Investigating a Complex Energetic Decomposition Incident using Kinetic Modelling to Establish Safe Manufacturing Conditions

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Abstract

Unexpected decomposition of a batch of pharmaceutical intermediate in 2019 at a pharmaceutical manufacturing facility in the UK led to overpressurisation of a drying vessel. There were no fatalities or serious injuries, despite the potential, but widespread contamination in the facility and the incident was reportable as a Dangerous Occurrence under UK RIDDOR legislation. During the investigation of the incident, supported by external process safety experts from DEKRA, it was identified that the pharmaceutical intermediate was prone to extremely energetic decomposition.

For modest thermal decomposition events, protection (emergency relief venting) is often deployed as the backstop layer of protection to prevent vessel overpressure and prevent harm. In the current case, the decomposition was sufficiently violent that vent size requirements were impractically large – requiring investigation of a reliable prevention strategy rather than protection.

Prevention required that conditions which could initiate the decomposition be fully identified and then reliably avoided. This can be relatively straight-forward when simple kinetic models or generic "rules of thumb" can be applied to calorimetric data to demonstrate a large margin between operating conditions and initiating conditions. In the absence of this large margin, much more in-depth, scientific analysis is required to answer the critical question "**What is a safe drying temperature for this material in this specific vessel?**".

This paper provides an overview of the decomposition incident in 2019 and the resulting incident investigation but focuses on the subsequent stages of assessment to derive a robust basis of safety for future manufacture. Specifically, calorimetric testing and kinetic modelling are presented for this kinetically complex, highly energetic decomposition, which enabled the "onset temperature" to be reliably predicted for specific vessel scenarios. The prevention strategy deployed to avoid this temperature is also discussed in the paper, rigorously applying IEC61511 principles for the safety critical elements.

Keywords: Thermal decomposition, calorimetry, kinetic modelling, onset temperature.

1. Material and Process Description

Manufacture of an active pharmaceutical ingredient (API) was undertaken at a pharmaceutical manufacturing site in the UK. The API is a relatively high molecular weight (350 – 450 $g.mol^{-1}$) substance including two functional groups which are known to be associated with energetic decomposition behaviour. The stage of relevance to this paper involved a chemical reaction followed by crystallisation of the intermediate of interest (referred to hereafter as Compound A). The wet cake is solvent washed, filtered dry in a filter dryer (operating at normal temperature of 55°C under vacuum) and discharged to Intermediate Bulk Containers (IBC's) via a delumper. The process had been in (non-continuous) production at the facility since 2015 and a full HAZOP study had been completed utilising an extensive range of process safety data on the material and process. Key process safety were as follows:

- Dust explosion characteristics: Material is dust explosible with a minimum ignition energy (MIE) of 80 – 100 mJ (electrostatic spark) and 60 - 80 mJ (mechanical spark). This is not considered particularly sensitive. Minimum ignition temperatures (MIT) were measured as 730°C (dust cloud) and 260°C (dust layer). The material exhibited weak dust explosion severity (Kst 62 $bar.m.s^{-1}$ / Pmax = 9.7 barg).
- Flammable solid characteristics: Material propagates a hot spot ignition and is classified as UN Class 4.1 (flammable solid).
- Thermal stability characteristics: Differential Scanning Calorimetry (DSC) shows a very energetic decomposition (1870 J/g) initiating at 244°C. Adiabatic calorimetry using Accelerating Rate Calorimetry (ARC) shows a violent, gas generating, decomposition initiating at 201°C with a calculated TD_{24} of 170°C. (TD_{24} is the temperature from which a material will take 24 h from onset to reach its maximum decomposition rate under adiabatic conditions).
- Explosive properties characteristics: Due to the high energy decomposition (as seen in DSC testing), the material was subjected to a wide range of explosive properties tests which demonstrated that the material tests negative towards impact and friction and also towards explosives classification tests as outlined in the UN Transportation of Dangerous Goods Recommendations (Koenen tube test, UN Gap test (series 2a) and UN Time / Pressure Test). This confirms that whilst high energy, the material is not considered a candidate for formal classification as an explosive substance.

2. Incident overview

In late June 2019, the fifth batch of a five batch campaign was being completed. The night shift had encountered powder flow difficulties during discharge of the dried Compound A. An initial 6kg of material had passed through the powder transfer system (PTS) to the IBC's. The intermediate hopper high level contact was still in alarm condition, indicating that the discharge had blocked at the hopper prior to the PTS. To overcome this problem, an operator tapped the edge of the hopper with a rubber mallet to encourage the material into the powder transfer system (PTS). This was sufficient to start the discharge.

The first big bag was filled. The system was placed on hold and the operators went for their break. After returning from their break the discharge was restarted only for the process to stop again. The delumper was recorded as tripping twice. After the third time of tripping, the system was left on hold for further investigation by the next shift.

