

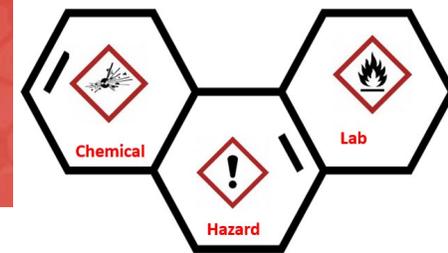
Automation in process safety information delivery

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Eli Lilly and Company

The Lilly logo, featuring the word "Lilly" in a white, cursive script font, is positioned in the bottom right corner of the slide.

Background- thermal hazard of chemicals



Thermal hazards of chemicals

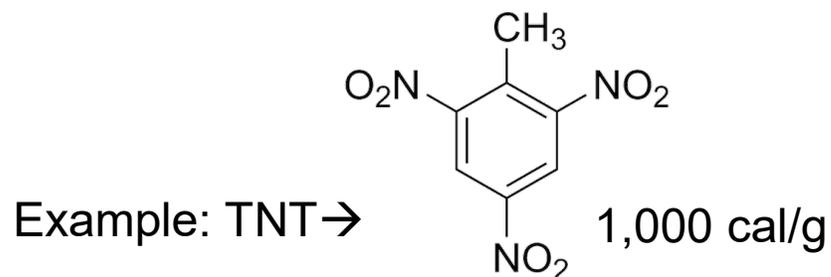


How Safe are the Materials that we're Using?

- ◆ Can we ship and store them?
- ◆ Can we safely use them in processing?

Structural Feature	Examples
C – C Unsaturation	Acetylene, acetylides, 1,2-dienes (allenes)
C-Metal, N-Metal	Grignard reagents, organo-lithium species
Contiguous nitrogen atoms	Azides, aliphatic azo compounds, diazonium salts, hydrazines, sulfonyl hydrazides
Contiguous oxygen atoms	Peroxides, ozonides
N-O	Nitro, nitroso, nitrates, hydroxylamines, N-oxides, 1,2-oxazoles
N-halogen, O-halogen	Chloramines, fluoroamines, chlorates, perchlorates, iodosyl compounds

High energy functional groups¹



It is no problem to use an energetic material in our processes,

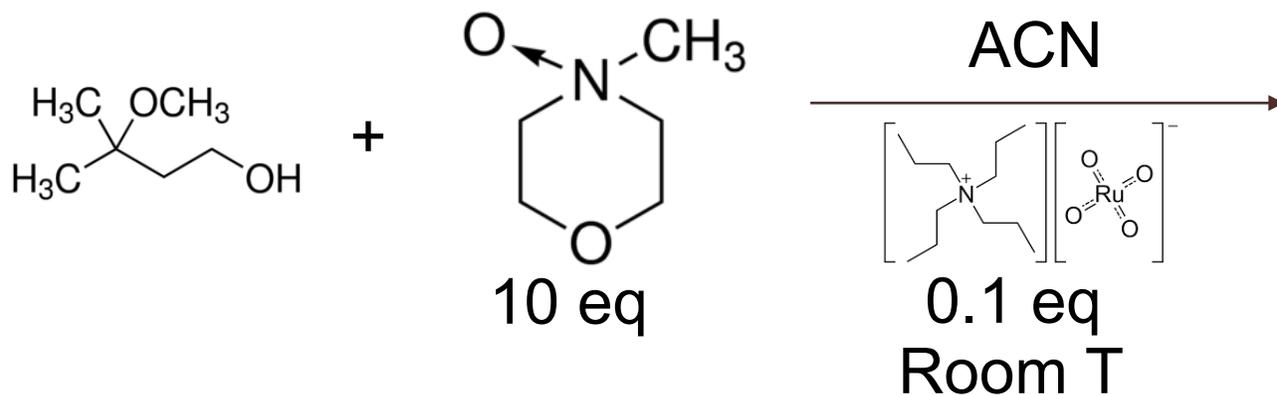
We work with lots of new chemicals everyday.

