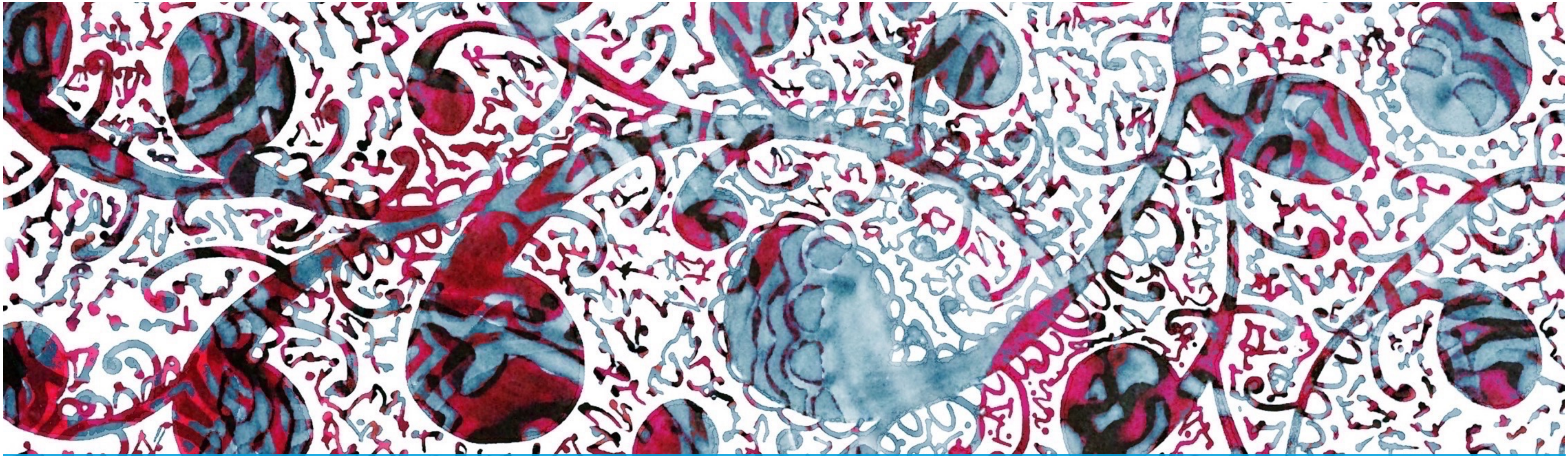

Enabling safe use of DMSO on Plant Scale

Process Safety Challenges

Dr. Brecht Egle

Senior Scientist Process Safety Center

13 –Sep - 2022

Michelle Hammer, *Surgical*

A New York City native living with schizophrenia, Michelle uses her talents to reduce stigma and start conversations about mental health.

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Introducing the Process Safety Center

Since 1984

Part of the Chemical Process R&D department

Based in the Beerse campus (Belgium)

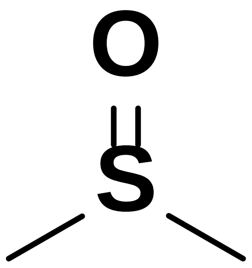
Center of Excellence for process safety at JnJ

Team of 5 dedicated members

Wide array of safety tests in-house

Contents

DMSO: General Properties



Boiling point	189 °C
Melting point	18.5 °C
Flash point	87 °C
Auto-ignition temperature	270 °C

High temperatures can be reached

May freeze in ambient conditions

High-boiling, polar aprotic solvent (water miscible)

Non-toxic, but skin permeable

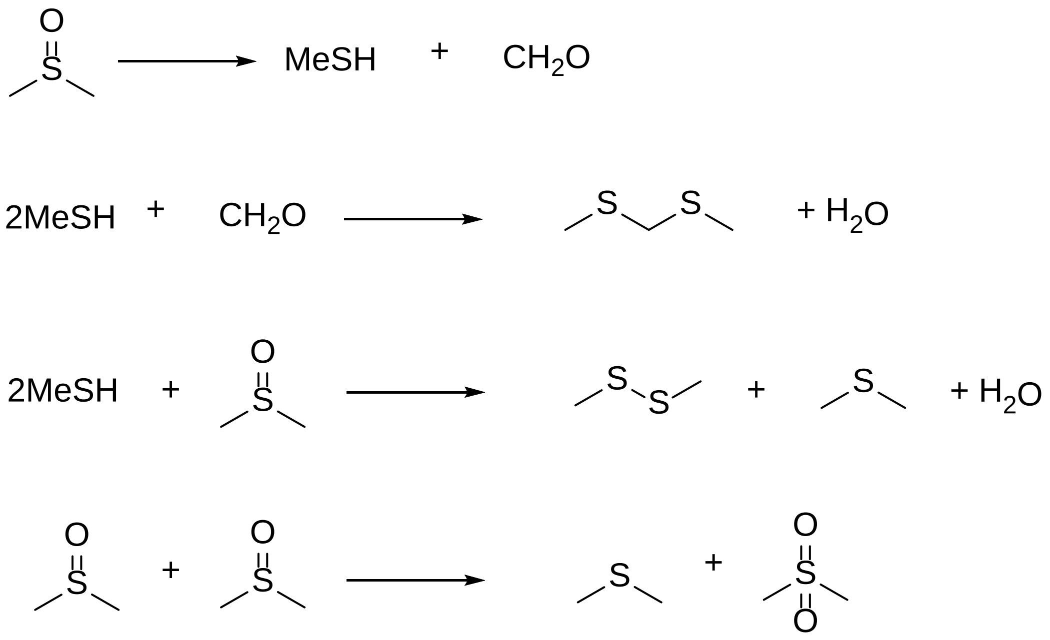
Common solvent in formulations and organic synthesis