The operator monitoring the discharge locally reported that the lump breaker / discharge assembly was quite warm, but he could keep his hand on it without fear of injury or involuntary action, i.e. less than hand hot, usually considered to be approximately 40 - 60°C. After approximately 10-11 minutes with the system on hold, an over-pressurisation incident occurred. The local fire and rescue service were called and attended site. On inspection, they located hot spots via thermal imaging camera at approximately 100°C in the vicinity of the discharge chute. External CCTV evidence showed a white powder/dust being emitted from the discharge system on the filter dryer, before the body gasket of the vessel failed, with material ejecting from the full circumference of the vessel. The plant area was filled with the white dust cloud. Further discharge was observed from the relief vent on the roof. Figure 1 shows the discharge in its incipient stage.

Figure 1: Discharge of White Dust from the Filter Dryer Gasket

There were no serious injuries or fatalities caused by the release, despite the hazardous nature of the released products. An extensive clean-up operation and incident investigation ensued with the incident notified to the UK Health and Safety Executive (HSE) under RIDDOR as a Dangerous Occurrence. However, the potential of this unforeseen event could have been so much worse had the released material been more toxic, ignited causing an unconfined deflagration or if the vessel had been fuller and consequently ruptured.

3. Review of potential causes and identification of root cause

A root cause analysis considered three possible causes of the top event (Loss of Containment):

1. Product decomposition
2. Internal deflagration, and
3. High pressure nitrogen supply.

High pressure nitrogen supply was discounted because the ejected powder had been chemically altered. A high pressure nitrogen supply would have been expected to expel the powder without a chemical change. Internal deflagration was also discounted for multiple reasons:

- The ignition energy and temperature characteristics of the powder were very high (well beyond the capability of possible ignition sources present).
- The event was a prolonged event occurring over a matter of minutes. A deflagration would be expected to complete in the millisecond / second timeframe.
- The powder released was not consistent with a combustion product.

The final cause was identified as product decomposition (self-reaction, not self-heating) which initiated in the delumper and propagated back into the filter dryer. Further studies focused on the decomposition characteristics of the material and establishing a safe system of work for further production.

4. Initial thermal stability studies

Prior data known by the operating company (see section 1) indicated that the onset temperature of decomposition measured using an adiabatic calorimeter (ARC) for a 2.0 g sample was 201°C (see Figure 2). Using rules of thumb outlined in Section 4.1, there was considered more than adequate safety margin between the operating temperature of the dryer (50°C) and the onset of decomposition (TD_{24} = 170°C).