Incidents/near misses happened when we failed to recognize the potential hazards

¹United Nations Recommendations for the Transport of Dangerous Goods, Manual of Tests and Criteria (Rev 7, 2019), Appendix 6, Section 3.3 (a)

WHY?? Near misses: What happened:

A pharma discovery lab, Scale:200 mLs



After 2 hours, no temperature change and the mixture was stirred overnight.

When coming back the 2nd day.
The reaction mixture was spilled everywhere.

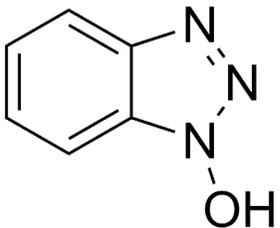
Automated PSI delivery

(# of high energy bond/molecular weight) *100

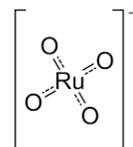
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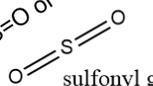
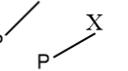
	Low energy density	Medium energy density	High energy density	Extremely high energy density
#HEB/MW*100	<=1	Between 1 and 2.5	Between 2.5 and 3.5	>3.5

High energy functional groups¹

1. Not quantitative:  How many high energy functional groups?? 2, 3, 4?

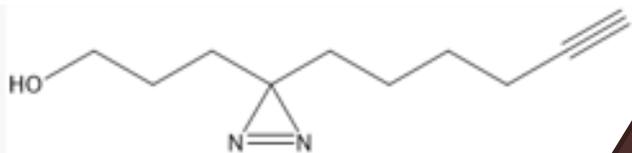
2. Not a full list: Less known high energy functional group:



 1	NON-AROMATIC	 1
Carbon-carbon double bond		3 member ring, any atoms
 2		 1
Carbon-carbon triple bond		4 member ring, any atoms
 1		 1
nitrogen-nitrogen bond		halogen-oxygen bond
 1		 1
Nitrogen-oxygen bond		halogen-oxygen bond
 1		 1 (not gas SO ₂)
Oxygen-oxygen bond		sulfonyl group
 1		 1
R-SO ₃ Sulfonate		phosphorus-halogen, phosphorus-carbon bond

An example

An example:

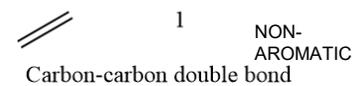


Mw. 194

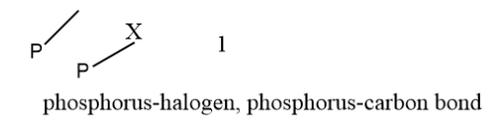
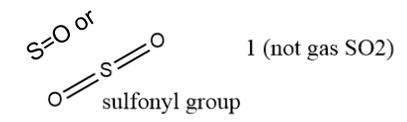
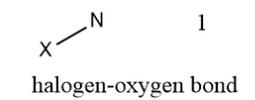
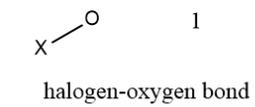
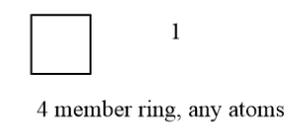
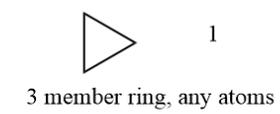
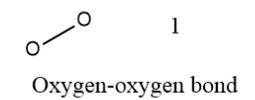
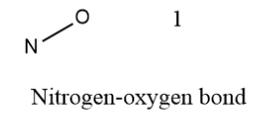
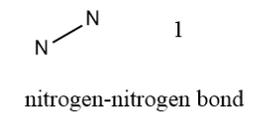
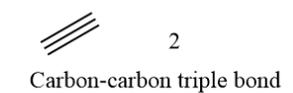
One ring: +1
N=N: +2
CC triple bond: +2

	Low energy density	Medium energy density	High energy density	Extremely high energy density
#HEB/MW*100	<=1	Between 1 and 2.5	Between 2.5 and 3.5	>3.5

