

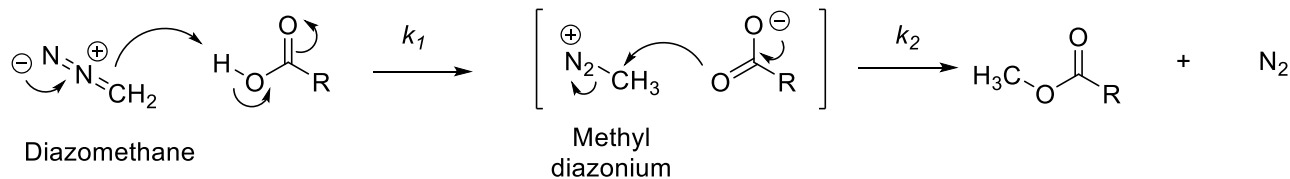
# THERMAL STABILITY OF TEMOZOLOMIDE (TMZ)

JEFFREY SPERRY

# DIAZOMETHANE

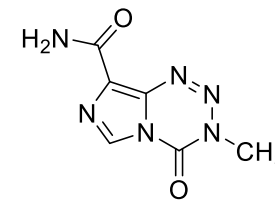


- Discovered in 1894 by Hans von Pechmann (born April 1, 1850; passed April 19, 1902)
- Highly acutely toxic and explosive gas
- Mechanism of action:



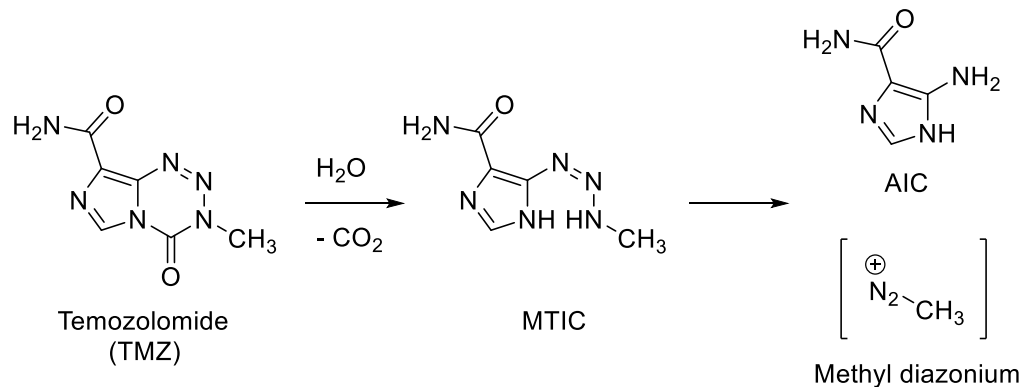
- *Bretherick's Handbook of Reactive Chemical Hazards* cites multiple reports of explosions and exposures
- "Safer" alternatives exist for the generation of diazomethane:  $\text{TMSCHN}_2$ , Diazald, etc.
- For an example of diazomethane generation in flow see: *Org. Process Res. Dev.* 2018, 22, 4, 446–456

# TEMOZOLOMIDE (TMZ)



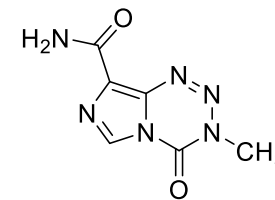
Temozolomide (TMZ)

- Belongs to imidazotetrazine class of molecules
- Developed by Malcolm Stevens and his team at Aston University (Birmingham, England) in 1970s
- TMZ serves as the standard of care for glioblastoma (GBM)
- TMZ hydrolyzes at physiological pH to MTIC which then releases the active methylating agent, methyl diazonium



*Temozolomide – birth of a blockbuster* [https://www.rsc.org/images/TEMOZOLOMIDE\\_ChemistryWorldJul09\\_tcm18-155909.pdf](https://www.rsc.org/images/TEMOZOLOMIDE_ChemistryWorldJul09_tcm18-155909.pdf)

# TEMOZOLOMIDE (TMZ)



Temozolomide  
(TMZ)



## Research Articles

**Angewandte**  
International Edition *Chemie*

### ***Diazo Compounds***

International Edition: DOI: 10.1002/anie.201911896

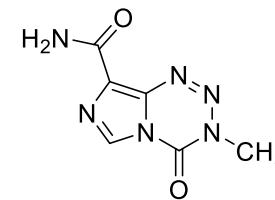
German Edition: DOI: 10.1002/ange.201911896

## Imidazotetrazines as Weighable Diazomethane Surrogates for Esterifications and Cyclopropanations

Angew. Chem. Int. Ed. 2020, 59, 1857 – 1862

# TEMOZOLOMIDE (TMZ)

*efficient and operationally simple. TMZ is a commercially available solid that is non-explosive and non-toxic, and should find broad utility as a replacement for diazomethane.*





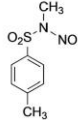

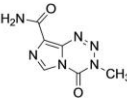
Temozolomide  
(TMZ)

Angew. Chem. Int. Ed. 2020, 59, 1857 – 1862

# TEMOZOLOMIDE (TMZ)

efficient and operationally simple. TMZ is a commercially available solid that is non-explosive and non-toxic, and should find broad utility as a replacement for diazomethane.

a)

				
Diazomethane	TMS-Diazomethane	Diazald	<b>1</b>	TMZ
(Reagent)	(Reagent)	(Precursor)	(Precursor/Reagent)	(Precursor/Reagent)
Esterification	Esterification	Esterification	Esterification	Esterification
Cyclopropanation	Cyclopropanation	Cyclopropanation	Cyclopropanation	Cyclopropanation
Explosive	Non-explosive	Non-explosive	Non-explosive	Non-explosive
Severe inhalation toxicity	Severe inhalation toxicity	No acute toxicity	No acute toxicity	No acute toxicity
Quenched in water	Quenched in water	Insoluble in water	Water soluble	Water soluble
Used as a solution	Used as a solution	Weighable solid	Used as a solution	Weighable solid

Temozolomide (TMZ)

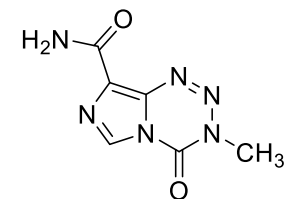
Angew. Chem. Int. Ed. 2020, 59, 1857 – 1862

# TEMOZOLOMIDE (TMZ)

efficient and operationally simple. TMZ is a commercially available solid that is non-explosive and non-toxic, and should find broad utility as a replacement for diazomethane.

equivalent, TMZ also exhibits considerably more thermal stability than other diazomethane precursors such as Diazald, which bears an *N*-methyl *N*-nitroso group; Diazald decomposes (explosively) at its melting point of 60 °C<sup>[38]</sup> while TMZ is stable up to its melting point, 212 °C. It should be noted that, while more convenient than other diazomethane precursors, proper caution is still warranted (particularly on large scale) when employing TMZ in these reactions. Finally, chemical

a)					
	Diazomethane	TMS-Diazomethane	Diazald	1	TMZ
	(Reagent)	(Reagent)	(Precursor)	(Precursor/Reagent)	(Precursor/Reagent)
	Esterification	Esterification	Esterification	Esterification	Esterification
	Cyclopropanation	Cyclopropanation	Cyclopropanation	Cyclopropanation	Cyclopropanation
	Explosive	Non-explosive	Non-explosive	Non-explosive	Non-explosive
	Severe inhalation toxicity	Severe inhalation toxicity	No acute toxicity	No acute toxicity	No acute toxicity
	Quenched in water	Quenched in water	Insoluble in water	Water soluble	Water soluble
	Used as a solution	Used as a solution	Weighable solid	Used as a solution	Weighable solid



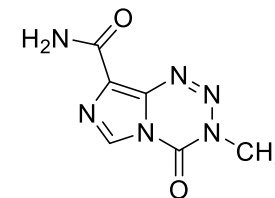
Temozolomide (TMZ)