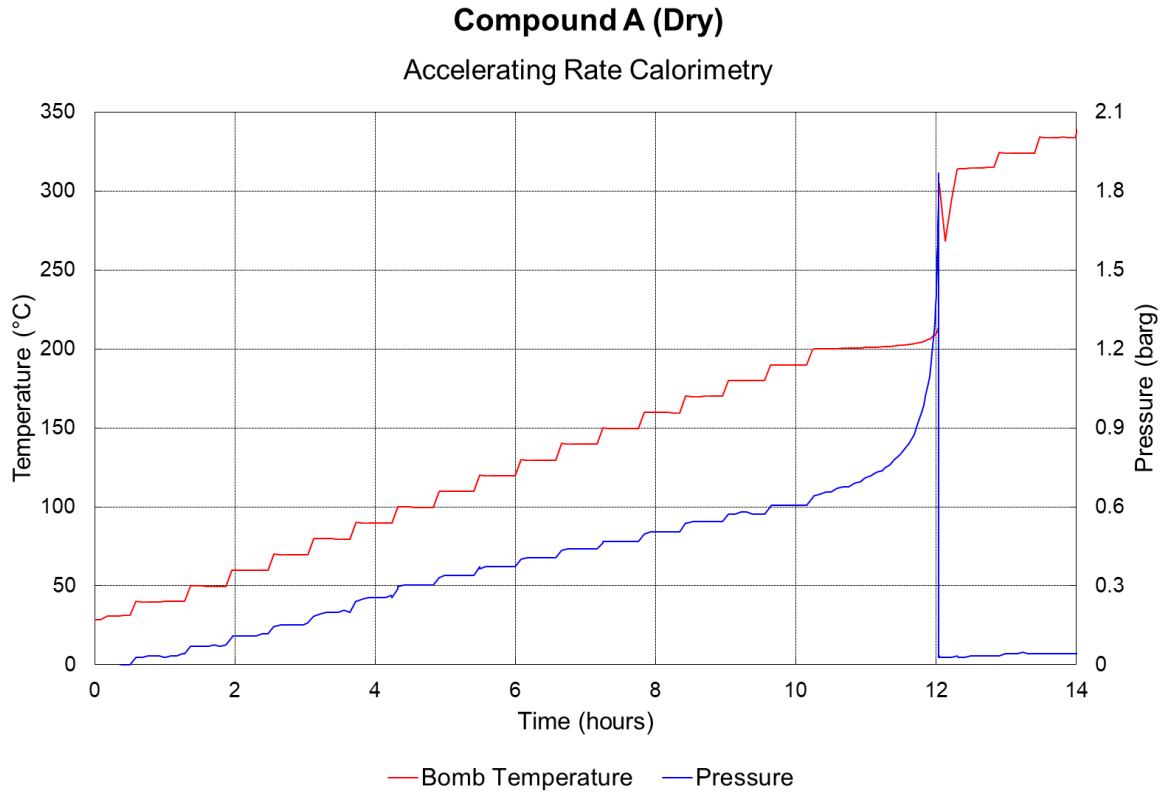

Figure 2: Adiabatic Calorimetry Data for Compound A (Dry)

The data shows the test cell rupturing at a last recorded pressure of 1.8 barg. As the test cell has a design pressure limit of 100 barg and the data collection interval is 1 second, it can be concluded that the maximum rate of pressure rise would be above 100 $bar.s^{-1}$.

The very high maximum pressure of the decomposition and the high rate of pressure rise lead to the conclusion that two potential bases of safety (runaway containment or emergency relief venting) are not feasible for the existing plant configuration. Containment design above 100 barg would be extremely expensive and the emergency vent required to safely relieve the pressure would be impractically large. The only conceivable basis of safety for such a violent decomposition is prevention – avoidance of temperatures which initiate this behaviour through process design and control.

The key question in design of safety systems, interlocks, alarms, etc, is therefore: "**what is the maximum safe handling temperature for this product, in the planned production vessels?**". The criticality of this data cannot be overstated. Deploying trips, alarms and temperature regulated products as safety critical devices requires that they are formally rated as safety instruments functions. The process to design, implement and maintain such functions can be extremely complex (expensive and time-consuming) but if the critical temperature for the product is incorrectly specified, then the system will be of no value (even worse, it could provide a false sense of safety).

4.1 Conventional Methods for Defining Maximum Allowable Safe Handling Temperatures

On the face of it, there is a very appreciable safety margin between the operating temperature of the dryer (50°C) and the raw onset temperature of the decomposition reaction (201°C). Most experienced hazard testing practitioners would suggest that the margin of safety is more than adequate. Various techniques are commonly applied to specifying maximum safe handling temperatures based on thermal hazard test data. The most common include:

- Applying a blanket "safety margin" to thermal stability test data which can vary from 100 K for (relatively insensitive) DSC test data, to 10 K for low phi factor, adiabatic calorimetry data.
- Using simple empirical correction equations which assume conservative kinetics.

- Using the TD_{24} value determined from adiabatic calorimetry (corrected for testing apparatus thermal inertia, the so-called 'phi factor').
- Performing multiple tests at different ramp rates to extract more accurate kinetic parameters.
- Using extreme sensitivity calorimetric techniques (such as Thermal Activity Monitors) to highlight early low level behaviour.
- Constructing a full kinetic model based on multiple isothermal calorimetry and / or adiabatic calorimetry data.

The above correlations typically work well for liquid materials and mixtures as the Semenov theory of thermal explosion applies (this model assumes that the mixture is at a uniform temperature throughout, heat generation is governed by Arrhenius kinetics and heat loss is governed by contact with, and conduction through, the walls). In the case of Compound A, the material varies in the process from a damp slurry to a dry solid – moving as it does so from the Semenov model towards the Frank-Kamenetskii model where increasing importance of conductance through the solid itself dominates the heat dissipation rate.

A further complication in the case of Compound A is that the kinetics of the decomposition were not simple zero or first order. The event was identified as having multiple steps, one or more of which is autocatalytic in nature.

Few techniques above usually involve assessing the heat loss of the vessel – most focus on the expected adiabatic behaviour of the material and assuming that the adiabatic assumption makes the data directly usable. Furthermore, autocatalysis invalidates several of the techniques above and warrants a deeper understanding of material behaviour.

Given that the material was a solid and exhibited some autocatalytic behaviour, a more rigorous analysis of critical temperatures and pressures was required and pursued.

5. Defining safe process temperatures

As avoidance of decomposition is the only realistic basis of safety, three effects must be considered to ensure safe temperatures are reliably specified:

- Normal material composition variability (including foreseeable contaminants) – the most demanding composition (that with the lowest onset temperature) should be the basis for maximum operating temperature specification.
- Detailed kinetics of the decomposition event.
- Heat loss characteristics of the system (vessel + material)

5.1 Identifying the most hazardous composition

Testing across a range of material compositions was performed on Compound A. This included several potential and foreseeable contaminants. It was identified that high chloride concentrations could exist (from materials present in the preceding process steps), as could rust (from materials of construction). Figures 3 and 4 illustrate the significantly reduced raw onset temperatures of 121°C (chloride contaminated) and 172°C (rust contaminated), compared to 201°C for dry Compound A.