(# of high energy bond/molecular weight) *100



NON-AROMATIC



Reagent thermal stability grid

	Low energy density	Medium energy density	High energy density	Extremely high energy density
#HEB/MW*100	<=1	Between 1 and 2.5	Between 2.5 and 3.5	>3.5
Reagent amount				
<1g	Green	Green	Yellow	Yellow
1-10g	Green	Yellow	Yellow	Red
10-1000g	Green	Yellow	Red	Red
1000-10 kg	Yellow	Red	Red	Red
>10kg	Yellow	*	*	*

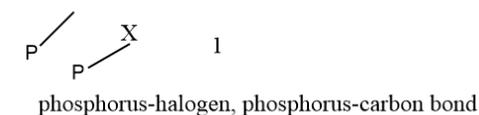
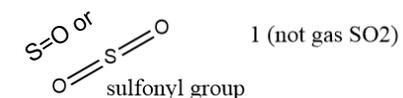
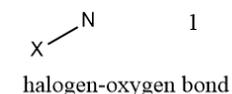
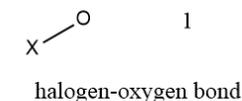
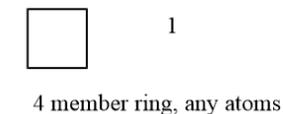
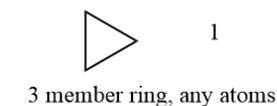
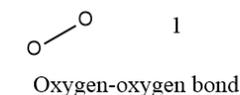
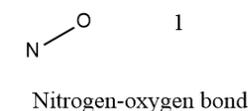
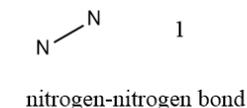
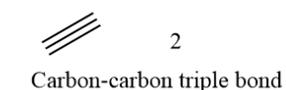
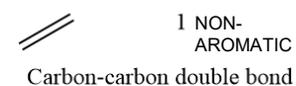
Green: safety assessment not required (general lab safety practices)

Yellow: consult safety SME/ screening safety data might be required for internal projects. CHL(chemical hazard lab) does not review external data from trusted vendors

Red: CHL generates detailed safety data for internal projects

CHL review and approve data for external projects (*if shipping is involved, the official UN classification tests might be required, 2nd tier supplier might need to be audited if commercial)

HEB=high energy bond
CHL= chemical hazard lab



How do we define “trusted vendors”

Current procedure:



Collection of process information (process safety data, design information, operating parameters, and equipment specifications?)

Self-assessment answer

Completed by supplier prior to audit

	low risk (1)	Medium Risk (3-5)	High risk (7-10)	Potential questions for CMO
Handling thermal unstable reagents	CMO has platform to look for thermally unstable reagents (e.x. DSC, TSU) and CMO has internal experts that execute these tests and interpret the data and provide recommendation for handling. Familiarity with Yoshida correlations and Stoessel classifications.	CMO might have the platform to look for thermally unstable reagents (e.x. DSC, TSU) and CMO does not have internal experts that execute these tests and rely on a 3rd party testing facility to do the tests and data interpretation.	CMO have no experience or expose to testing or handling thermally unstable reagents	Do you conduct thermal hazard screening (like DSC) in your facility 1-Yes, we have the platform and SME to conduct these tests and analyze them and provide recommendations. (provide SOP or example reports from each platform, hide proprietary information) 2-No, but we work with a 3rd party thermal hazard lab equipped with these platforms and they have SMEs to analyze the date and provide recommendations (Elaborate) 3-Others (Elaborate)

HOW?

- Set up questionnaires to rate CMOs and incorporate it into our current HSE audit
- Audit CMO’s process safety lab’s SOP If necessary, CHL provides training to CMO about PSI generation (Pfizer has done formal training to their CMOs)
- Set up awards for CMOs that go beyond compliances (award plaque)

Safety grid- web interface/App

Thermal Hazard Screening

This interface will outline the thermal risk associated with a molecule.

Enter SMILES structure

AND

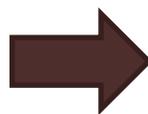
Select the reagent amount

Input SMILES string

- <1gm
- 1 to 10gm
- 10 to 1000gm
- 1000gm to 10kg
- >10kg

Lilly

Chemical Hazard Lab



Results

Medium energy density

Not a Yoshida Explosive

Low risk: Safety assessment not required (follow general lab safety practices).

