor' and reduce the number of 'false positives'.
- Use:
  - Successfully used on 8 compounds to speed plant entry by doing risk assessment and set-up based on predicted data and starting once real data available.
  - Successfully used on 8 compounds for which there were no data prior to campaign start and either MIE or full results now available.
  - Further 6 compounds in plant or completed campaigns for which no test results are available.

# Acknowledgements

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