Having examined the effect of contaminants, the impact of process solvents was examined. In the absence of any chemical interaction (or self-reaction) of the solvent, it would normally be expected that a solvent would act as an inert diluent – reducing the severity and increasing the onset temperature of the decomposition (e.g. as a phlegmatizer in explosives handling). As is often the case though, with Compound A, solvents were seen to in some way catalyse or initiate decomposition at lower temperatures. Figures 5 and 6 illustrate the reduced raw onset temperatures of 140°C (wet cake) and 130°C (solvent slurry).

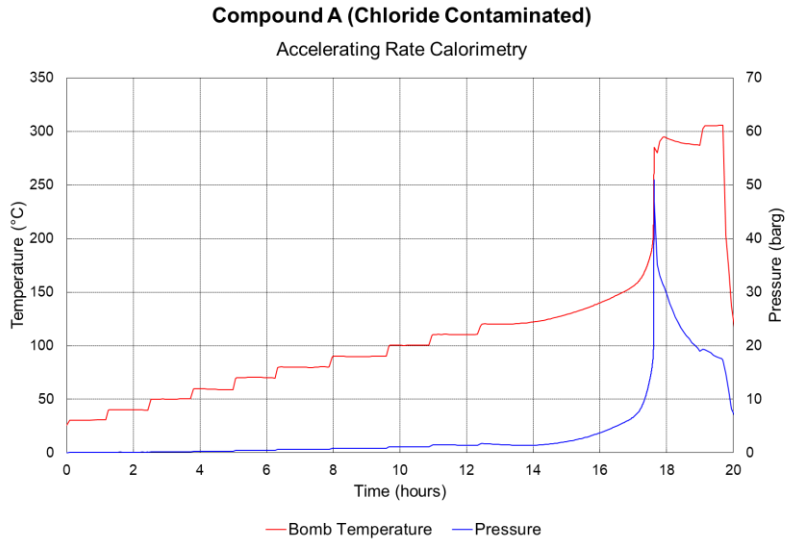

Figure 3: Compound A with Chloride Contamination (Accelerating Rate Calorimetry)

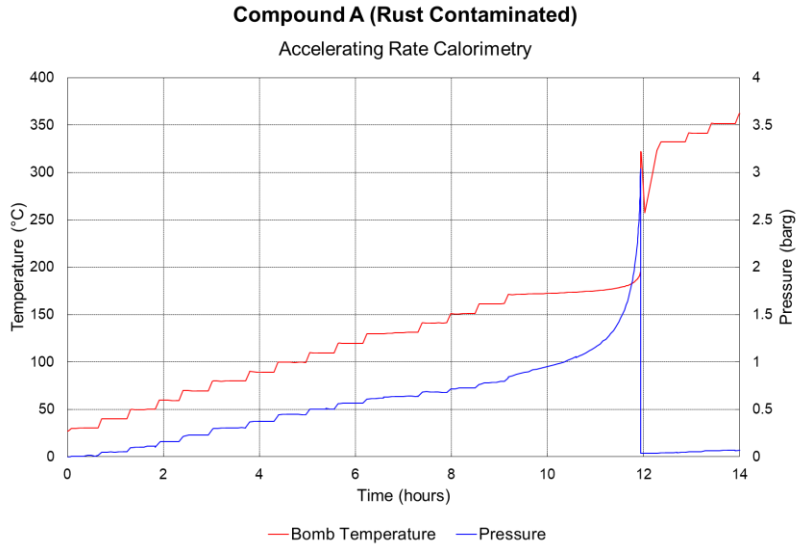

Figure 4: Compound A with Rust Contamination (Accelerating Rate Calorimetry)