Angew. Chem. Int. Ed. 2020, 59, 1857 – 1862

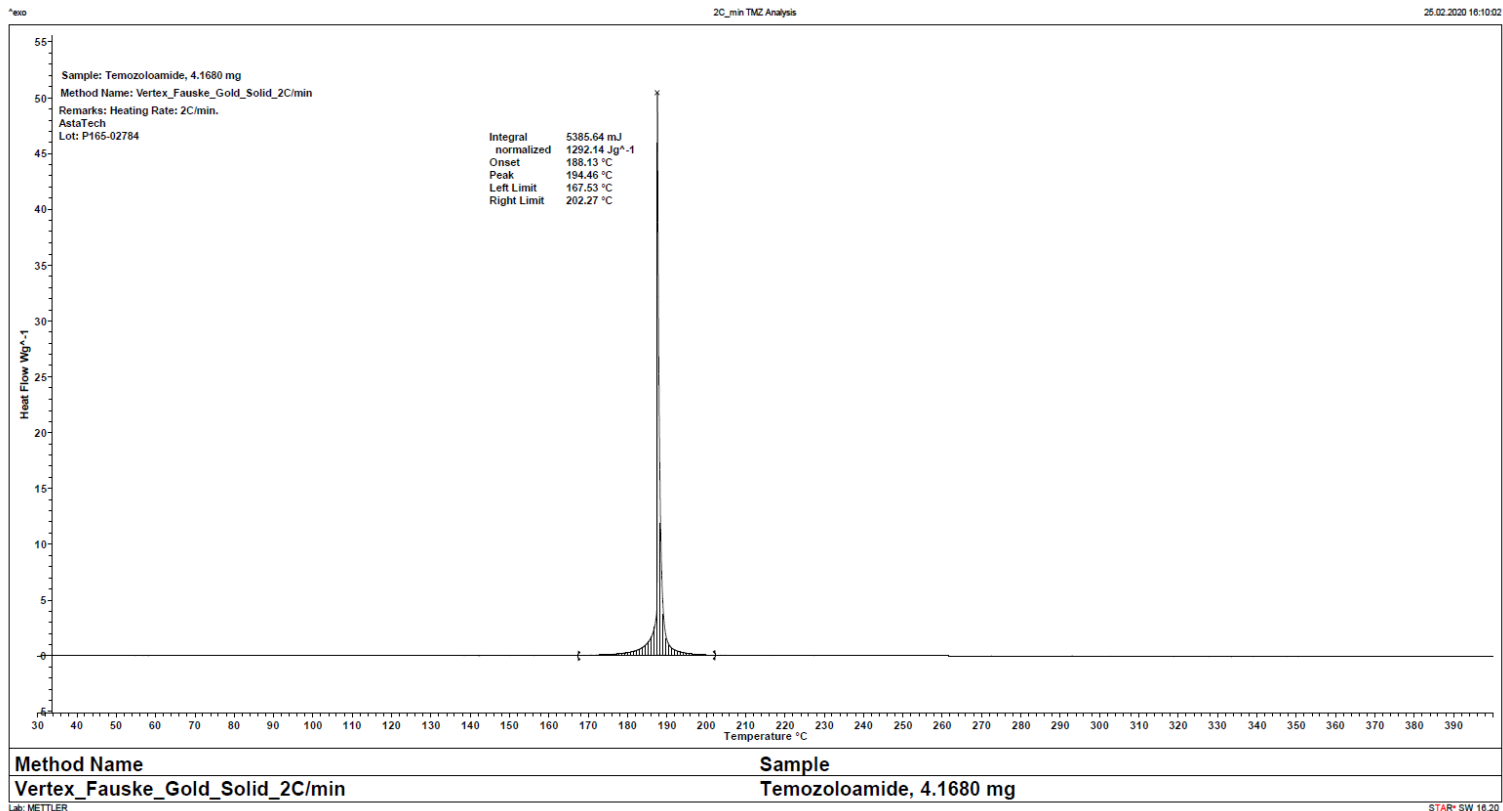
# DIFFERENTIAL SCANNING CALORIMETRY



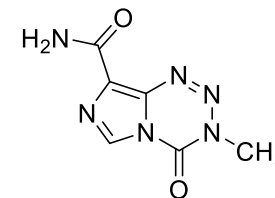
# TEMOZOLOMIDE (TMZ) - DSC



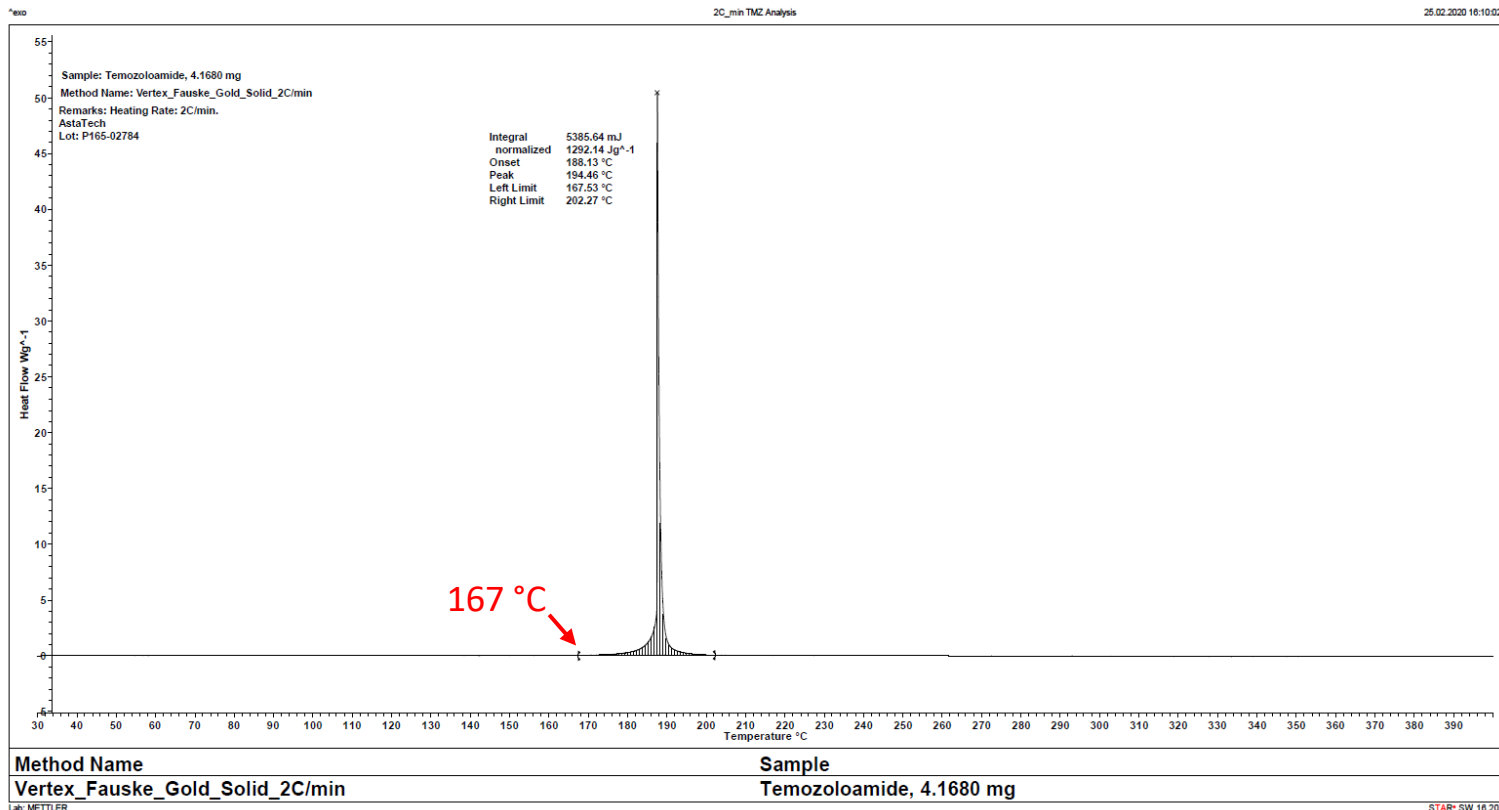
Temozolomide  
(TMZ)



# TEMOZOLOMIDE (TMZ) - DSC

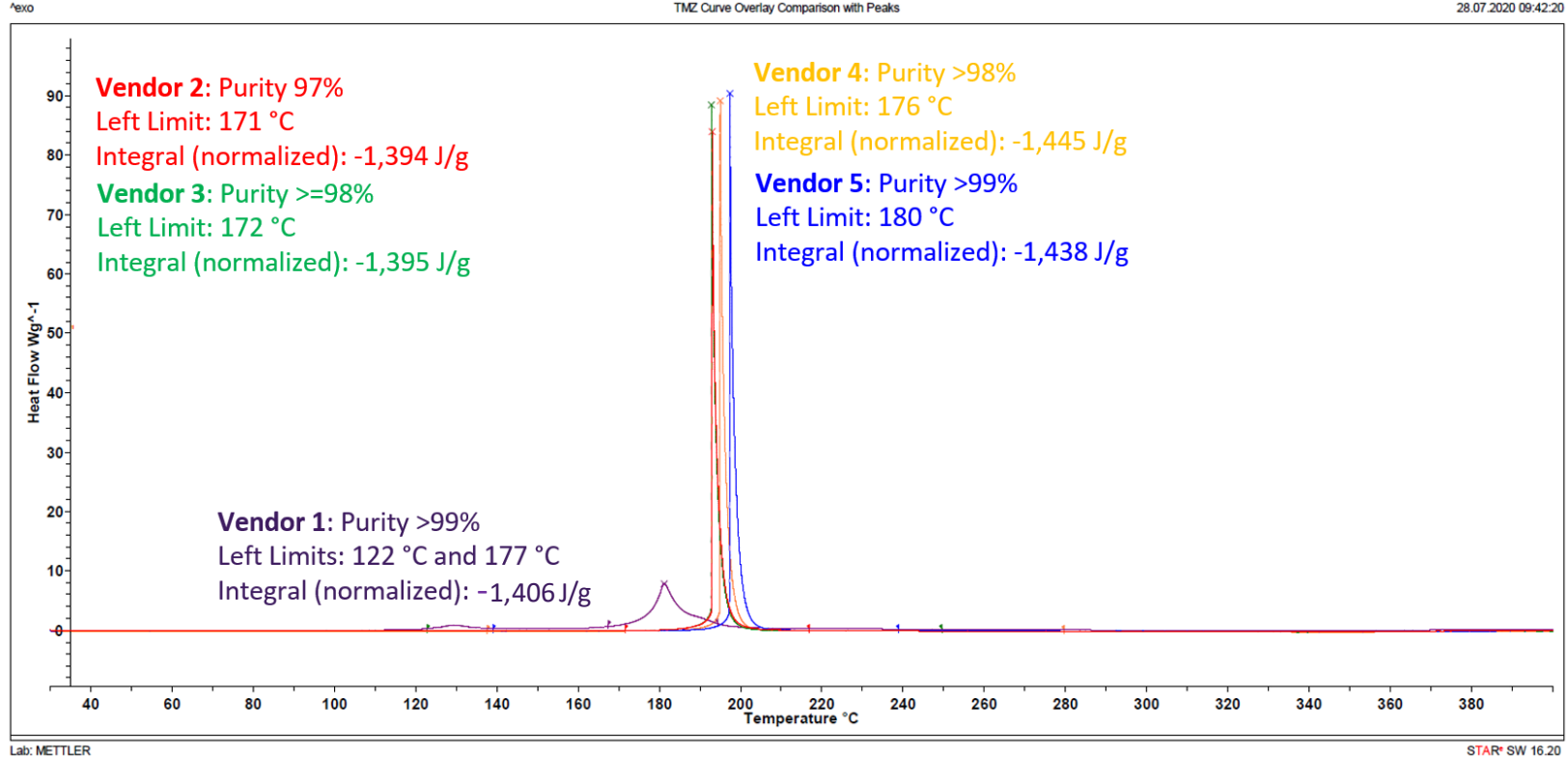


Temozolomide  
(TMZ)

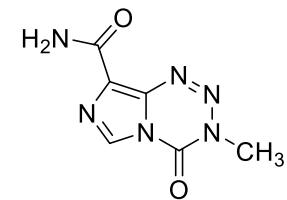


# ANALYSIS OF 5 COMMERCIAL LOTS

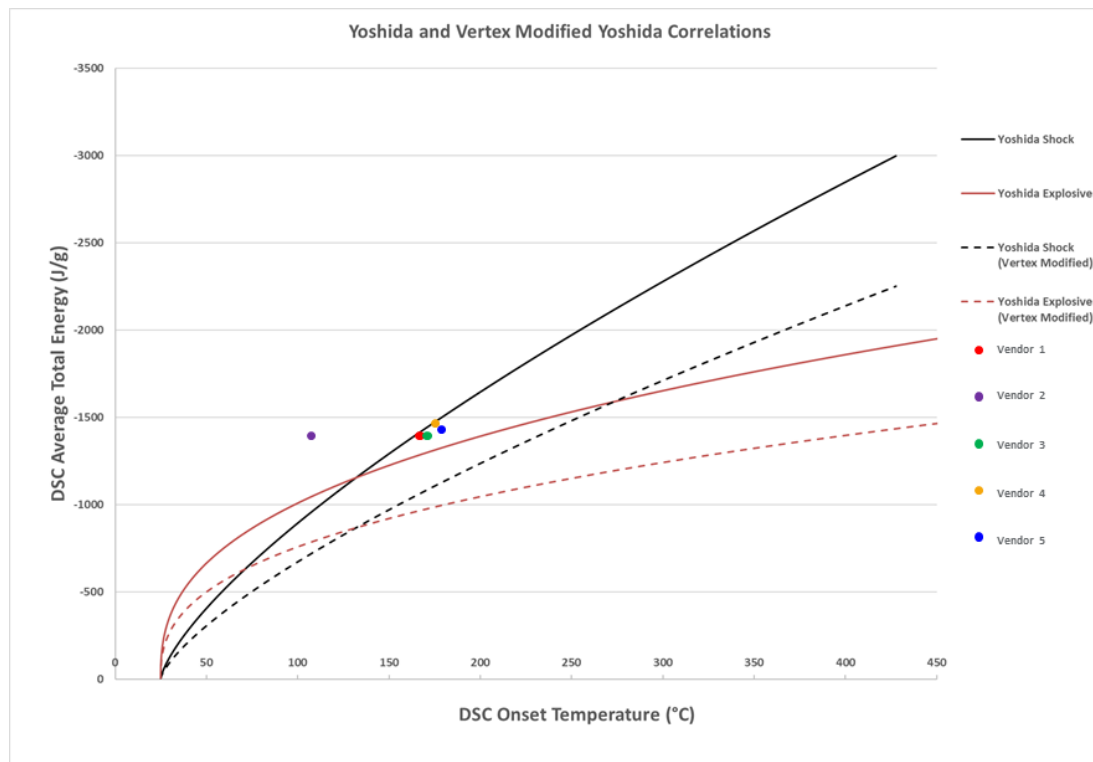
# COMMERCIAL LOT ANALYSIS



# TEMOZOLOMIDE (TMZ) - DSC



Temozolomide  
(TMZ)



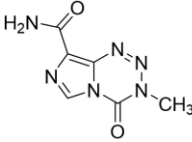
# O.R.E.O.S. ASSESSMENT

## O.R.E.O.S. ASSESSMENT

	Points			
	1	2	4	8
Oxygen Balance Hazard		Low	Med	High
Rule of 6 calculation		Pass		Fail
Explosive Functional Group?	No			Yes
Onset temperature	>300	200-300	125-200	<125
Scale	1mg to 5g	5g to 100g	101g to 500g	>500g
<b>O.R.E.O.S. Total:</b>				
		Low Hazard	Medium Hazard	High Hazard
<b>Points:</b>		7 to 17	18 to 27	28 to 40

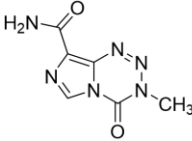
Sperry, J.B.; Azuma, M.; Stone, S. *Org. Process Res. Dev.*, **2021**, 2, 212-224

# O.R.E.O.S. ASSESSMENT

Material	OB	Rule of 6	ExFG	Onset	Scale			
					<5g	5g to <100g	100g to 500g	>500g
 temozolomide	High (8)	Pass (2)	Yes (8)	125- 200 (4)	Medium Hazard	Medium Hazard	Medium Hazard	High Hazard



# O.R.E.O.S. ASSESSMENT

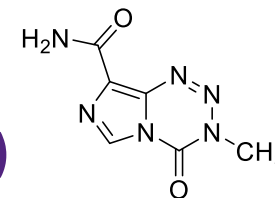
Material	OB	Rule of 6	ExFG	Onset	Scale			
					<5g	5g to <100g	100g to 500g	>500g
 temozolomide	High (8)	Pass (2)	Yes (8)	125-200 (4)	Medium Hazard	Medium Hazard	Medium Hazard	High Hazard

O.R.E.O.S. Hazard Rank	Example Recommendations
Low Hazard	<ul style="list-style-type: none"> <li>Proceed using internal guidance on handling energetic compounds.</li> </ul>
	<ul style="list-style-type: none"> <li>ARC testing <i>recommended</i>.</li> </ul> <p style="text-align: center;">-or-</p> <ul style="list-style-type: none"> <li>Quantitative small-scale explosivity screening is <i>recommended</i></li> </ul>
Medium Hazard	<ul style="list-style-type: none"> <li>Proceed using internal guidance on handling energetic compounds.</li> </ul>
	<ul style="list-style-type: none"> <li>ARC testing is <i>required</i>.</li> </ul> <p style="text-align: center;">-or-</p> <ul style="list-style-type: none"> <li>Quantitative small-scale explosivity screening is <i>required</i></li> </ul>
	<ul style="list-style-type: none"> <li>Select Test Series 1 is <i>recommended</i> based on ARC testing, likely failure modes and available material (Koenen Test, Time/Pressure Test, and/or U.N. Gap)</li> </ul>
High Hazard	<ul style="list-style-type: none"> <li>Consider alternative methods.</li> </ul>
	<ul style="list-style-type: none"> <li>ARC testing is <i>required</i>.</li> </ul> <p style="text-align: center;">-or-</p> <ul style="list-style-type: none"> <li>Quantitative small-scale explosivity screening is <i>required</i></li> </ul>
	<ul style="list-style-type: none"> <li>Select Test Series 1 is <i>required</i> based on likely failure mode and available material (Koenen Test, Time/Pressure Test, and/or U.N. Gap)</li> </ul>