- Accelerates some types of reactions, like SN2
- Can dissolve poorly soluble compounds

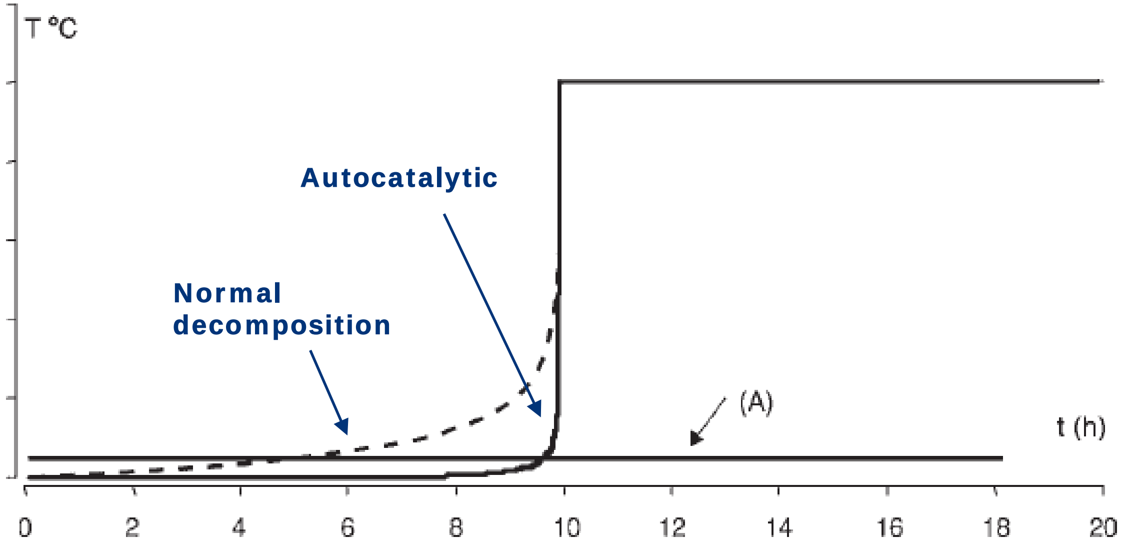
DMSO: Process Safety Challenges

DMSO can undergo **autocatalytic** decomposition:

- Decomposition can accelerate very rapidly
- “Thermal memory”



Exact mechanism not fully known



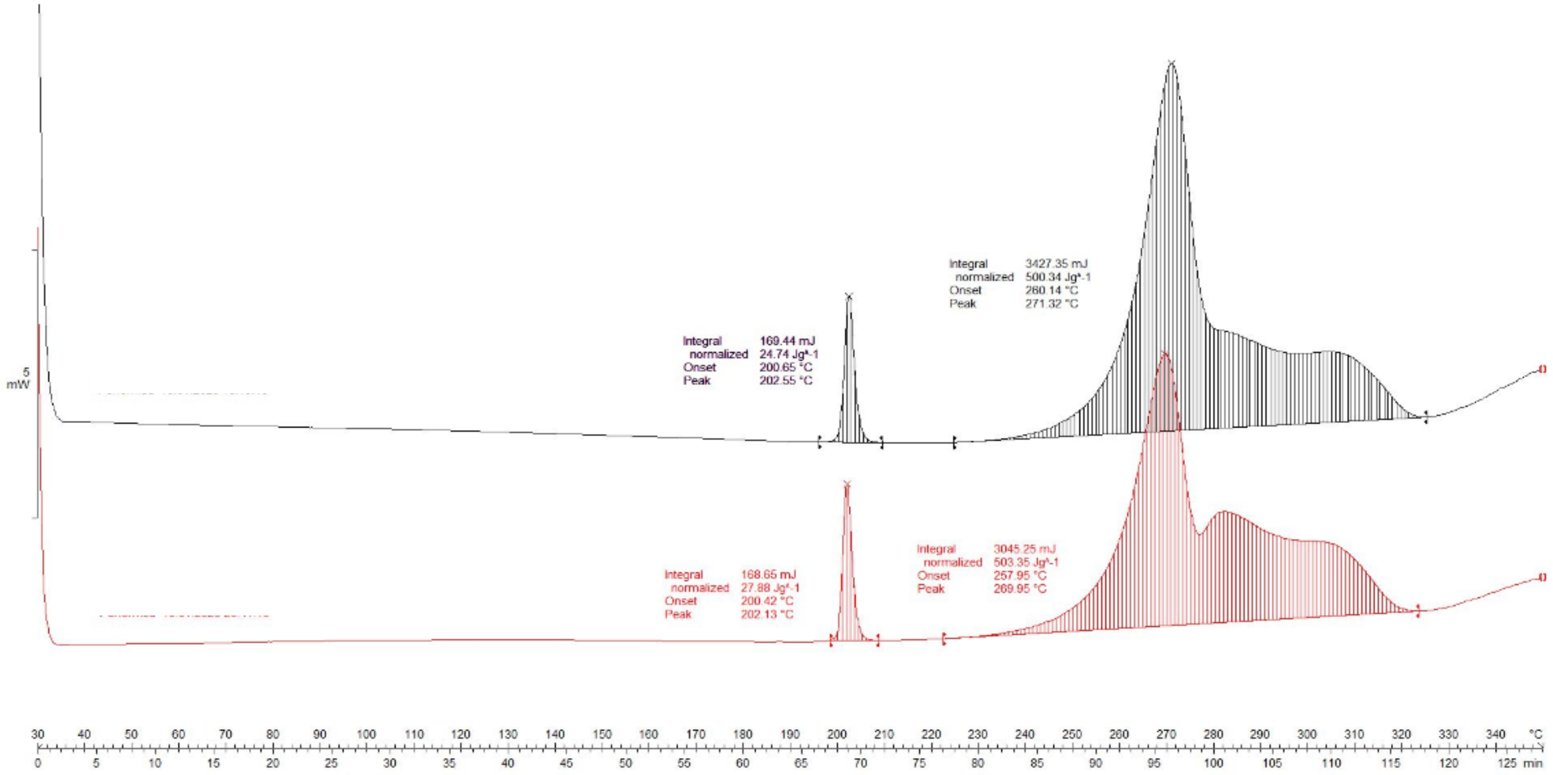
From F. Stoessel, "Thermal Safety of Chemical Processes: Risk Assessment and Process Design", Wiley-VCH, 2008