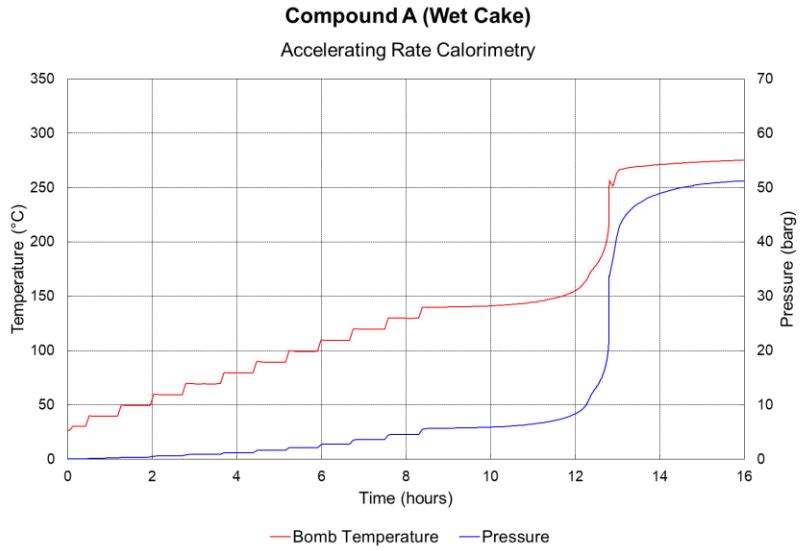

Figure 4: Compound A – Wet Cake (Accelerating Rate Calorimetry)

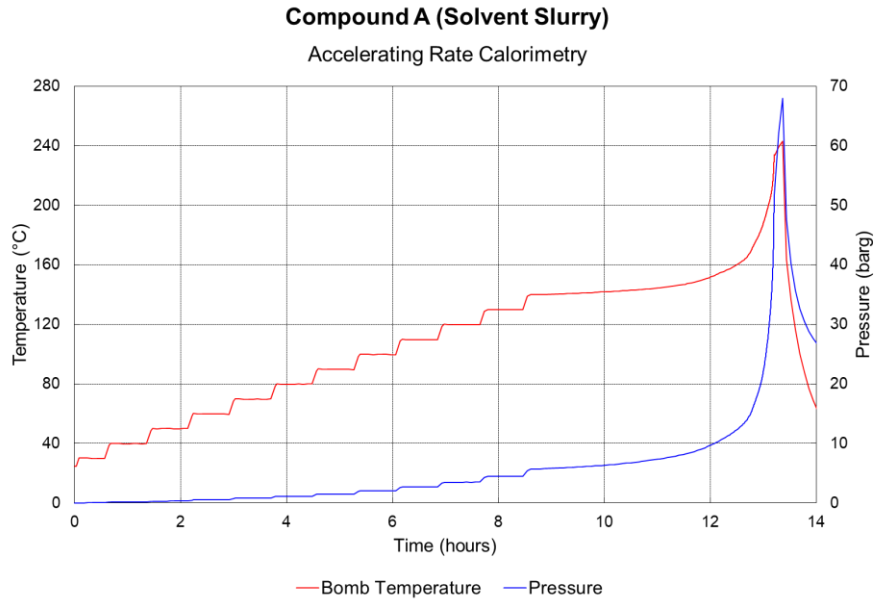

Figure 5: Compound A – Solvent Slurry (Accelerating Rate Calorimetry)

Data for the composition variants is summarised in Table 1.

Material	Compound A Dry	Chloride Contaminated	Rust Contaminated	Wet Cake (39% solids)	Solvent Slurry (24% solids)
Measured onset temperature (°C)	201	124	172	141	141
TD_{24} (°C)	170	93	158	110	124

Table 1: Summary of ARC Data for Compound A and its Compositional Variants

The chloride contaminated case is observed to be worst case (lowest TD_{24}), followed by the wet cake. (The chloride contamination case was subsequently removed from further investigation as additional in-process checks were implemented to ensure this scenario did not arise in subsequent production). The wet cake was retained for further study as the worst conceivable formulation (although slurry and dry product studies were performed in parallel).

5.2 Kinetic model development

To develop a comprehensive kinetic model for the decomposition reaction, the whole reaction must be observed and analysed. Due to the highly energetic nature of the Compound A decomposition, even low fill volumes in the ARC resulted in overpressurisation and failure to capture the entire decomposition event in all dry product tests. The wet cake material was tested at a fill level which provided full containment and characterisation of the event. Inert diluents (alumina for the solid tests, extra solvent for the 'wet' tests) were deployed to partially phlegmatise the activity in other tests to contain the full runaway reaction within the limits of the ARC.

Kinetic modelling of the data from the ARC testing was undertaken using 'ARKS AC' and 'ARKS FK' (Adiabatic Calorimetry analysis, and Formal Conversion-Based Kinetic Modelling software), from ChemInform St. Petersburg (CISP). This modelling considered the whole reaction behaviour, including multiple reaction phases where appropriate, accounting and correcting for the phi factor of the ARC, the solvents, and has regressed kinetic equations.