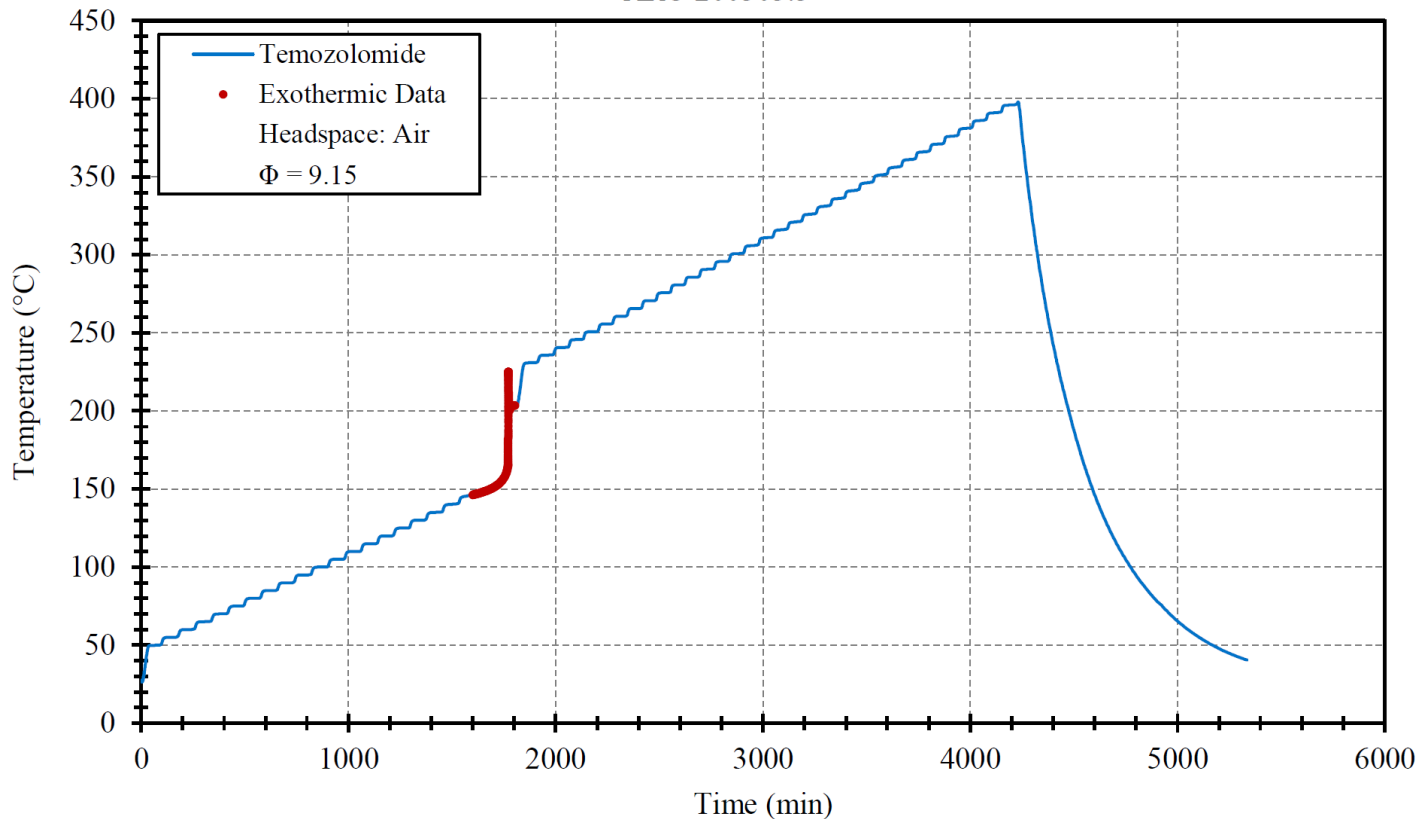
# ACCELERATING RATE CALORIMETRY (ARC)

# TEMOZOLOMIDE (TMZ) – ACCELERATING RATE CALORIMETRY (ARC)

ARC-200303.3



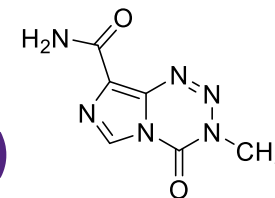
Temozolomide  
(TMZ)



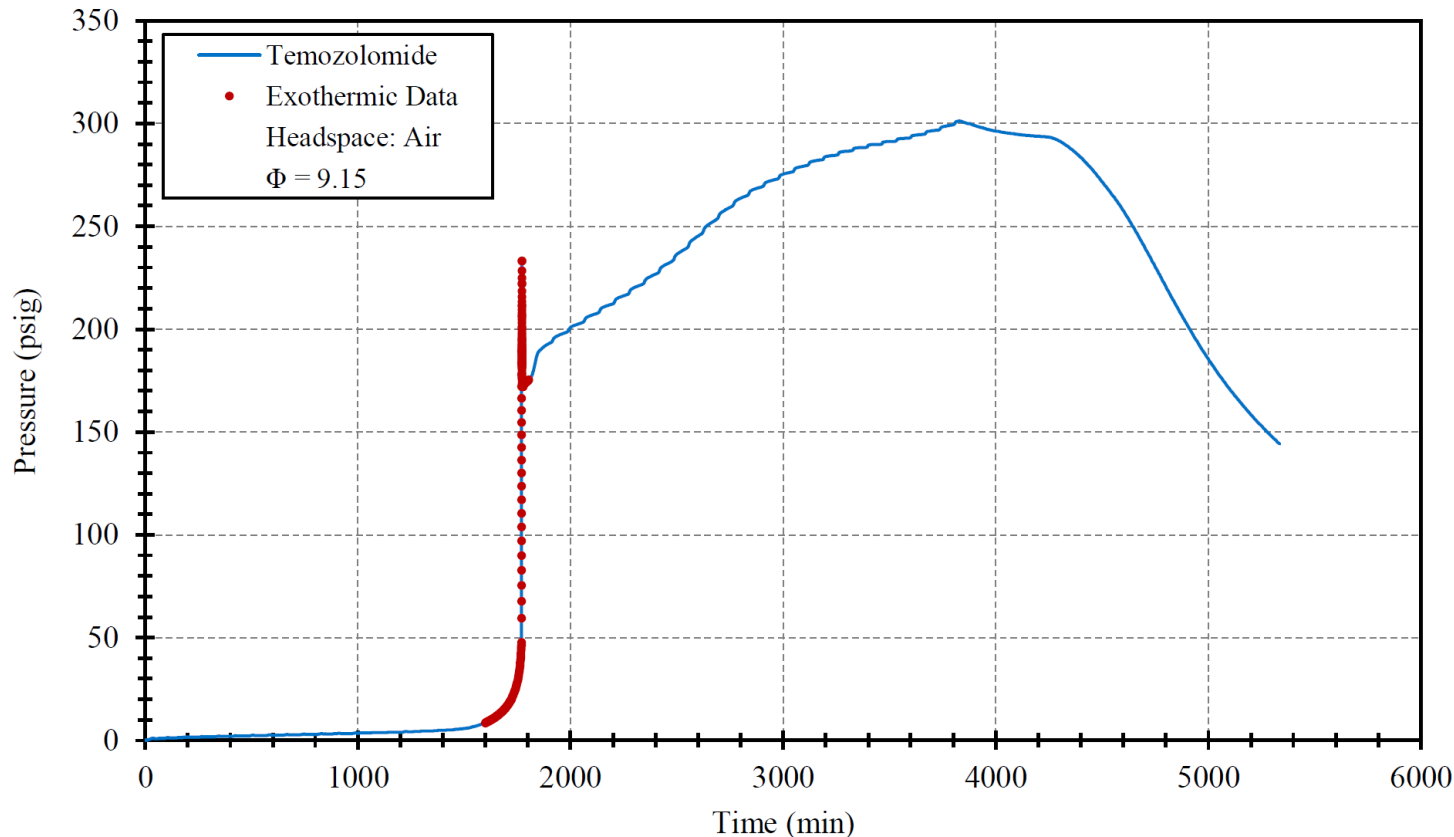
$\phi$	9.15
Onset Temp (°C)	145
Adiabatic Temp Rise (°C)	>732
$-\Delta H_R$ (J/g)	>1,100
Max Self-Heat Rate (°C/min)	>341

# TEMOZOLOMIDE (TMZ) – ACCELERATING RATE CALORIMETRY (ARC)

ARC-200303.3



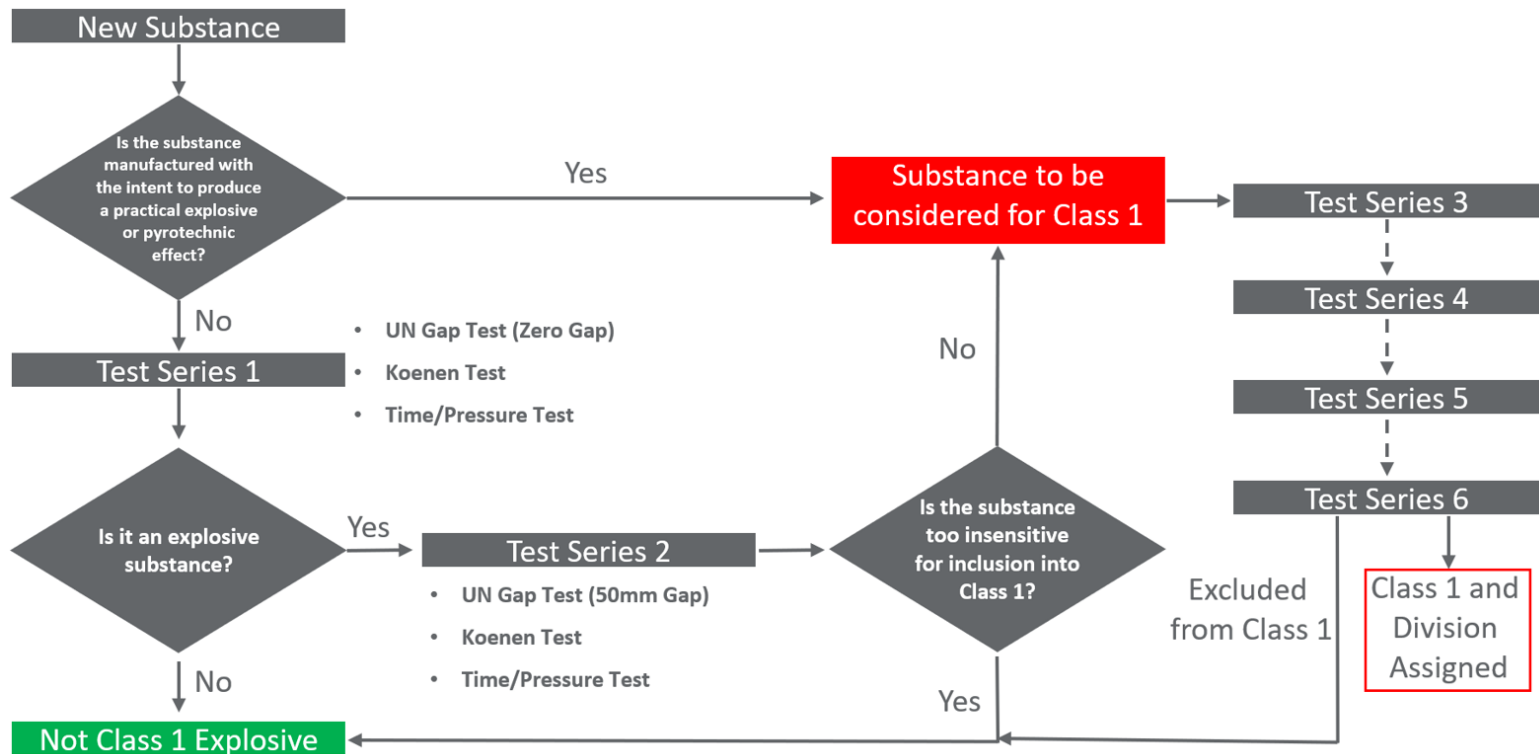
Temozolomide  
(TMZ)



$\phi$	9.15
Onset Temp (°C)	145
Max Pressure Rate (psi/min)	1,114
T at Max Pressure Rate (°C)	187
Pressure at end of exotherm (psia)	248

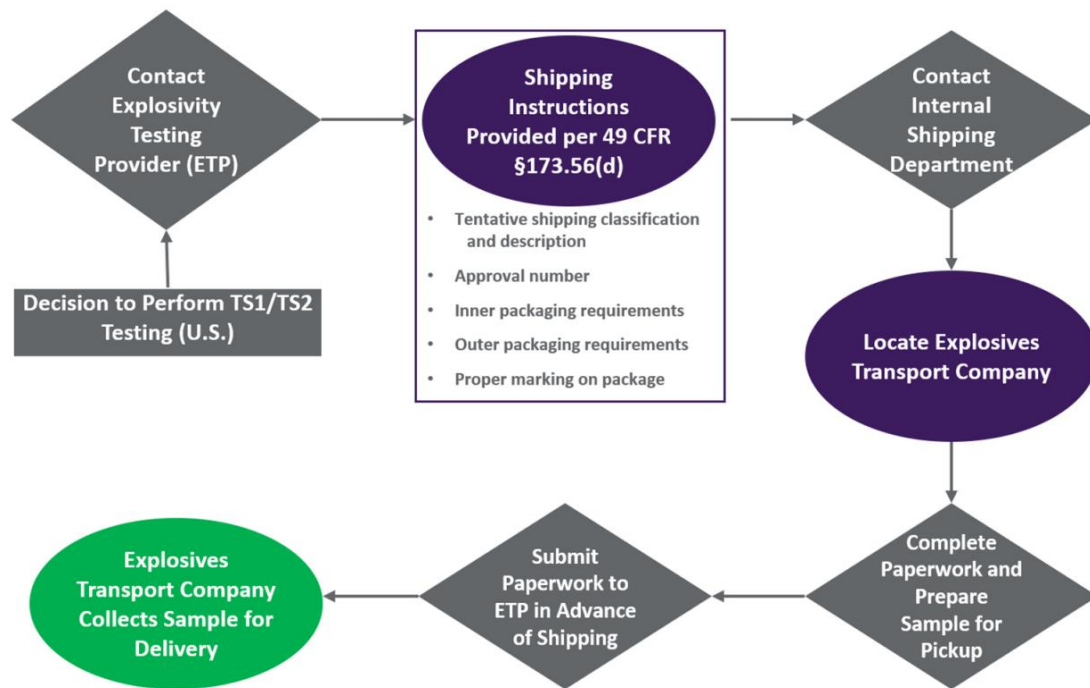
# **CLASSIFYING EXPLOSIVE SUBSTANCES PER U.N. MODEL REGULATIONS (UNMR)**

# CLASSIFYING EXPLOSIVE SUBSTANCES



Sperry, J.B.; Azuma, M.; Stone, S. *Org. Process Res. Dev.*, **2021**, 2, 212-224