DMSO: Process Safety Challenges

DMSO can undergo **autocatalytic** decomposition

The decomposition of DMSO has a **high severity**

- High heat of decomposition (**> 500 J/g**: ΔT_{ad} = ± 250 °C)
- Generates gas

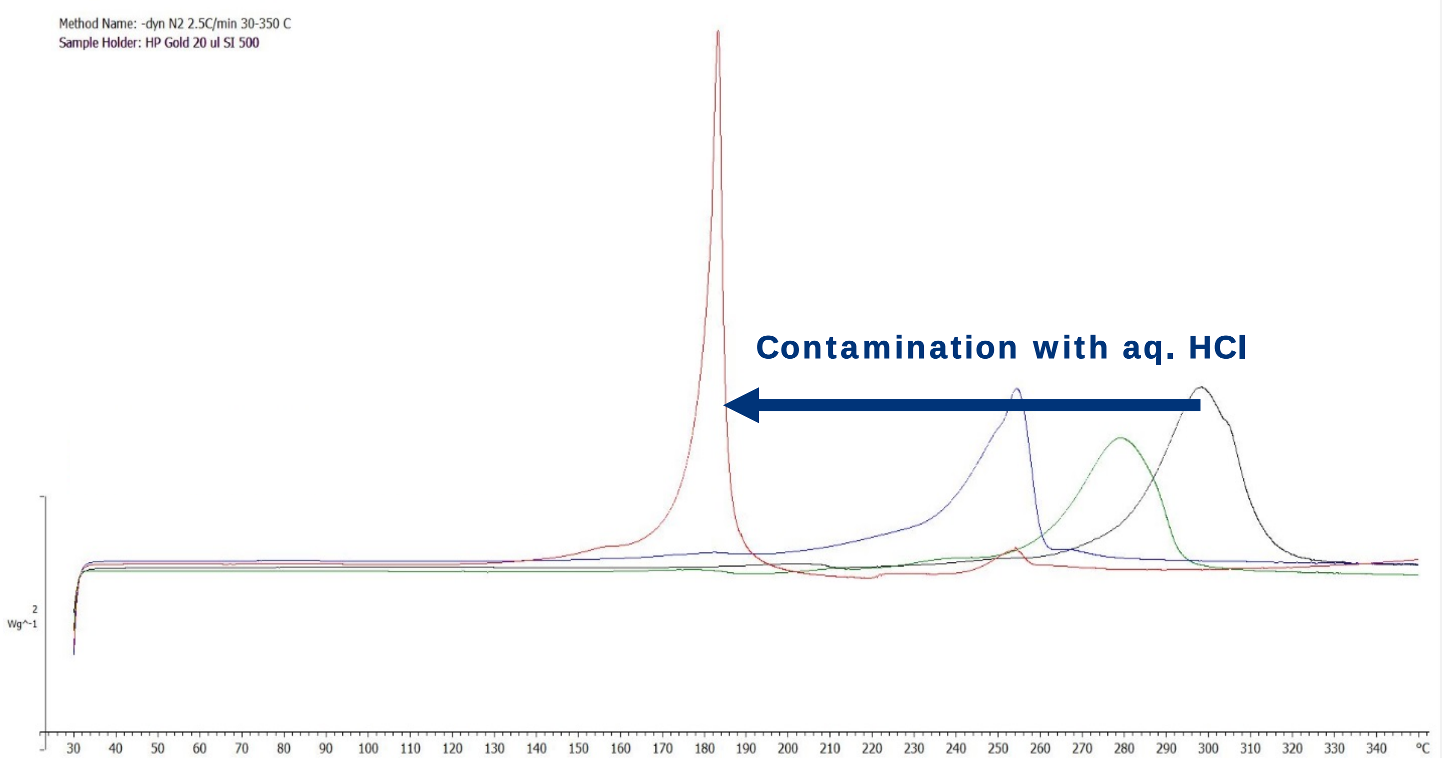


DMSO: Process Safety Challenges

DMSO can undergo **autocatalytic** decomposition

The decomposition of DMSO has a **high severity**

Contamination may (strongly) reduce the stability of DMSO



Destabilizing contaminants:

- Acids
- (Alkyl) halides (esp. bromide)
- Oxidizers
- Anhydrides
- Strong bases (e.g. NaH)
- Reductants
- …

Using DMSO is strongly discouraged at Janssen

First line of defense: **don’t use DMSO** (eliminate – substitute)

- DMSO is a **strongly discouraged** solvent @ Janssen
  - Approval required
  - Prove that alternatives have been tried (and failed)
- **Not allowed** in our plants without explicit site management approval
- Create awareness via safety training sessions

Some of the typical replacements (NMP, DMF, …) are also not recommended (SVHC)

No restrictions for small scale lab research

A Solvent of Last Resort

Project X: Final API crystallisation requires DMSO as the solvent

> 80 (!) solvents tested (+ pairs)

Procedure:

1. Dissolve crude API in pure DMSO at 60 °C (takes 30 min)
2. Dose the cosolvent (ACN)
3. Cool to 10 °C
4. Filter + wash

Low forecast: only few batches / year expected

How to proceed (safely)?

DMSO: Hazards need Mitigation

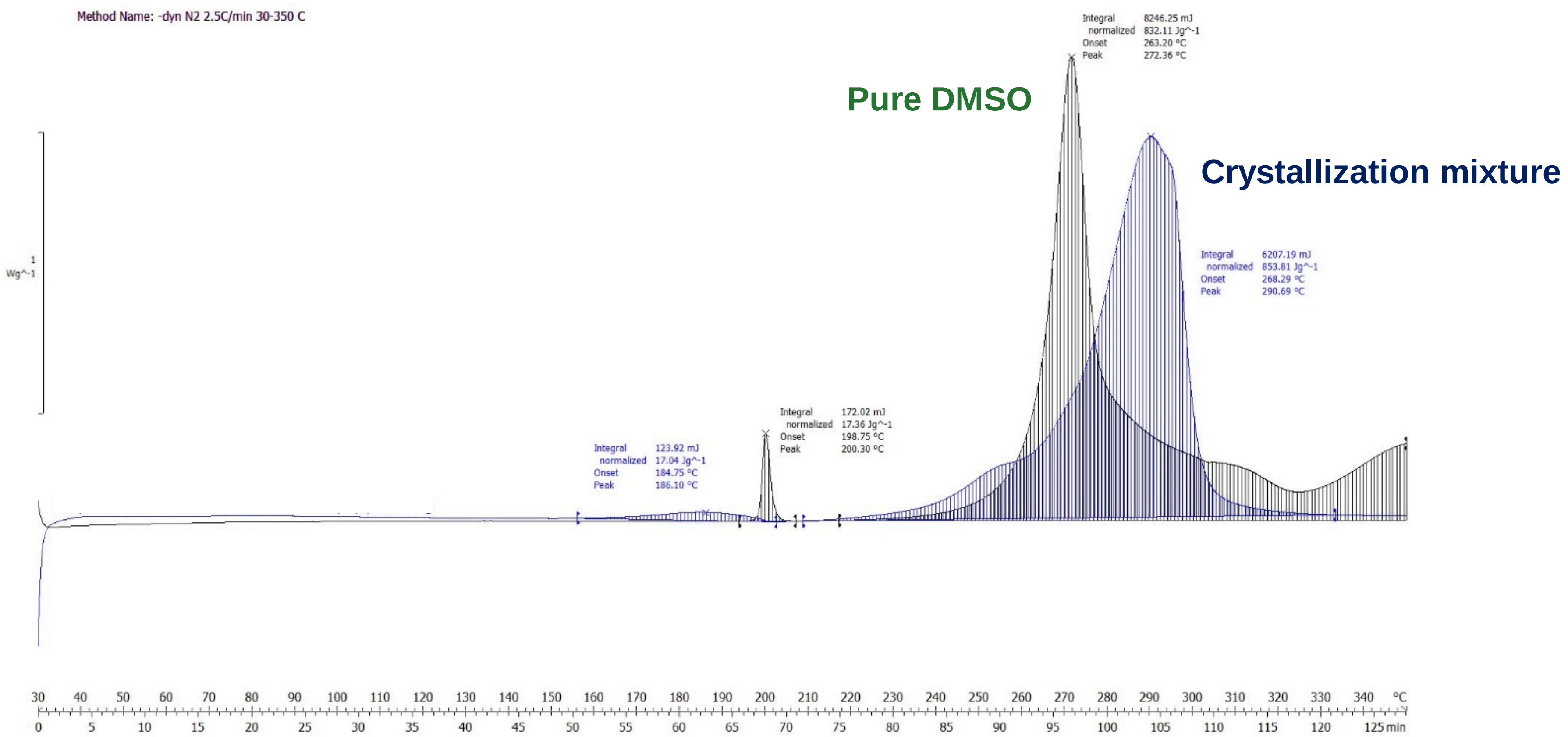
Using DMSO in a multipurpose plant requires a rigorous safety assessment:

Hazard	Mitigation
Autocatalytic decomposition	Control of logistic flow DMSO Thermal stability testing Define max temp. Waste management
High severity decomposition	(Venting not an option) Dilute with lower boiling solvent
Contamination	Control of logistic flow DMSO Contamination effect study

Thermal Stability Testing: Pure mixture

The severity of a potential runaway decomposition is high (as expected)

Decomposition onset (T_{D24h} = **136 °C**) is significantly above the maximum process temperature (**60 °C**).