In order to analyse the data, operational parameters from the ARC apparatus (bomb mass, volume and specific heat capacity, sample mass, heat-up steps, etc), were used. Additionally, values for the powder particle density, specific heat capacity and thermal conductivity were measured to ensure the most accurate models. A few assumptions were nevertheless necessary:

- The pad gas present in the ARC bomb during set-up was subtracted from the pressure trace in order to reveal the underlying gas generation and solvent vapour pressure evolution
- Owing to the heat-wait-search (HWS) nature of the tests, the history of the sample needed consideration including the initial heating steps

The kinetic modelling involved an assessment of linked reactions according to the phases of the test data (e.g. a reaction step for each exotherm), and the application of either a generalised autocatalytic, or an n^{th} order kinetic model, as relevant. The temperature ('Q' model, exotherm) and pressure ('G' model, gas generation) curves were analysed using the multi-reaction approach. Analysis of the results in all tests indicated that exothermic reaction occurs before the detection of an onset in the HWS profile; this is consistent with the observation of early gas generation.

The complexity of the decomposition required simulation using multiple reactions linked in series. The model parameters apply equally to both the temperature and pressure, indicating that the gas generation (pressure) is directly caused by the temperature increase (occasionally for other materials, the two parameters are seen to involve different kinetics). The degree of agreement between the model and the experimental data was seen to be good in the comparative plots.

Kinetic modelling identified four kinetic steps associated with the decomposition of Compound A, the first three of which were autocatalytic.

A → B1 → B2 → B3 → B

Where: **A → B1** *Generalized Autocatalysis*

B1 → B2 *Generalized Autocatalysis*

B2 → B3 *Generalized Autocatalysis*

B3 → B *N-Order*

The model was found to fit the test data well and was validated through a series of isothermal tests at different start temperatures. The correlation between experimental data and model data (for temperature and pressure) is illustrated in Figure 6.

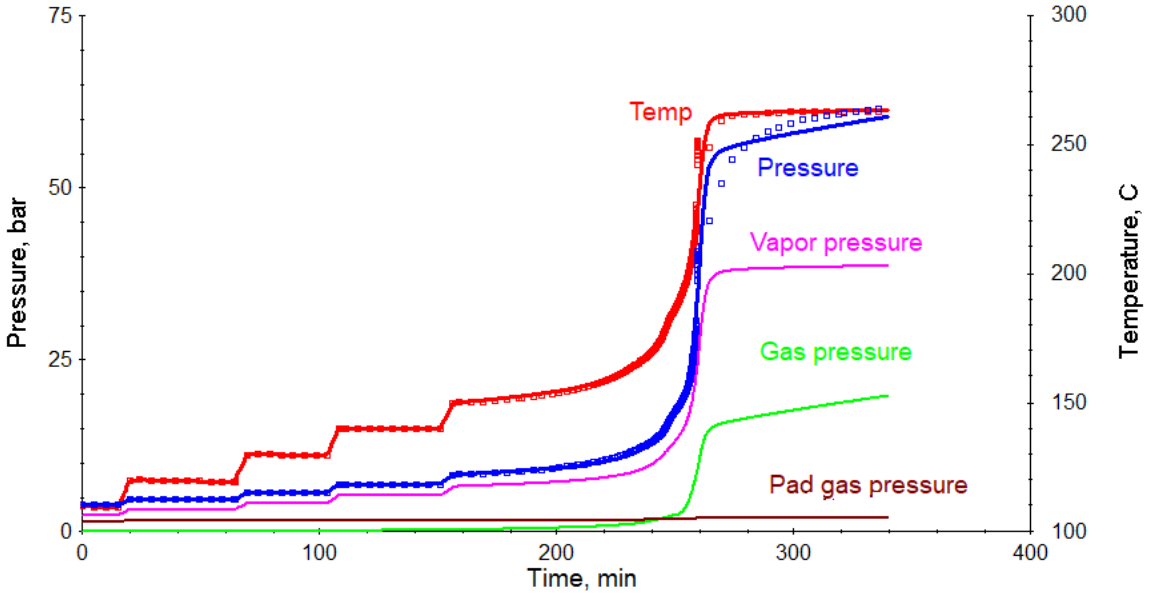

Figure 6: Compound A (Wet Cake) Model Correlation (Solid Lines) with Experimental Data (Symbols)

Using the model created, time to maximum rate (TMR) predictions and temperature at which the TMR is 24 hours (TD_{24}) were calculated for the Wet Cake (see Table 2). It should be stressed that these calculations assume adiabatic conditions (i.e. zero heat loss) and are thus more severe than would be seen in plant equipment.

Temp (°C)	TMR (h)
50	20085
60	5541
70	1648
80	525.9
90	178.7
100	64.4
110	245
120	9.7
130	4.0
140	1.7
150	0.8
T_{D24} (°C)	**110.2**

Table 2: Adiabatic Simulation Results – Time to Maximum Rate – Compound A Wet Cake

5.3 Modelling decomposition in process vessels

The previous section considers the material characteristics assuming a uniform temperature throughout and to be fully adiabatic (i.e. no heat loss to the environment). However, the simulations of the plant vessels using ARKS TE software have examined the behaviour, taking into account heat losses and the non-homogeneous internal temperature distribution. Simulation considered the Compound A Slurry, Wet Cake, and the Dry powder, since this represents the evolution of conditions in the filter dryer as the product is produced. Results are provided below for the wet cake. The details of the plant filter dryer (4.9 m^3) have been used in the model along with critical information on the thermal conductivity of the solid.