# SHIPPING POTENTIALLY EXPLOSIVE MATERIALS FOR TESTING



Sperry, J.B.; Azuma, M.; Stone, S. *Org. Process Res. Dev.*, **2021**, *2*, 212-224

## SHIPPING POTENTIALLY EXPLOSIVE MATERIALS FOR TESTING



Sperry, J.B.; Azuma, M.; Stone, S. *Org. Process Res. Dev.*, **2021**, 2, 212-224

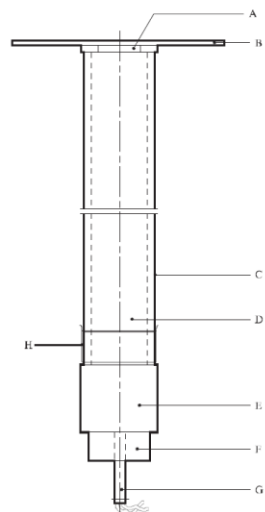


# U.N. TEST SERIES 2

## TEST SERIES 2 - METHODS

Test	What is Measured	Failure Results if
U.N. Gap Test	Sensitivity of material to a shock stimulus	Tube fragments completely or hole is punched through witness plate
Koenen Test	Effect of heating under confinement	<ol style="list-style-type: none"><li>1. Tube is fragmented into three or more mainly large pieces which in some cases may be connected with each other by a narrow strip, or</li><li>2. Tube fragmented into many mainly small pieces, closing device unchanged, or</li><li>3. Tube fragmented into many very small pieces, closing device bulged out or fragmented</li></ol>
Time/Pressure Test	Effect of ignition under confinement	Rate of the overpressure from 100 psig to 300 psig is less than 30 ms

# U.N. GAP TEST



(A)	Spacers	(B)	Witness plate
(C)	Steel tube	(D)	Substance under investigation
(E)	RDX/wax or PETN/TNT booster charge	(F)	Detonator holder
(G)	Detonator	(H)	Plastics membrane

Figure 11.4.1.1: UN GAP TEST

# U.N. GAP TEST

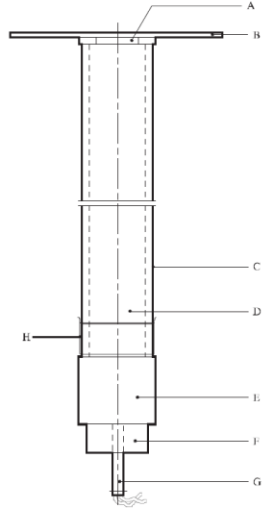
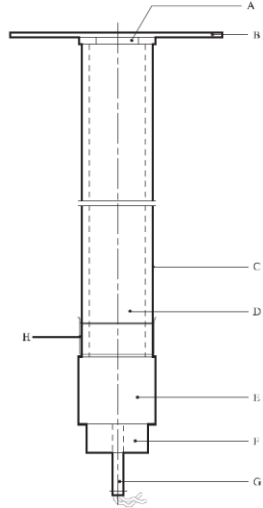


Photo 2: UN 2-Inch Gap Test Setup – Trials 1 & 2

- |  |                                   |
|--|-----------------------------------|
| (A) Spacers                            | (B) Witness plate                 |
| (C) Steel tube                         | (D) Substance under investigation |
| (E) RDX/wax or PETN/TNT booster charge | (F) Detonator holder              |
| (G) Detonator                          | (H) Plastics membrane             |

Figure 11.4.1.1: UN GAP TEST

# U.N. GAP TEST



- |  |                                   |
|--|-----------------------------------|
| (A) Spacers                            | (B) Witness plate                 |
| (C) Steel tube                         | (D) Substance under investigation |
| (E) RDX/wax or PETN/TNT booster charge | (F) Detonator holder              |
| (G) Detonator                          | (H) Plastics membrane             |

Figure 11.4.1.1: UN GAP TEST

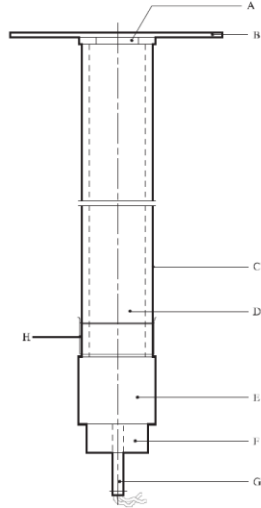


Photo 2: UN 2-Inch Gap Test Setup – Trials 1 & 2



Photo 3: UN 2-Inch Gap Test Results – Trials 1 & 2

# U.N. GAP TEST



- |  |                                   |
|--|-----------------------------------|
| (A) Spacers                            | (B) Witness plate                 |
| (C) Steel tube                         | (D) Substance under investigation |
| (E) RDX/wax or PETN/TNT booster charge | (F) Detonator holder              |
| (G) Detonator                          | (H) Plastic membrane              |

Figure 11.4.1.1: UN GAP TEST



Photo 2: UN 2-Inch Gap Test Setup – Trials 1 & 2



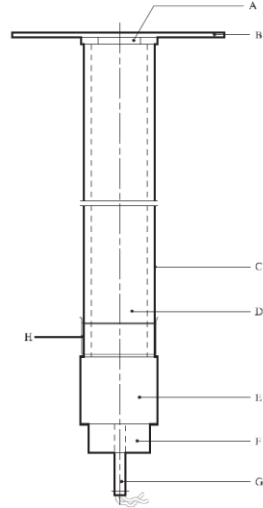
Photo 3: UN 2-Inch Gap Test Results – Trials 1 & 2

Table 2: 2-Inch Gap Testing Results Summary

Sample	Trial	Sample Weight (grams)	Conditions and Results	Pass/Fail
Temozolomide Substance	1	246	No pipe damage. No hole or perforation in witness plate.	Pass
	2	245	No pipe damage. No hole or perforation in witness plate.	Pass



# U.N. GAP TEST



- |  |                                   |
|--|-----------------------------------|
| (A) Spacers                            | (B) Witness plate                 |
| (C) Steel tube                         | (D) Substance under investigation |
| (E) RDX/wax or PETN/TNT booster charge | (F) Detonator holder              |
| (G) Detonator                          | (H) Plastic membrane              |

Figure 11.4.1.1: UN GAP TEST



Photo 2: UN 2-Inch Gap Test Setup – Trials 1 & 2




Photo 3: UN 2-Inch Gap Test Results – Trials 1 & 2

Table 2: 2-Inch Gap Testing Results Summary

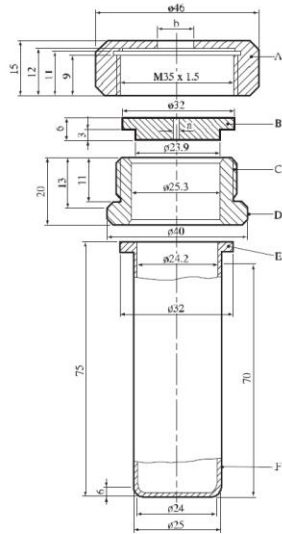
Sample	Trial	Sample Weight (grams)	Conditions and Results	Pass/Fail
Temozolomide Substance	1	246	No pipe damage. No hole or perforation in witness plate.	Pass
	2	245	No pipe damage. No hole or perforation in witness plate.	Pass

## TEST SERIES 2 - METHODS

Test	What is Measured	Failure Results if
U.N. Gap Test	Sensitivity of material to a shock stimulus	Tube fragments completely or hole is punched through witness plate 
Koenen Test	Effect of heating under confinement	<ol style="list-style-type: none"> <li>1. Tube is fragmented into three or more mainly large pieces which in some cases may be connected with each other by a narrow strip, or</li> <li>2. Tube fragmented into many mainly small pieces, closing device unchanged, or</li> <li>3. Tube fragmented into many very small pieces, closing device bulged out or fragmented</li> </ol>
Time/Pressure Test	Effect of ignition under confinement	Rate of the overpressure from 100 psig to 300 psig is less than 30 ms



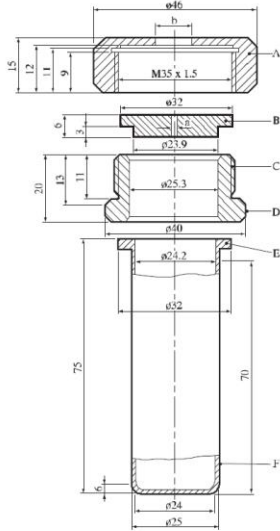
# KOENEN TEST



- |  |  |
|--|--|
| (A) Nut (b = 10.0 or 20.0 mm) with flats for size 41 spanner | (B) Orifice plate (a = 1.0 → 20.0 mm diameter) |
| (C) Threaded collar  | (D) Flats for size 36 spanner                  |
| (E) Flange   | (F) Tube                                       |

Figure 11.5.1.1: TEST TUBE ASSEMBLY

# KOENEN TEST



- |  |  |
|--|--|
| (A) Nut (b = 10.0 or 20.0 mm) with flats for size 41 spanner | (B) Orifice plate (a = 1.0 → 20.0 mm diameter) |
| (C) Threaded collar  | (D) Flats for size 36 spanner                  |
| (E) Flange   | (F) Tube                                       |

Figure 11.5.1.1: TEST TUBE ASSEMBLY



Photo 4: Koenen Test Result (2mm Orifice) for Temozolomide Substance Results

FAUSKE  
TNR  
Koenen Test 2m  
Trial 1, 2, 3 1st 1st  
OUT: Jason Ford  
WMS  
FSKE-6048  
10/1/2020

Sample	Trial	Conditions and Results	Pass/Fail
Temozolomide Substance	1	Bottom of tube bulged out slightly, resulting in Effect Type "A"	Pass
	2	Bottom of tube bulged out slightly, resulting in Effect Type "A"	Pass
	3	Bottom of tube bulged out slightly, resulting in Effect Type "A"	Pass

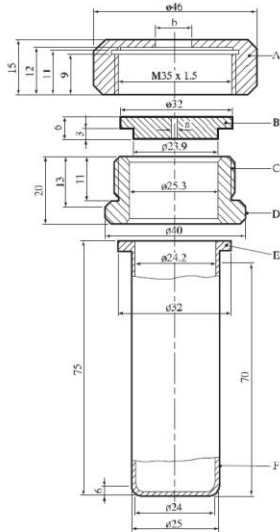
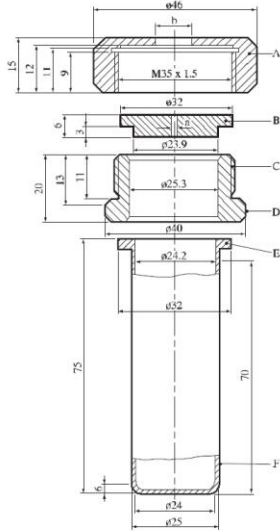


Figure 11.5.1.1: TEST TUBE ASSEMBLY

(A)	Nut ( $b = 10.0$ or $20.0$ mm) with flats for size 41 spanner	(B)	Orifice plate ( $a = 1.0 \rightarrow 20.0$ mm diameter)
(C)	Threaded collar	(D)	Flats for size 36 spanner
(E)	Flange	(F)	Tube

# KOENEN TEST



- (A) Nut (b = 10.0 or 20.0 mm) with flats for size 41 spanner  
(B) Orifice plate (a = 1.0 → 20.0 mm diameter)  
(C) Threaded collar  
(D) Flats for size 36 spanner  
(E) Flange  
(F) Tube

Figure 11.5.1.1: TEST TUBE ASSEMBLY



Photo 4: Koenen Test Result (2mm Orifice) for Temozolomide Substance Results

Table 3: Koenen Testing Results Summary

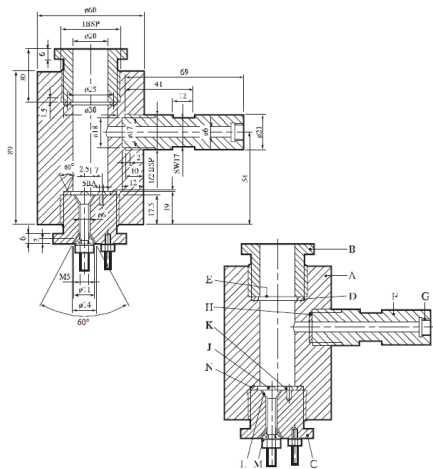
Sample	Trial	Conditions and Results	Pass/Fail
Temozolomide Substance	1	Bottom of tube bulged out slightly, resulting in Effect Type "A"	Pass
	2	Bottom of tube bulged out slightly, resulting in Effect Type "A"	Pass
	3	Bottom of tube bulged out slightly, resulting in Effect Type "A"	Pass