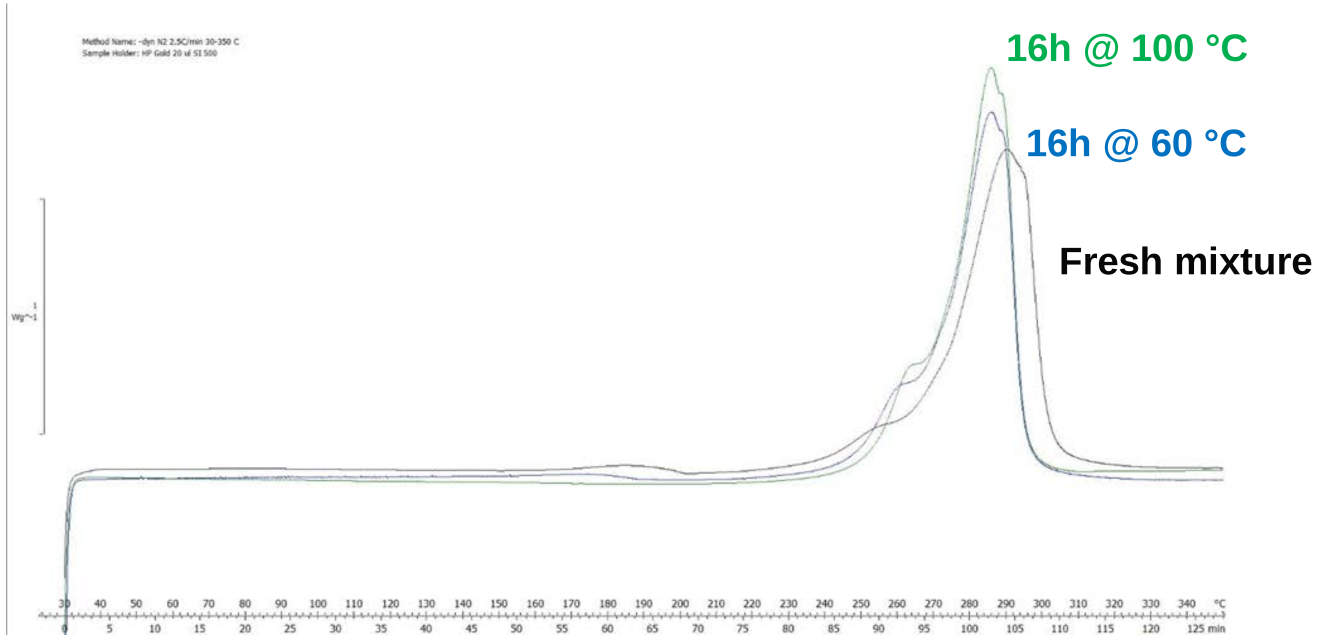


AKTS kinetic analysis:

Initial Temp. (°C)	TMR_{ad} (h)
176	2
152	8
136	**24**
126	48
121	72
60	2.6 years

Thermal Stability Testing: Thermal aging

No significant effect by thermal aging (at process relevant temperatures/time spans)



Contamination Impact Assessment

Critical contaminants identified:

	Contaminant	Effect on main decomposition exotherm		
		Onset	*Peak temp.*	*Peak width*
No effect	Metals[a]	=	=	=
	n-BuOH	=	=	=
	50 w/w% $NaOH_{(aq)}$	=	=	=
	Acrylonitrile	=	=	=
Minor effect	Water[c]	↓	↓	↓
	SM previous step	↓	↓	↓
	TMG.HBr[d]	↓	↓	↓
	Tetramethylguanidine	↓	↓	↓
Critical	Alkyl bromide SM	↓↓	↓↓	↓↓[b]
	AcOH	↓↓	↓↓	↑
	30 w/w% $HCl_{(aq)}$[c]	↓↓	↓↓	↓↓

=: no significant change ($\Delta T < 5$°C). ↓: slight decrease ($\Delta T \leq 20$ °C), ↓↓: strong decrease ($\Delta T > 20$ °C). a: Stainless steel, Hastelloy and rust powder. b: Very sharp exotherm. c: Concentration dependent. d: Tetramethylguanidinium bromide.