Link for literature on Yoshida correlation:

<https://pubs.acs.org/doi/10.1021/acs.oprd.9b00422>

	HEFB	Energy Density	Onset Temp (C)	Exothermal heat (J/g)	ADT24 (C)
0	2.0	1.23	156.3	18.4	79.66

Energy Density	Low	Medium	High	Extreme High
#HEB*100/MW	<=1	Between 1~2.5	Between 2.5~3.5	>3.5
Reagent amount				
<1g	Green	1.23	Yellow	Yellow
1 - 10g	Green	Yellow	Yellow	Red
10g - 1000g	Green	Yellow	Red	Red
1000g - 10kg	Yellow	Red	Red	Red
> 10kg	Yellow	Red	Red	Red

Application example 1

- A radiopharmaceuticals firm (a wholly-owned subsidiary of Eli Lilly)
- Commercial scale is less than 10 kg batch.
- Shipping/using tetrazole compounds with thermal hazard data using **TGA** (at a CMO)



The App identified the potential risk → provided training material to the CMO → switched to another CMO

Energy Density	Low	Medium	High	Extreme High
#HEB*100/MW	<1	Between 1~2.5	Between 2.5~3.5	>3.5
Reagent amount				
<1g	Green	Green	Yellow	Yellow
1 - 10g	Green	Yellow	Yellow	Red
10g - 1000g	Green	Yellow	Red	Red
1000g - 10kg	Yellow	Red	2.98	Red
> 10kg	Yellow	Red	Red	Red

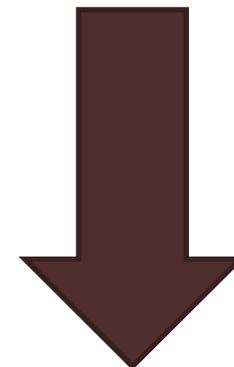
Application example 2

a starting material used by Lilly:

of high energy bond(HEB) = 2
molecular weight > 200
HEB/mw*100 < 1

Energy Density	Low	Medium	High	Extreme High
#HEB*100/MW	<=1	Between 1~2.5	Between 2.5~3.5	>3.5
Reagent amount				
<1g	Green	1.23	Yellow	Yellow
1 - 10g	Green	Yellow	Yellow	Red
10g - 1000g	Green	Yellow	Red	Red
1000g - 10kg	Yellow	Red	Red	Red
> 10kg	Yellow	Red	Red	Red

Vendor's export team onset <70°C, >1700J/g! → potential explosive → **could not be shipped** to Lilly

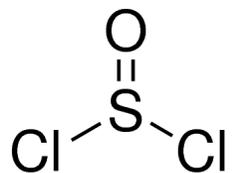


vendor's hazard lab was using stainless steel testing vessel → measured heat of corrosion + heat of decomposition

Guided the vendor to obtain accurate thermal hazard data/shipping classification

In addition to thermal hazards->reactive hazard

thionyl chloride:



MW=119

A near miss in a pharma lab:

A chemist was treating a tiny amount of unused SOCl_2 in front of a lab sink. He was aware of the potential hazard between SOCl_2 and water/EtOH, but he still used water to treat it because he thought the amount of SOCl_2 is so small

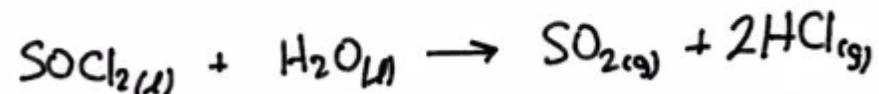


observed heat/gas, sealed the bottle, and took it to a hood.



The glass bottle exploded, and the chemist was injured

This incident could be prevented if these info were to be delivered to this chemist:



At room temperature, when 1ml of SOCl_2 react with water, 993 ml of non-condensable gas will be generated

What's next/conclusion

- Grow the metabase with HSE related information
corporate memory of accidents only last 3 years
- Includes graphics in the database
- Implement this into Lilly's new E-notebook
- Stop by if you want to see the app