## TEST SERIES 2 - METHODS

Test	What is Measured	Failure Results if
U.N. Gap Test	Sensitivity of material to a shock stimulus	Tube fragments completely or hole is punched through witness plate
Koenen Test	Effect of heating under confinement	<ol style="list-style-type: none"><li>1. Tube is fragmented into three or more mainly large pieces which in some cases may be connected with each other by a narrow strip, or</li><li>2. Tube fragmented into many mainly small pieces, closing device unchanged, or</li><li>3. Tube fragmented into many very small pieces, closing device bulged out or fragmented</li></ol>
Time/Pressure Test	Effect of ignition under confinement	Rate of the overpressure from 100 psig to 300 psig is less than 30 ms



## TIME/PRESSURE TEST



(A) Pressure vessel body	(B) Bursting disc retaining plug
(C) Firing plug	(D) Soft lead washer
(E) Bursting disc	(F) Side arm
(G) Pressure transducer thread	(H) Copper washer
(J) Insulated Electrode	(K) Earthed electrode
(L) Insulation	(M) Steel cone
(N) Washer distorting groove	

**Figure 11.6.1.1: APPARATUS**

# TIME/PRESSURE TEST

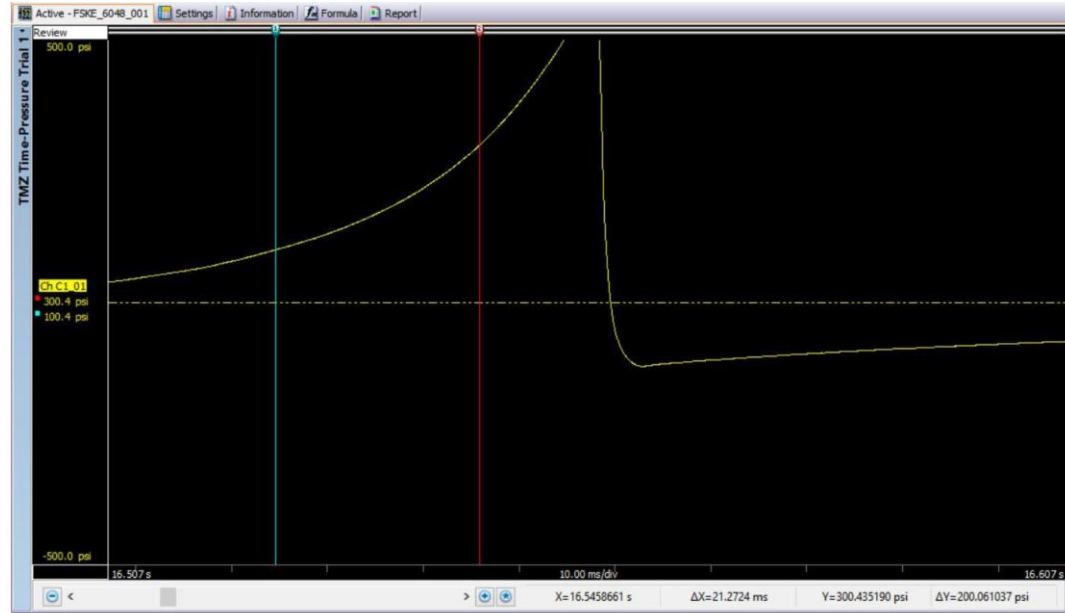
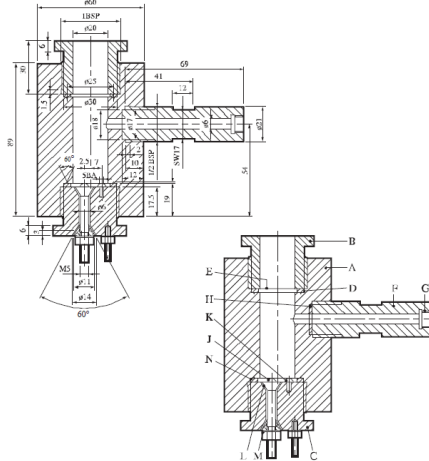
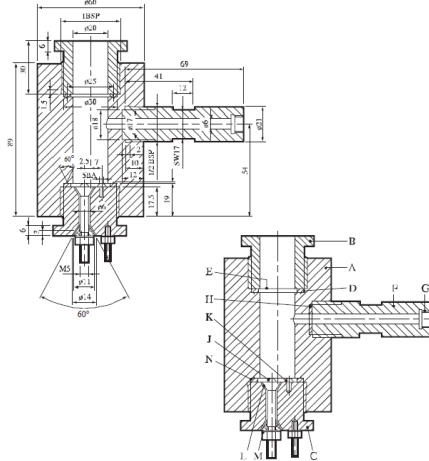


Figure A1: Time/Pressure Results for TMZ Substance – Trial 1

(A) Pressure vessel body	(B) Bursting disc retaining plug
(C) Firing plug	(D) Soft lead washer
(E) Bursting disc	(F) Side arm
(G) Pressure transducer thread	(H) Copper washer
(J) Insulated Electrode	(K) Earthed electrode
(L) Insulation	(M) Steel cone
(N) Washer distorting groove	

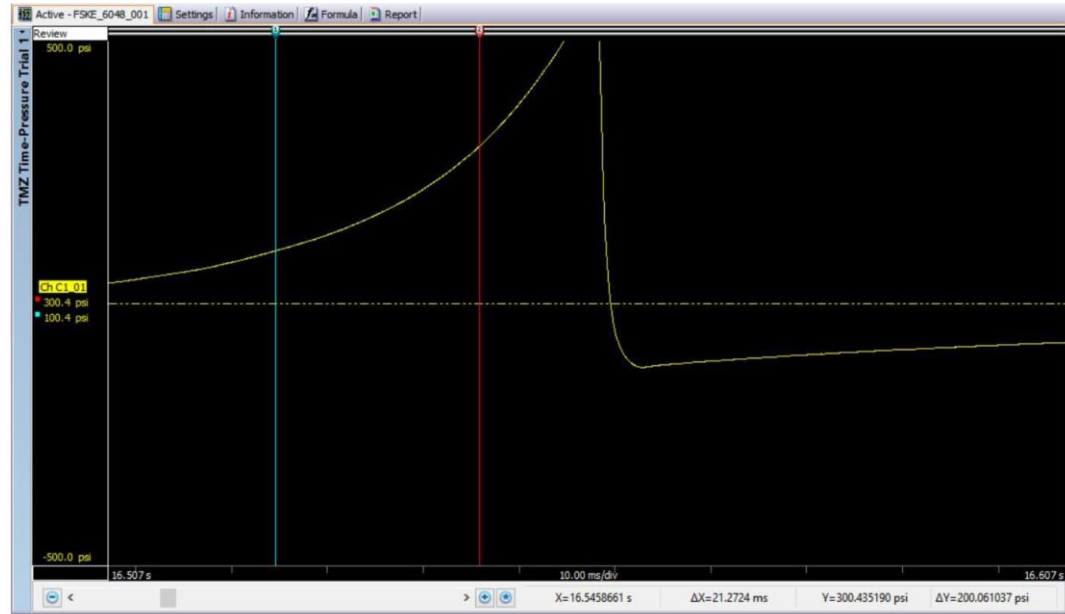
Figure 11.6.1.1: APPARATUS

## TIME/PRESSURE TEST



**Figure 11.6.1.1: APPARATUS**

(A) Pressure vessel body	(B) Bursting disc retaining plug
(C) Firing plug	(D) Soft lead washer
(E) Bursting disc	(F) Side arm
(G) Pressure transducer thread	(H) Copper washer
(J) Insulated Electrode	(K) Earthed electrode
(L) Insulation	(M) Steel cone
(N) Washer distorting groove	



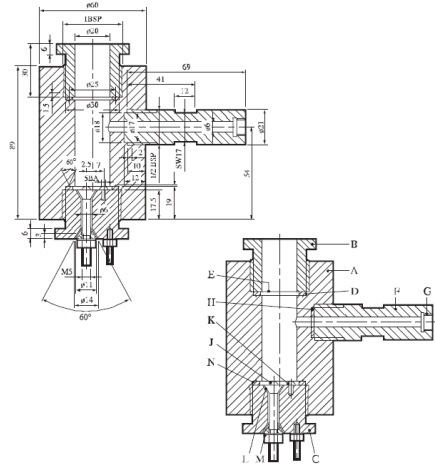
**Figure A1: Time/Pressure Results for TMZ Substance – Trial 1**

### Table 4: Time/Pressure Testing Results Summary

Sample	Trial	Conditions and Results	Pass/Fail
Temozolomide Substance	1	The pressure reached 2,070 kPa (300 psi) in <b>21.2 ms</b>	<b>Fail</b>
	2	The pressure reached 2,070 kPa (300 psi) in <b>25.8 ms</b>	<b>Fail</b>
	3	N/A	N/A



# TIME/PRESSURE TEST



- |                                |                                  |
|--------------------------------|----------------------------------|
| (A) Pressure vessel body       | (B) Bursting disc retaining plug |
| (C) Firing plug                | (D) Soft lead washer             |
| (E) Bursting disc              | (F) Side arm                     |
| (G) Pressure transducer thread | (H) Copper washer                |
| (J) Insulated Electrode        | (K) Earthed electrode            |
| (L) Insulation                 | (M) Steel cone                   |
| (N) Washer distorting groove   |                                  |