Worst-case contamination (30 w/w% conc HCl), tested in detail: T_{D24h} = **100 °C**

Contamination Impact Assessment: Highlights

Strong concentration dependency with acids:

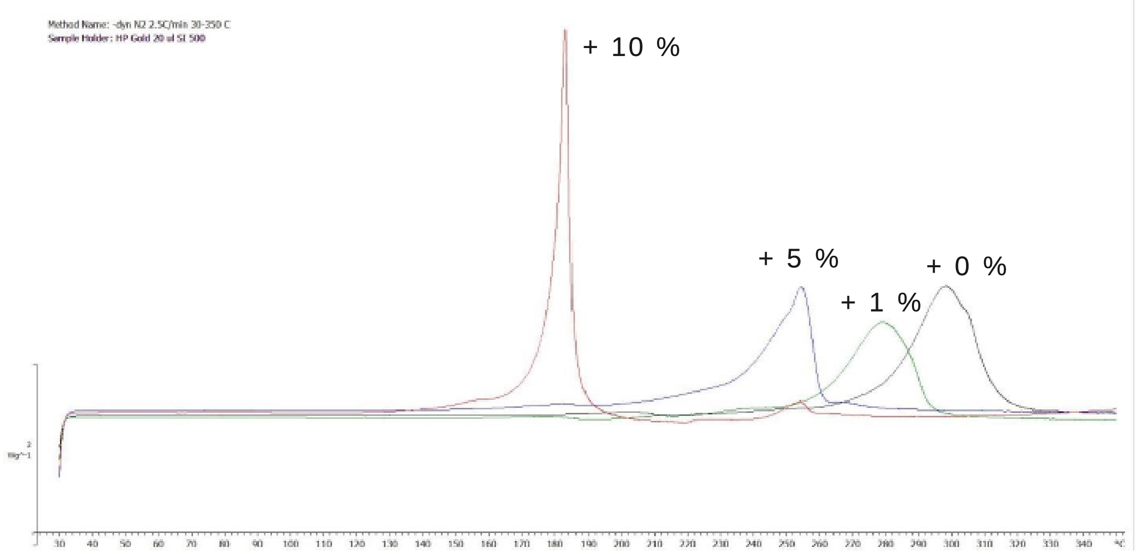
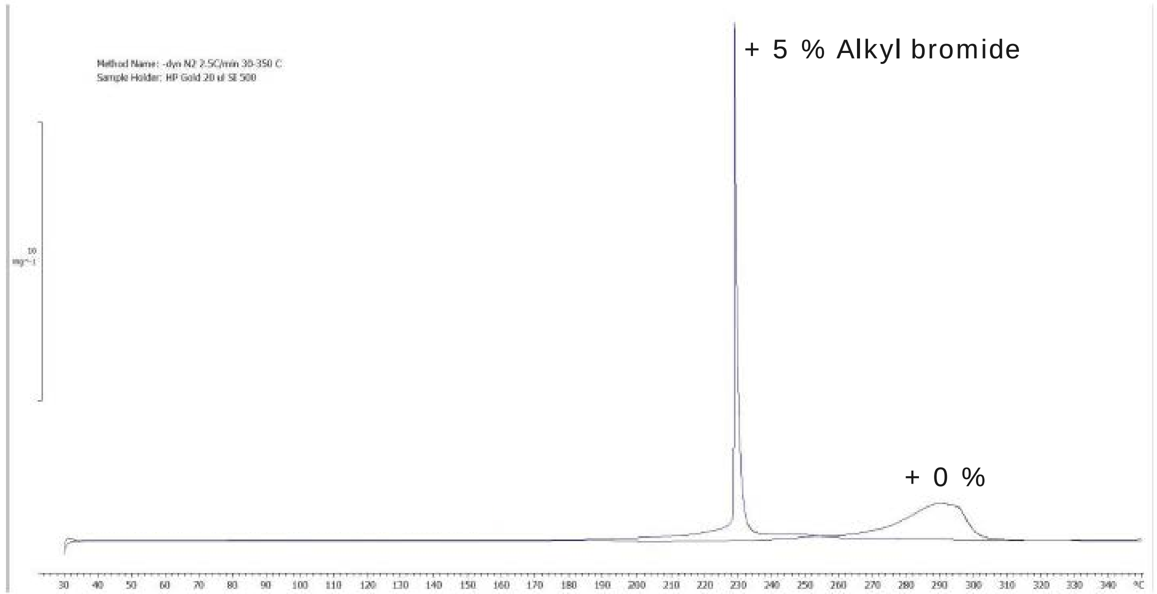


Figure 8: Effect of varying content of Aq. HCl (30wt%): 1 w/w% (green), 5 w/w% (blue) or 10 w/w% (red), compared to the uncontaminated mixture (black).

Alkyl bromide strongly enhances autocatalyic behavior:



Conclusions from Testing

Decomposition is severe

Maximum allowable temperature (136 °C) >> Max. Process temperature (60 °C)