Whilst the aim of the study was to define maximum allowable handling temperature for the material, the selection has to be rooted in the reality of the plant equipment. The study initially examined the effect of overheating to the maximum possible jacket temperature (140°C in the event of steam heating failure) and the initial estimate of the intended high temperature interlock (85°C). The normal maximum operating temperature is 50°C. When conducting the simulations, the vessel walls and contents are assumed to be at the chosen initial temperature, with the walls being held at a constant temperature as any exotherm progresses. This model is specific to the vessel, input scale and concentration – but once the physical vessel

dimensions, reaction kinetics and fill / initial temperature conditions are established, the model can be used to study multiple potential configurations.

The failure mode under consideration involves heating of the contents by a maloperation of the vessel heating system. Consequently, the simulations have considered a constant temperature applied to the walls, and the wet cake to initially be uniformly at the same temperature. The simulations then assume that heat generated by the decomposition can be lost to the constant temperature walls, according to the capabilities afforded by the powder thermal conductivity and the wall heat transfer. Realistically, for a wet cake or dry powder, all heat transfer occurs via conduction. Thus, there will be temperature gradients from a hotter centre to the cooler walls as the exotherm develops. For a slurry, accounting for convection could be considered, whilst modelling agitation as a fully stirred homogeneous fluid is not conservative owing to the possible fallibility of the agitator.

The calculations have established a 'critical temperature' for the above set of parameters. At temperatures below the "critical temperature", the heat exchange to the walls allows efficient removal of heat from the system during the incipient decomposition phase, and wet cake temperature varies gradually, slowly rising to a maximum overheat before subsequently reducing (i.e. acceleration to the very rapid decomposition does not occur). During this period, gas will still be generated at a slow rate and hence pressure would rise in a closed vessel, although in an open vessel this may potentially be vented. In contrast, at temperatures above the 'critical' value, the exotherm can progress into a thermal explosion, at a rate and timescale determined by the overall system characteristics. In the non-uniform simulations, the temperature will rise more steeply in the centre of the settled material as heat is lost to the constant temperature walls and depending upon the balance of heat generation against heat transfer, the decomposition will transition into an explosive runaway.

5.4 Safe temperature conclusions

The critical temperature for the Compound A Wet Cake was determined to be **80.5°C** (albeit, the time to maximum rate is very long from just above this temperature). This is 30 K **below** the calculated TD_{24} value which would often be used as the maximum safe handling temperature for a product and 60 K below the raw onset temperature in the adiabatic calorimeter. The reinforces the importance of applying a much deeper and more rigorous analysis for highly energetic solid materials. Corresponding critical temperature for the dry product was found to be 159°C (calculated on the same basis) whilst for the slurry, the inclusion of convection in the model yielded a value of 125°C

The kinetic model and vessel simulations inevitably contain numerous assumptions. Although most are conservative, this still warrants a small safety margin applied to the calculated critical temperature. In the current case, the operating company installed SIL-rated interlocks at 75°C on the vessel heating system – as a central control strategy, along with numerous other measures to avoid other possible initiation causes (localised hot spots, tramp metal inclusion / friction, etc).

6. Building reliable assessment methods for thermal stability risks

6.1 Recommended approach for new substances with thermal decomposition risk

Highly energetic, self-reactive, solid substances pose a particular challenge when specifying allowable temperature limits. A simplified flow chart is provided in Figure 7 to illustrate a recommended strategy for assessment for self-reactive substances.