Figure 11.6.1.1: APPARATUS

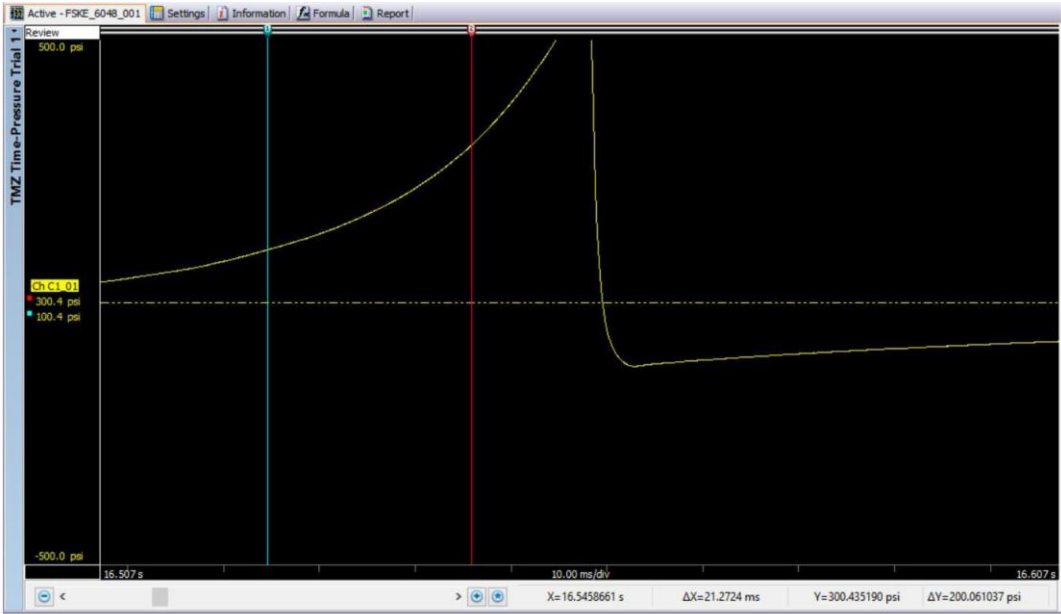


Figure A1: Time/Pressure Results for TMZ Substance – Trial 1

Table 4: Time/Pressure Testing Results Summary

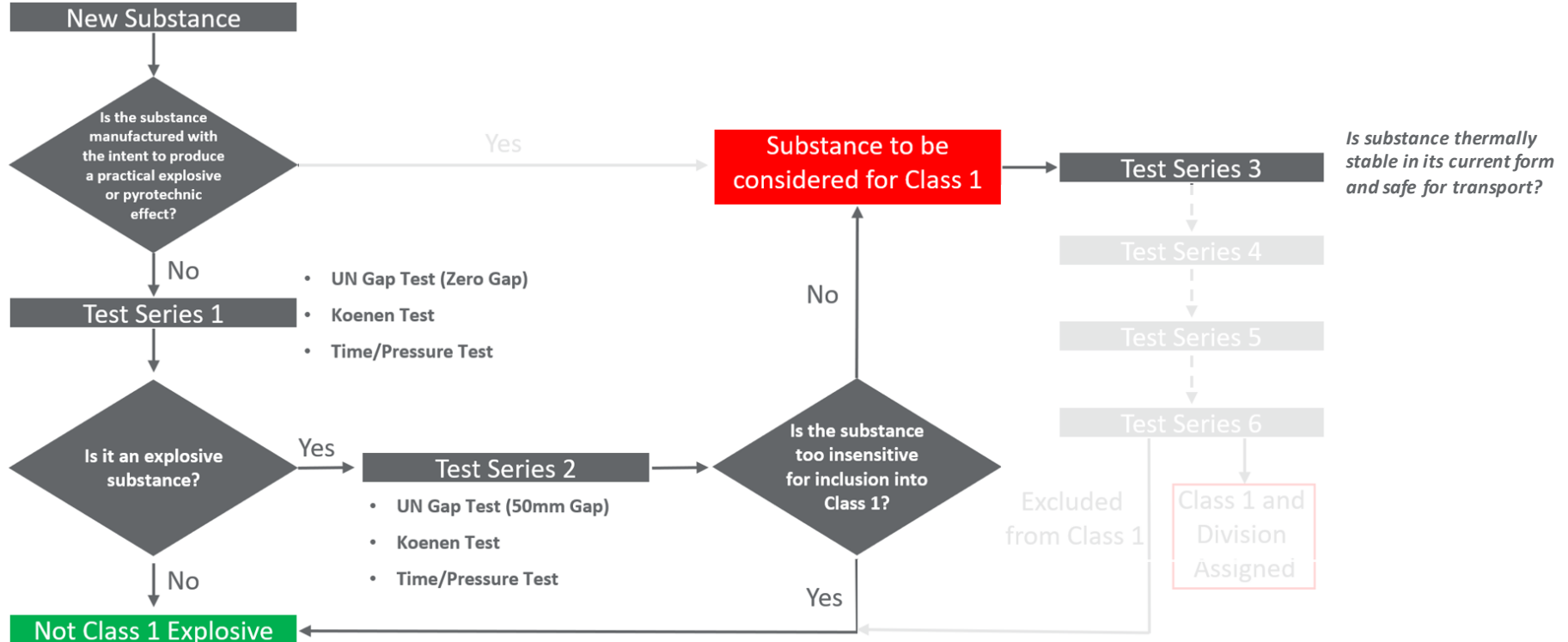
Sample	Trial	Conditions and Results	Pass/Fail
Temozolomide Substance	1	The pressure reached 2,070 kPa (300 psi) in 21.2 ms	Fail
	2	The pressure reached 2,070 kPa (300 psi) in 25.8 ms	Fail
	3	N/A	N/A



## TEST SERIES 2 - METHODS

Test	What is Measured	Failure Results if	
U.N. Gap Test	Sensitivity of material to a shock stimulus	Tube fragments completely or hole is punched through witness plate	✓
Koenen Test	Effect of heating under confinement	<ol style="list-style-type: none"> <li>1. Tube is fragmented into three or more mainly large pieces which in some cases may be connected with each other by a narrow strip, or</li> <li>2. Tube fragmented into many mainly small pieces, closing device unchanged, or</li> <li>3. Tube fragmented into many very small pieces, closing device bulged out or fragmented</li> </ol>	✓
Time/Pressure Test	Effect of ignition under confinement	Rate of the overpressure from 100 psig to 300 psig is less than 30 ms	✗

# CLASSIFYING EXPLOSIVE SUBSTANCES



# U.N. TEST SERIES 3

## TEST SERIES 3 - METHODS

Test	What is Measured	Failure Results if
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	Sensitiveness to impact (3.63 kg at 10 cm)	A flame or audible report is observed in at least 5 out of 10 trials
UN Series 3 (b)(i) BAM friction sensitivity test	Sensitiveness to friction (including impacted friction)	The lowest load at which one “explosion” occurs in six trials is less than 80N
UN Series 3 (c)(i) Thermal stability test at 75°C	Thermal stability of a substance	An ignition or explosion occurs in 48 hours
UN Series 3 (d) Small-scale burning	Response of a substance to fire	The substance explodes


# TEST SERIES 3 - RESULTS

Test	What is Measured	Failure Results if
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	Sensitiveness to impact (3.63 kg at 10 cm)	A flame or audible report is observed in at least 5 out of 10 trials

Test	Conditions and Results	Pass/Fail
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	No reaction was observed at 10 cm in 6 trials.	Pass

# TEST SERIES 3 - RESULTS

Test	What is Measured	Failure Results if
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	Sensitiveness to impact (3.63 kg at 10 cm)	A flame or audible report is observed in at least 5 out of 10 trials



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UN Series 3 (a)(i) Bureau of Explosives Impact machine test	No reaction was observed at 10 cm in 6 trials.	Pass

## TEST SERIES 3 - RESULTS

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## TEST SERIES 3 - RESULTS

Test	What is Measured	Failure Results if
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	Sensitiveness to impact (3.63 kg at 10 cm)	A flame or audible report is observed in at least 5 out of 10 trials
UN Series 3 (b)(i) BAM friction sensitivity test	Sensitiveness to friction (including impacted friction)	The lowest load at which one “explosion” occurs in six trials is less than 80N



UN Series 3 (b)(i) BAM friction sensitivity test	No reaction was observed at 80 N in 6 trials.	Pass
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## TEST SERIES 3 - RESULTS

Test	What is Measured	Failure Results if
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	Sensitiveness to impact (3.63 kg at 10 cm)	A flame or audible report is observed in at least 5 out of 10 trials
UN Series 3 (b)(i) BAM friction sensitivity test	Sensitiveness to friction (including impacted friction)	The lowest load at which one “explosion” occurs in six trials is less than 80N



UN Series 3 (b)(i) BAM friction sensitivity test	No reaction was observed at 80 N in 6 trials.	Pass
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## TEST SERIES 3 - RESULTS

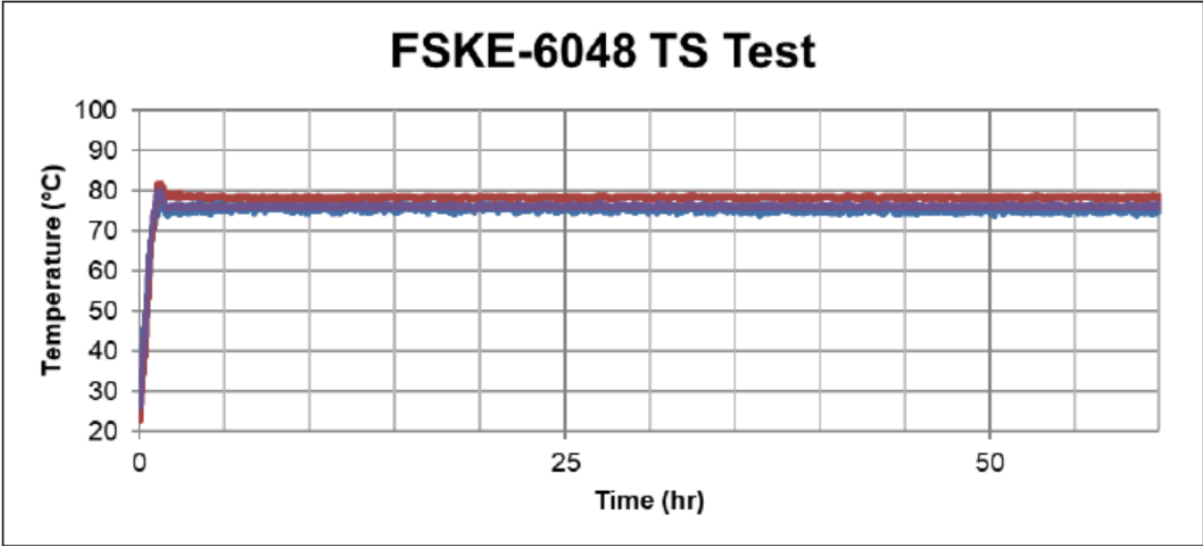
Test	What is Measured	Failure Results if
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	Sensitiveness to impact (3.63 kg at 10 cm)	A flame or audible report is observed in at least 5 out of 10 trials 
UN Series 3 (b)(i) BAM friction sensitivity test	Sensitiveness to friction (including impacted friction)	The lowest load at which one “explosion” occurs in six trials is less than 80N 
UN Series 3 (c)(i) Thermal stability test at 75°C	Thermal stability of a substance	An ignition or explosion occurs in 48 hours

## TEST SERIES 3 – THERMAL STABILITY AT 75 °C



Photo 2: Thermal Stability Test Setup

# TEST SERIES 3 – THERMAL STABILITY AT 75 °C



**Figure 1: Temperature Plot for the Thermal Stability Test**

# TEST SERIES 3 – THERMAL STABILITY AT 75 °C

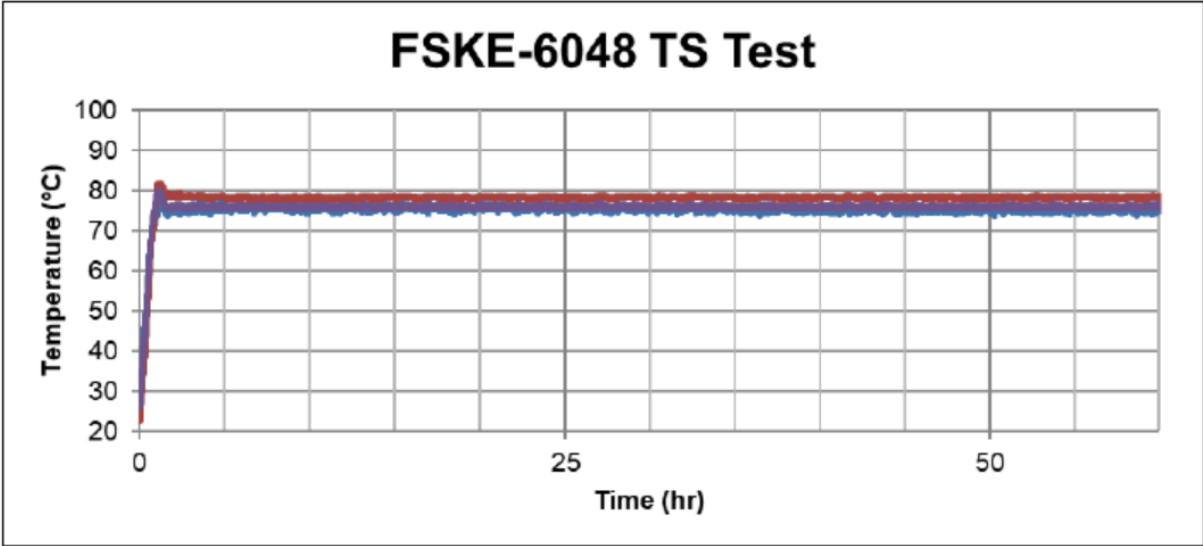


Figure 1: Temperature Plot for the Thermal Stability Test

UN Series 3 (c)(i) Thermal stability test at 75°C (un-instrumented)	No fuming, decomposition, ignition or explosion occurred. No physical changes to the 50-gram sample.	Pass (thermally stable)
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## TEST SERIES 3 - RESULTS

Test	What is Measured	Failure Results if
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	Sensitiveness to impact (3.63 kg at 10 cm)	A flame or audible report is observed in at least 5 out of 10 trials
UN Series 3 (b)(i) BAM friction sensitivity test	Sensitiveness to friction (including impacted friction)	The lowest load at which one “explosion” occurs in six trials is less than 80N
UN Series 3 (c)(i) Thermal stability test at 75°C	Thermal stability of a substance	An ignition or explosion occurs in 48 hours
UN Series 3 (d) Small-scale burning	Response of a substance to fire	The substance explodes



## TEST SERIES 3 – SMALL-SCALE BURNING TEST



**Photo 3: Small-scale Burning Test Setup**







## TEST SERIES 3 – SMALL-SCALE BURNING TEST



Photo 4: Small-scale Burning Test Results (Trial 1)

UN Series 3 (d) Small-scale burning	Two trials of 100-gram samples ignited and burned. The burn time was approximately 25 seconds for each trial. No explosion was observed	Pass
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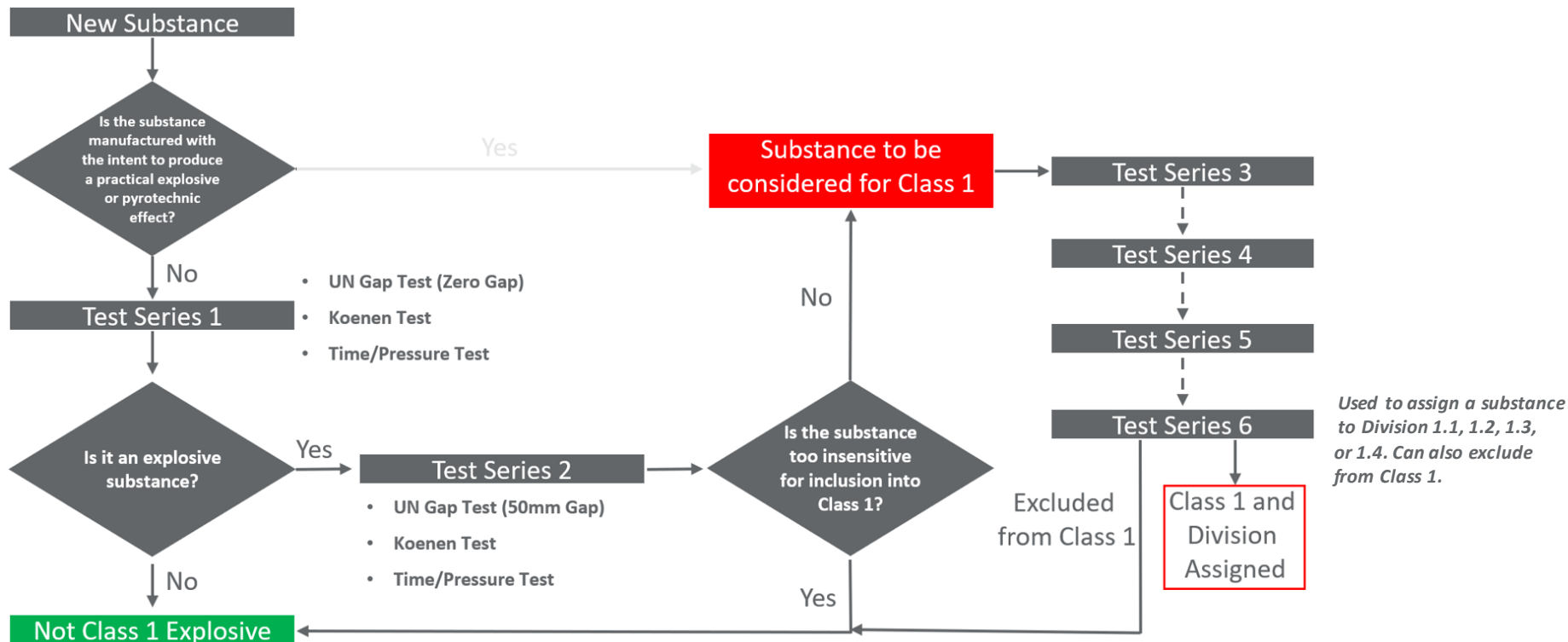
## TEST SERIES 3 - RESULTS