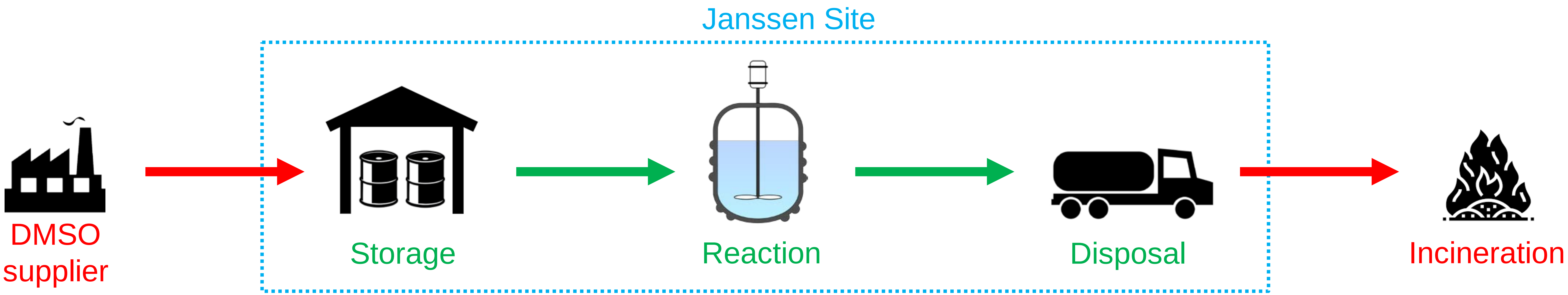
No change in thermal stability at the max process temperature

Contamination with critical contaminants must be strictly avoided

Next challenge is technical and operational measures

Safeguarding against DMSO hazards at every step

DMSO risks must be mitigated from start to finish



Safeguarding against DMSO hazards at every step

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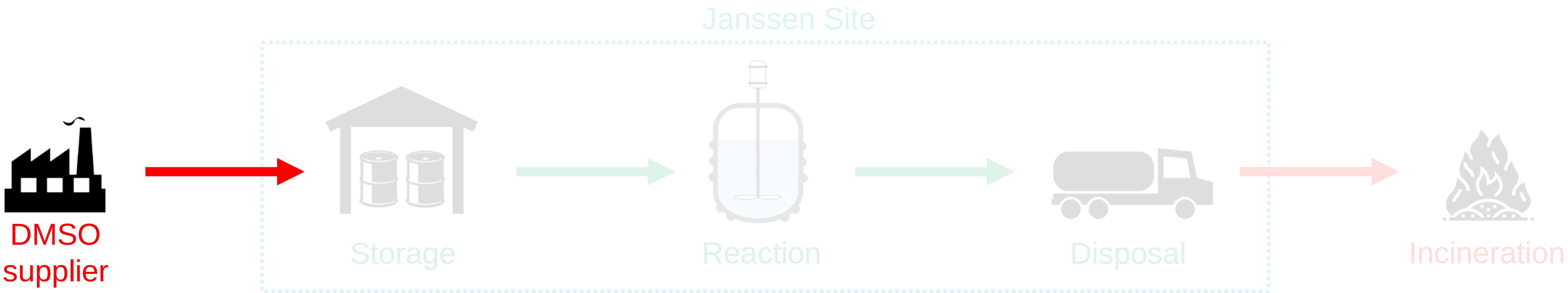


Supplier:

Communication

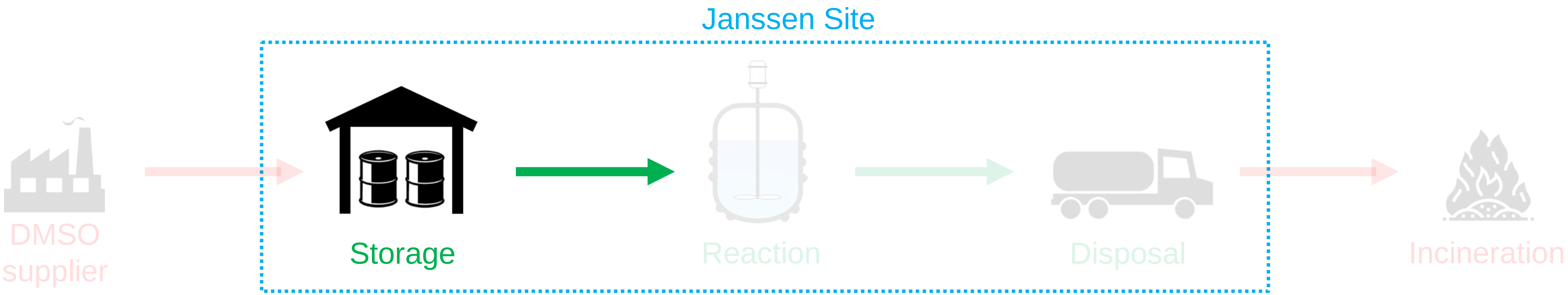
Understand production + transport method (only non-recycled product)

Scope and limitation of specs

Ultimately beyond our control

Safeguarding against DMSO hazards at every step

DMSO risks must be mitigated from start to finish



Storage:

Perform thermal stability test (DSC) on reception

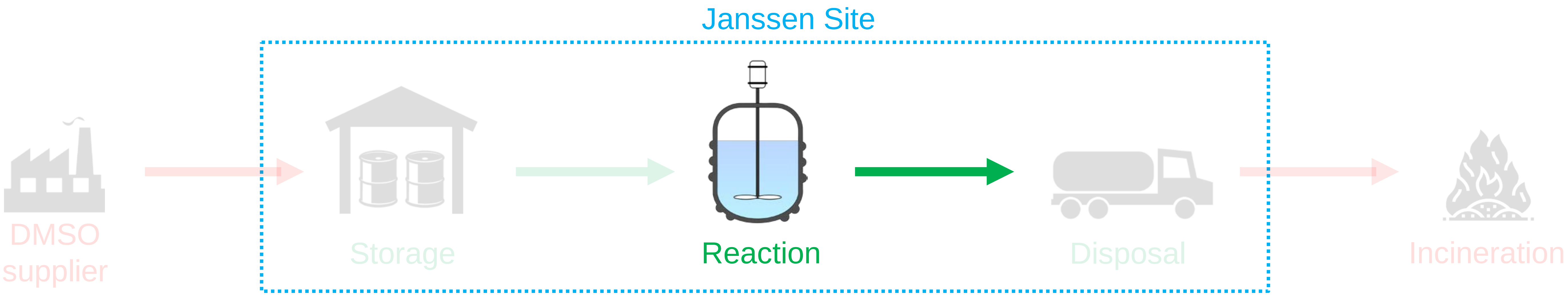
Temperature controlled storage (20 - 30 °C), logged

No manipulation until used

Periodic retesting

Safeguarding against DMSO hazards at every step

DMSO risks must be mitigated from start to finish



Reaction:

Extensive cleaning & conditioning + validation before every batch

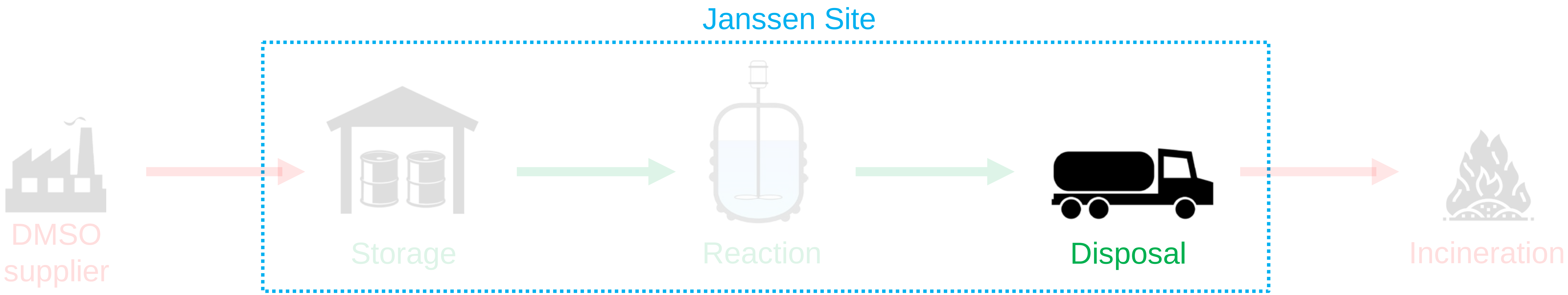
Extra precautions against accidental heating of the reactor

Antisolvent ready to be added rapidly in case of calamity

Tight specs on starting material

Safeguarding against DMSO hazards at every step

DMSO risks must be mitigated from start to finish



Disposal:

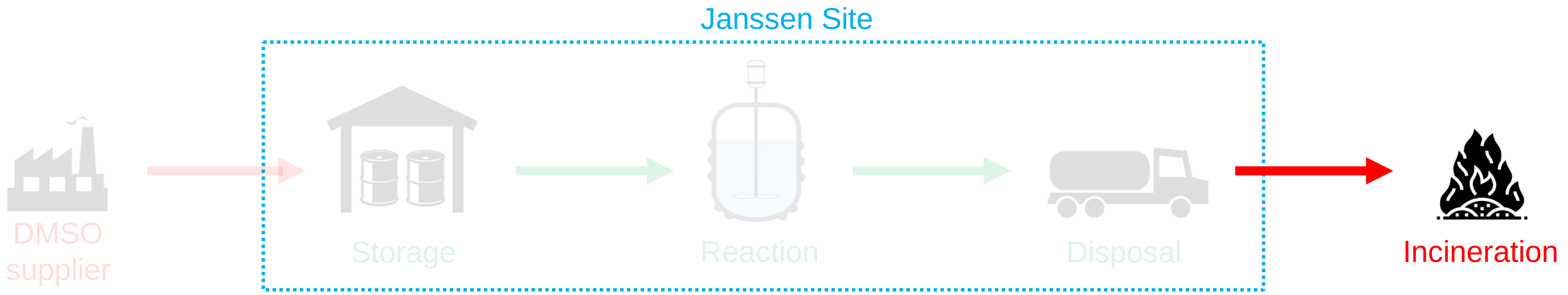
Diluted DMSO waste layer not mixed with other waste streams

Separate + prompt disposal

No solvent recuperation, incinerated

Safeguarding against DMSO hazards at every step

DMSO risks must be mitigated from start to finish



Incineration:

Disposal company informed of risks

Direct injection + incineration (no storage/mixing)

Conclusions

Create awareness around hazards of DMSO + encourage alternatives

Thorough process safety investigation is essential

Expect operational and technical challenges

Communication with **all** stakeholders to map the logistic flow

>150 kg of API made to date without incident

Conclusions

Ultimately, we had a best case scenario:

- Pure crystallisation: no reagents/intermediates/…
- Only short exposure time in pure DMSO
- Relatively low process temperature
- Limited # batches / campaign size

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