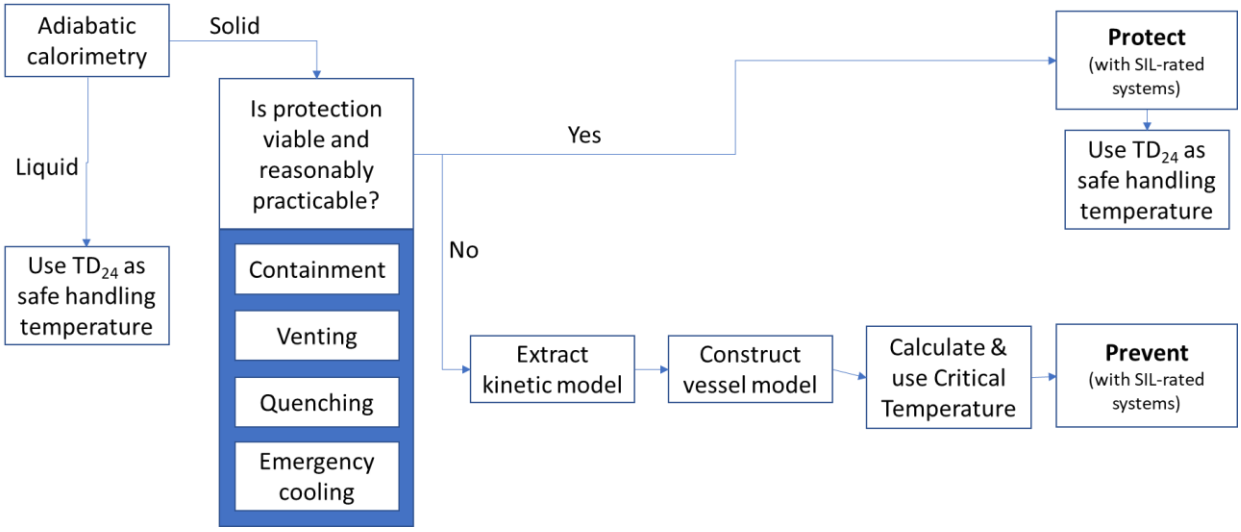

Figure 7: Recommended strategy for assessment of thermal risks associated with handling energetic substances

Self-heating substances (ie those undergoing oxidation reactions) are subject to alternative testing regimes. Differentiating the two types of behaviour can usually be achieved by testing in both air-abundant test methods and air-excluded test equipment.

6.2 Key learning points

Key learning points / advice for organisations studying stability of energetic solids:

- Do not focus on pure substances alone, consider potential destabilising effect of solvents / impurities and specify safe temperature limits based on the most demanding (conceivable) case, although sometimes the adiabatic assumption may be overly conservative and financially ruinous.
    - The default assumption may be that the pure substance will be most energetic and concentrated and hence will exhibit the lowest onset temperature. This study suggests that this is often not true.
- Conventional rules of thumb and use of TD_{24} extrapolated values may considerably overstate safe handling temperatures – potentially resulting in unsafe operating conditions – particularly for solid substances where conduction is the primary heat transfer mechanism. This is further exacerbated where autocatalytic behaviour is observed.
    - Autocatalysis can be identified by trying to fit kinetics to adiabatic calorimetry data assuming zero or first order kinetics and plotting ln(reaction constant) versus reciprocal of temperature. If the reaction accelerates beyond these model fits (ie. if the model is a curved line, not a straight line), it should indicate the potential presence of autocatalysis. Some commercial calorimetry software (eg that supplied with the ARC) can automatically perform such calculations and highlight this phenomena. Similarly, isothermal calorimetry (eg DSC) can be performed. If the heat flow increases at a constant temperature – this decisively indicates autocatalysis.
- If a material can propagate a hot spot (is classified as UN Class 4.1) then maximum temperature limits must be respected (monitored and controlled) in all production areas where the material can reside, not just inside bulk vessels.
- For very energetic solid substances, extraction of kinetic parameters enables development of a rigorous kinetic model which should be combined with accurate physical property information and vessel geometry information to enable critical temperature to be established.
- Prevention of violent decomposition initiation by temperature control measures inevitably involves the use of high integrity systems (these will be safety critical elements, likely subject to SIL rating and evaluated according to IEC 61511).
- Care must be taken in identifying potential heating sources such as friction from agitator, bearings, delumpers, etc (the initiating probable cause of the incident described here), electrostatic discharges, etc. Monitoring and control of such sources is a non-trivial exercise.

7. Summary and Conclusions

The specification of maximum safe handling temperatures for materials which undergo self-reaction is a non-trivial science, especially for solid substances (where conduction dominates heat loss) and even more so when reaction mechanisms are complex and involve autocatalysis. Commonly deployed generic safety margins and short-cut methods can easily be inadequate.

In the 2019 incident, initiation of an overpressure event was caused by frictional heating of a powder in a delumper which propagated back to bulk powder in the upstream filter / dryer. Due to the extremely highly energetic nature of the decomposition, prevention was the only viable basis of safety for future production, requiring development of a rigorous kinetic model and simulation of vessel conditions to yield a conservative maximum safe handling temperature around which high integrity interlock systems could be designed to prevent process temperatures exceeding the critical temperature.

The study also illustrated the destabilising effect that contaminants (intrinsic and extrinsic to the process) can have on stability – highlighting the need to study material from all stages of the process and with all conceivable impurities.

8. Acknowledgements

The operating company are thanked sincerely for allowing publication and sharing of data and information regarding the incident and subsequent assessment. A cornerstone of the science of process safety is learning from previous incidents. The selfless sharing of information such as this is crucial in helping others avoid such potentially serious loss.