Test	What is Measured	Failure Results if	
UN Series 3 (a)(i) Bureau of Explosives Impact machine test	Sensitiveness to impact (3.63 kg at 10 cm)	A flame or audible report is observed in at least 5 out of 10 trials	
UN Series 3 (b)(i) BAM friction sensitivity test	Sensitiveness to friction (including impacted friction)	The lowest load at which one “explosion” occurs in six trials is less than 80N	
UN Series 3 (c)(i) Thermal stability test at 75°C	Thermal stability of a substance	An ignition or explosion occurs in 48 hours	
UN Series 3 (d) Small-scale burning	Response of a substance to fire	The substance explodes	

## CONCLUSION AND RECOMMENDATIONS

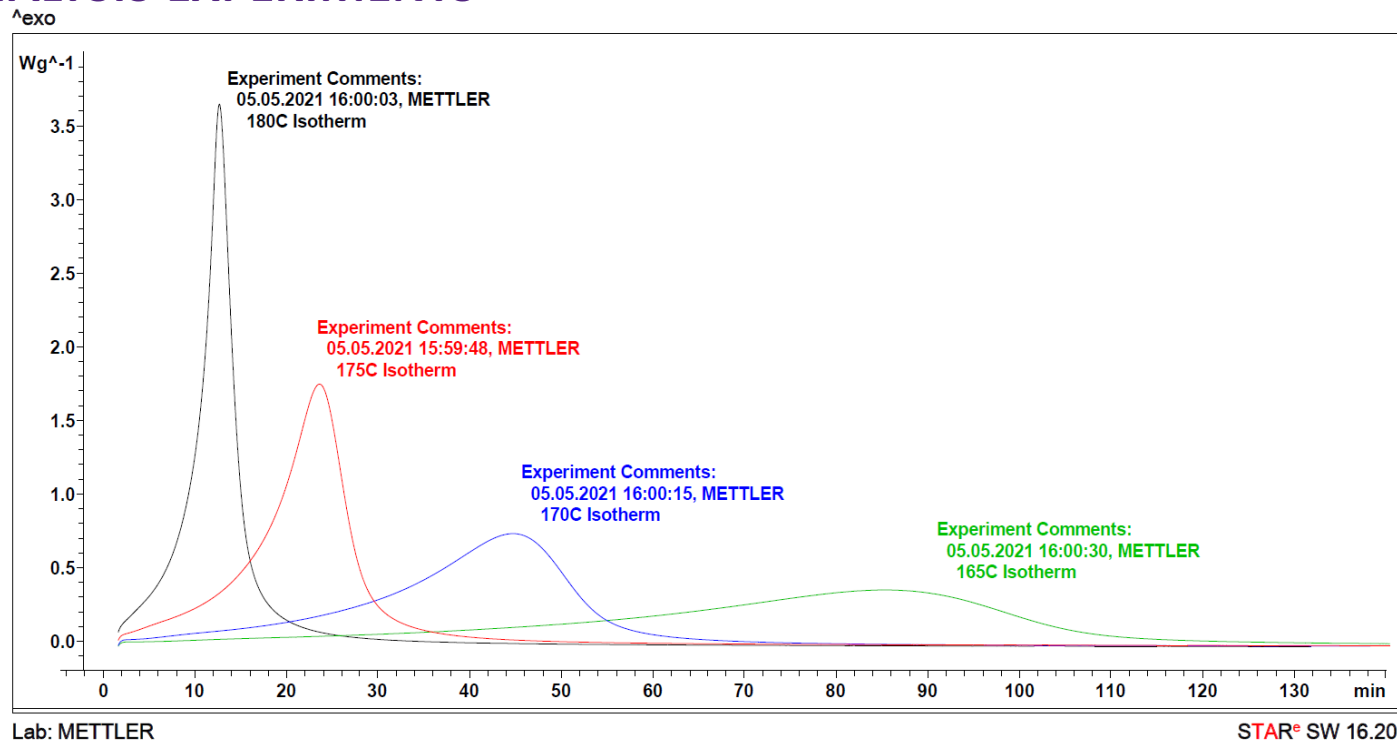
- Behavior of the TMZ material is consistent with a recommendation into Division 1.1 based on the tests conducted thus far
- The substance passed the UN Series 3 tests and is NOT considered too dangerous for transport in the form in which it was tested
- A lesser hazard division is still possible at the completion of UN Series 6 testing as mentioned in the introduction

# CLASSIFYING EXPLOSIVE SUBSTANCES

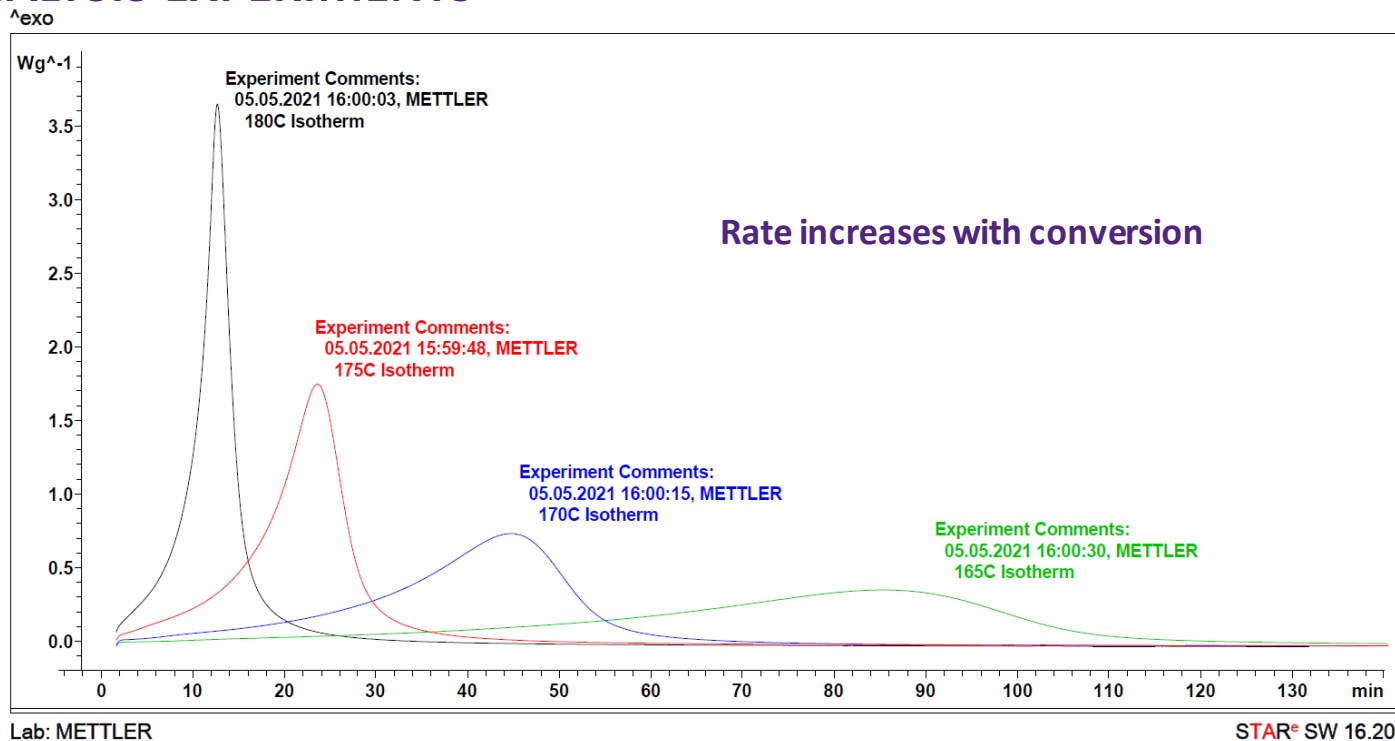


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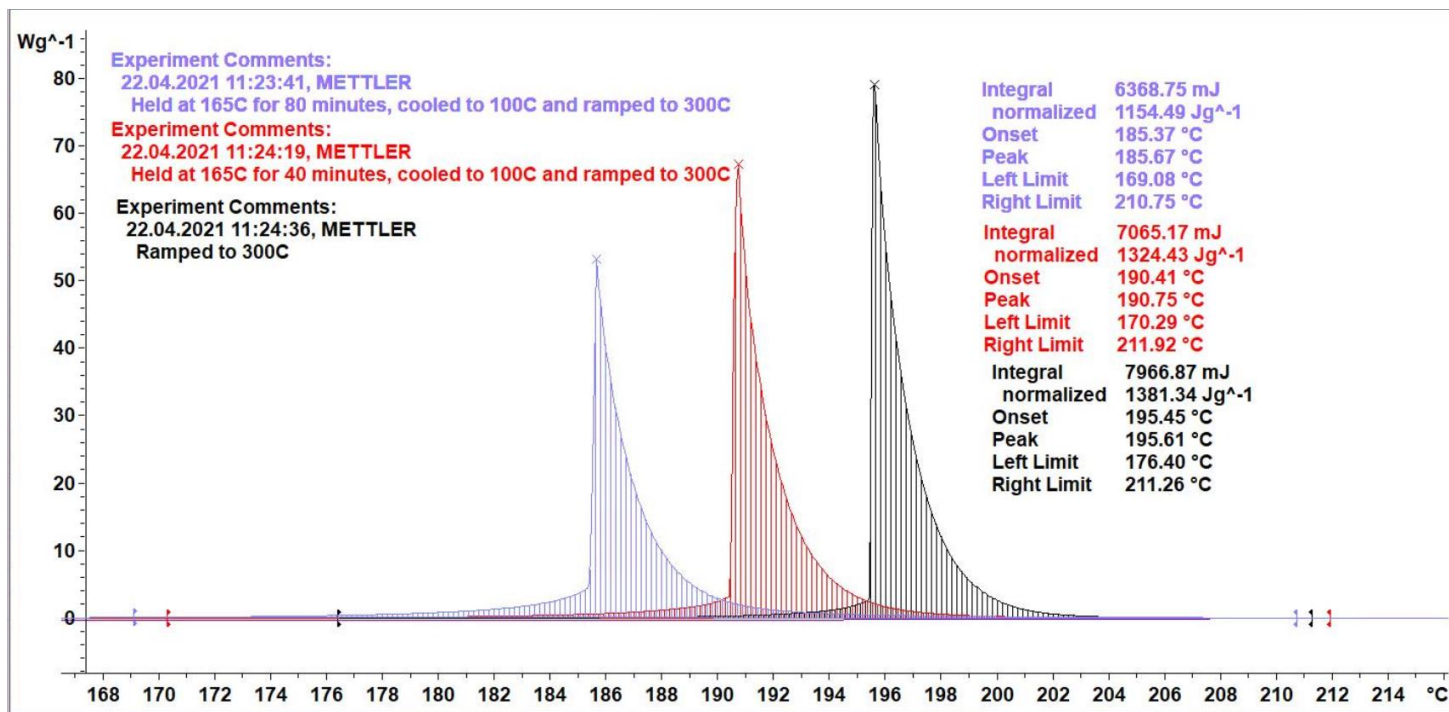
# AUTOCATALYSIS EXPERIMENTS



# AUTOCATALYSIS EXPERIMENTS

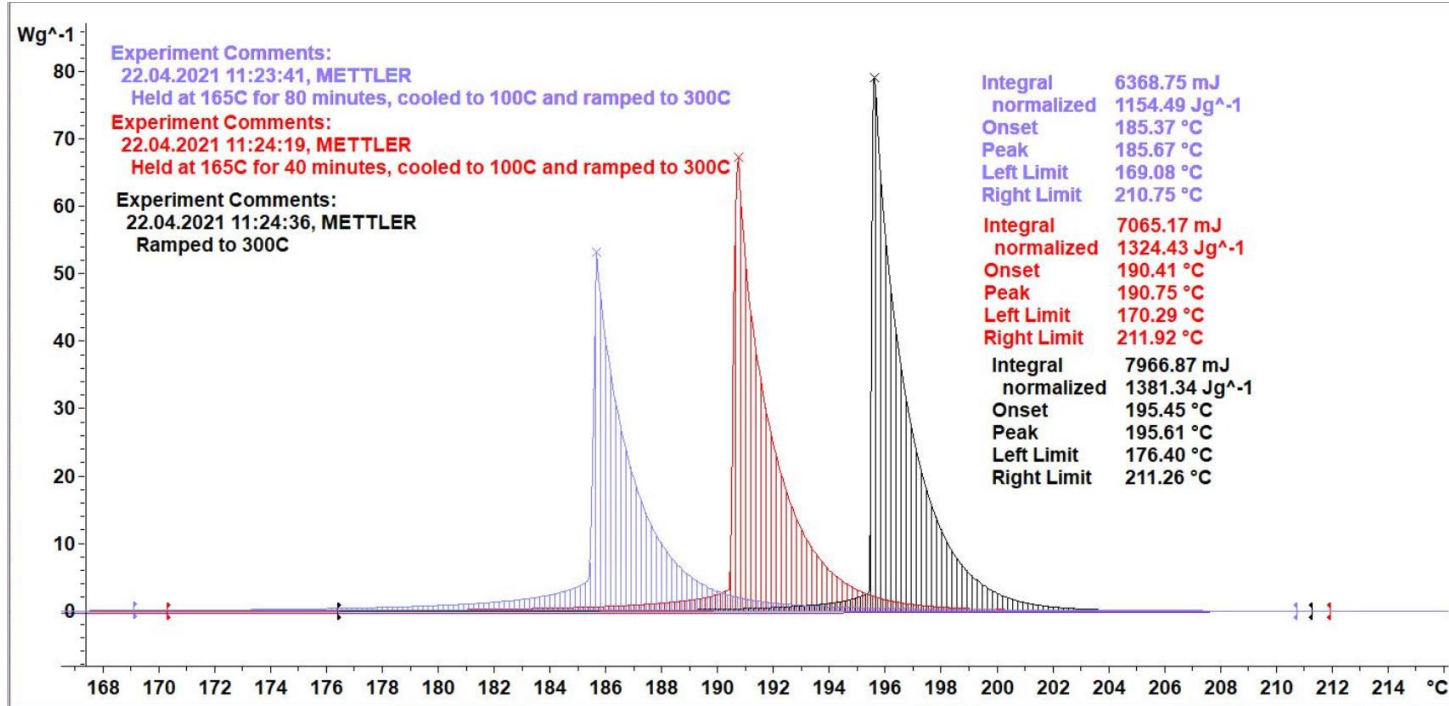


# AUTOCATALYSIS EXPERIMENTS





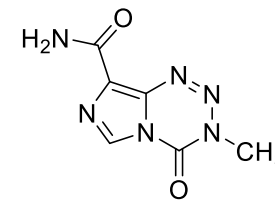
# AUTOCATALYSIS EXPERIMENTS



Additional data required...

## CONCLUSIONS

- Contrary to previous reports, TMZ is not stable up to its melting point
- DSC testing shows left limit onset of approximately 170 °C with -1,400 J/g of energy released
- The O.R.E.O.S. tool correctly predicted the risks associated with TMZ
- ARC testing revealed onset at 145 °C and an adiabatic temperature rise of >730 °C
- TMZ failed U.N. Test Series 2 but passed Test Series 3
- TMZ is considered for Class 1 explosivity designation but may be downgraded with Test Series 6



Temozolomide  
(TMZ)

# ACKNOWLEDGMENTS



Michael Azuma

Connor Barrett

Shane Stone



# QUESTIONS?

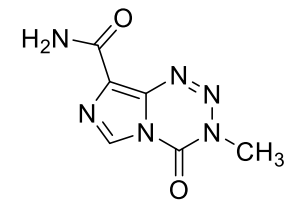


# QUESTIONS?

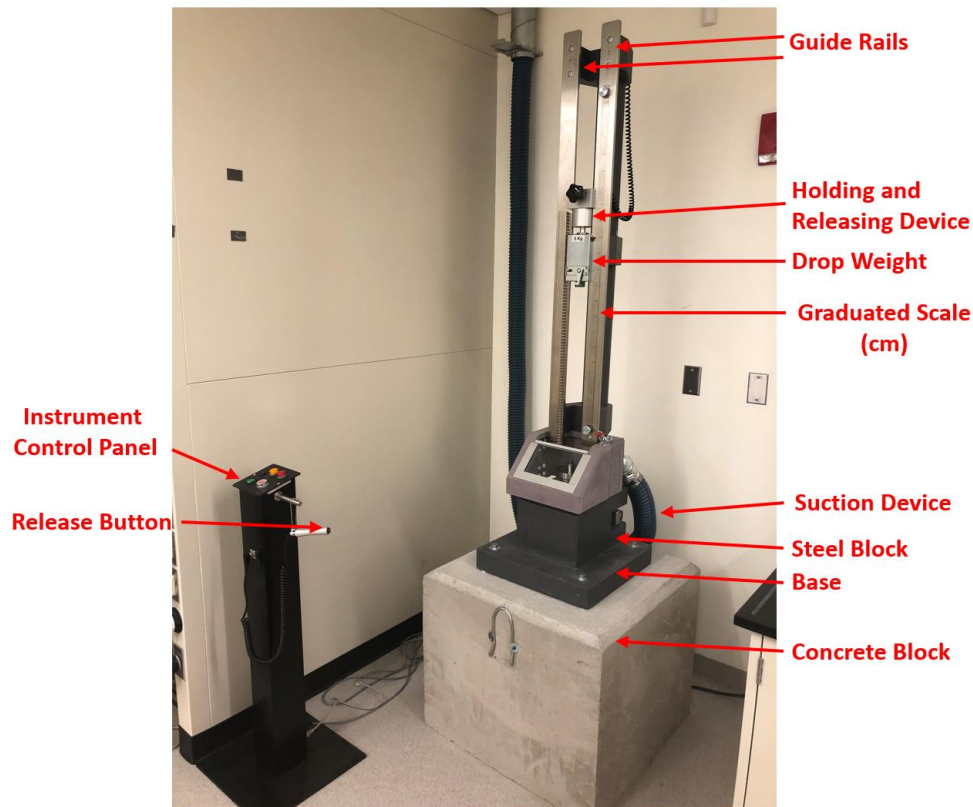


# IMPACT TESTING – BAM FALLHAMMER

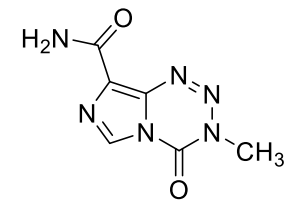
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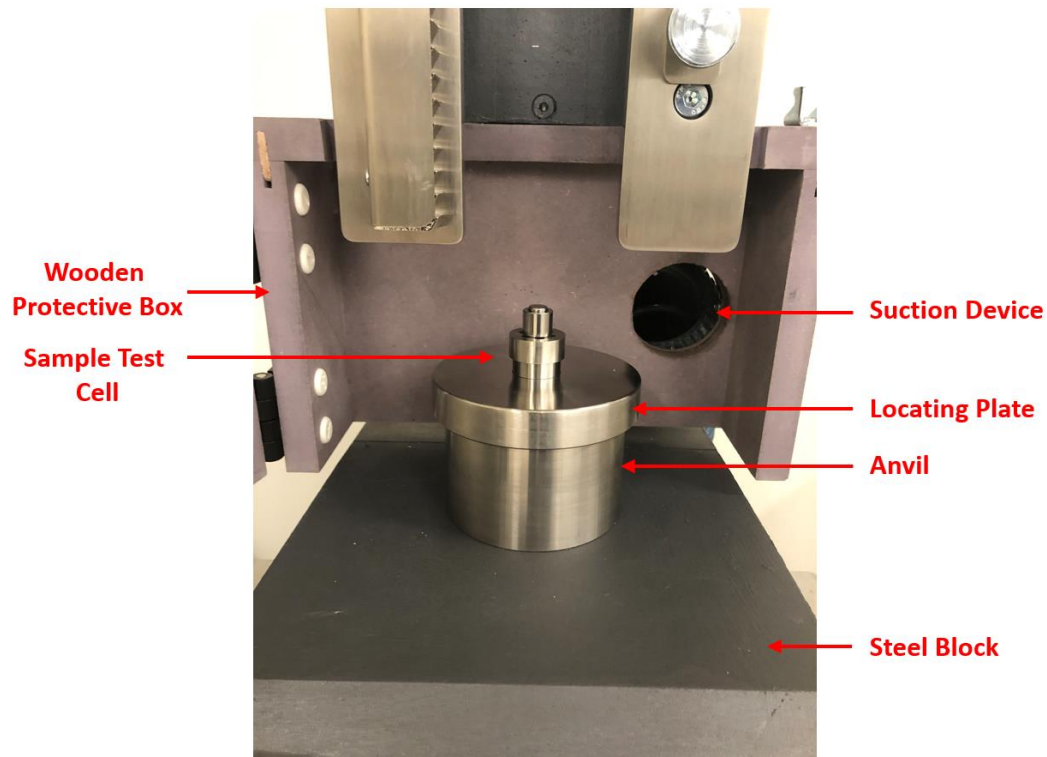
Temozolomide  
(TMZ)



# TEMOZOLOMIDE (TMZ) – IMPACT TESTING

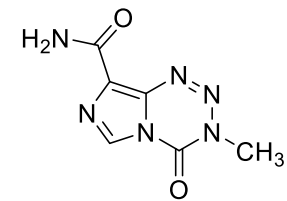


Temozolomide  
(TMZ)





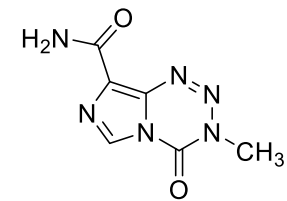
# TEMOZOLOMIDE (TMZ) – IMPACT TESTING



Temozolomide  
(TMZ)



# TEMOZOLOMIDE (TMZ) – IMPACT TESTING

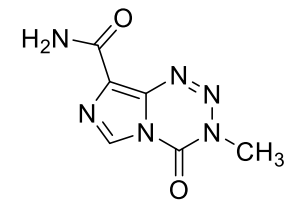


Temozolomide  
(TMZ)



Before

# TEMOZOLOMIDE (TMZ) – IMPACT TESTING



Temozolomide  
(TMZ)

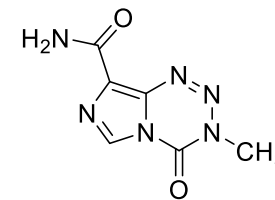


Before



After 60J Impact

# TEMOZOLOMIDE (TMZ) – IMPACT TESTING



Temozolomide  
(TMZ)

Possible Results  
(increasing severity)

No Reaction

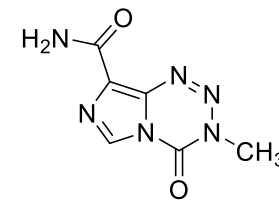
Decomposition

Smoke

Audible Report

Flame

# TEMOZOLOMIDE (TMZ) – IMPACT TESTING



Temozolomide  
(TMZ)

Possible Results  
(increasing severity)

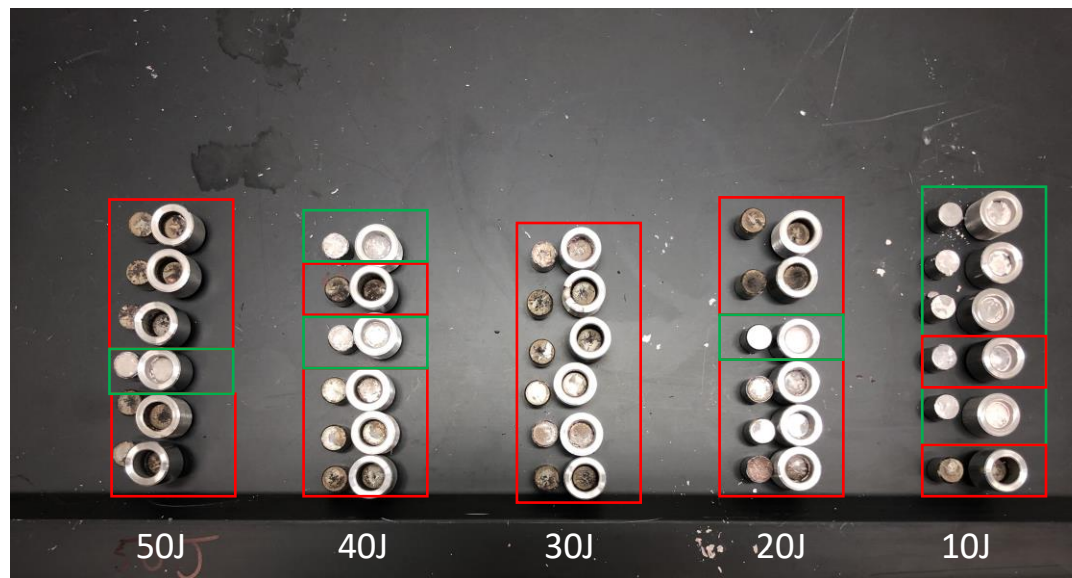
No Reaction

Decomposition

Smoke

Audible Report

Flame



 No Reaction

 Decomp or  
Smoke