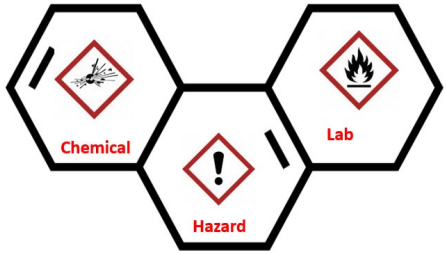
Automation in process safety information delivery

Han Xia, Senior Advisor, Chemical hazard lab
Syed Tanweer Ahmed, Consultant Engineer

Eli Lilly and Company

Background- thermal hazard of chemicals



Thermal hazards of chemicals

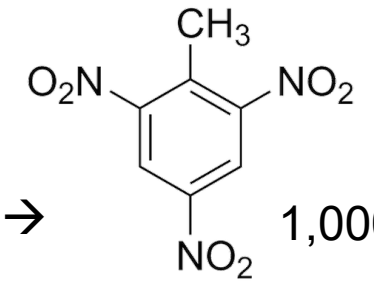
How Safe are the Materials that we're Using?

- 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 groups[1]

Example: TNT→



1,000 cal/g

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

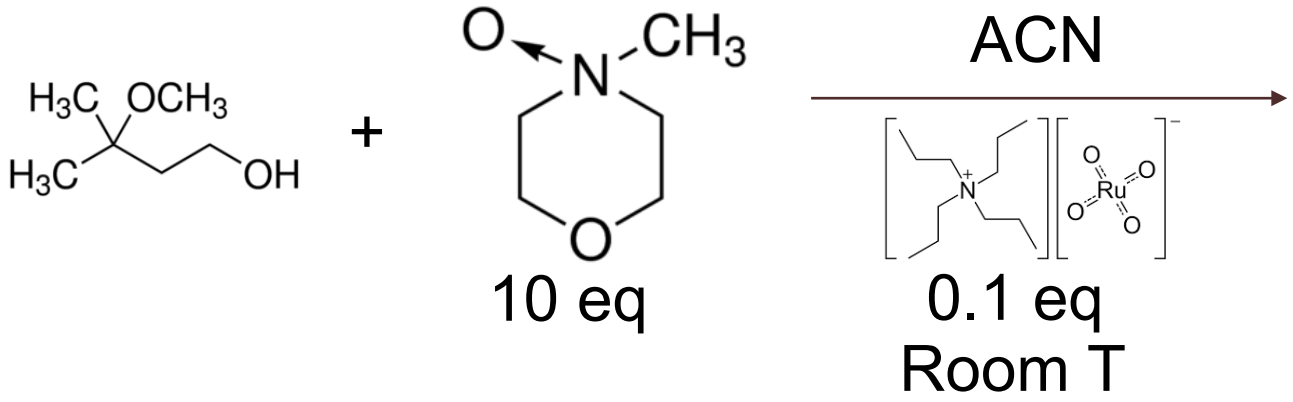
We work with lots of new chemicals everyday.

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

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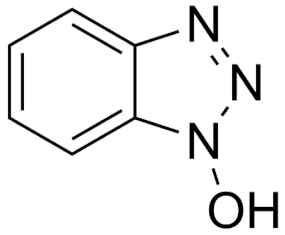
	Low energy density	Medium energy density	High energy density	Extremely high energy density
#HEB/MW* 100	<=1	Between 1 and 2.5	Between 2.5 and 3.5	>3.5

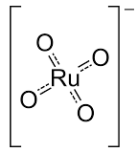
High energy functional groups[1]

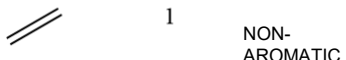
1. Not quantitative:



How many high energy functional groups?? 2, 3, 4?

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



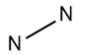


Carbon-carbon double bond

3 member ring, any atoms

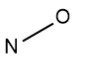
Carbon-carbon triple bond

4 member ring, any atoms



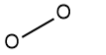
nitrogen-nitrogen bond

halogen-oxygen bond

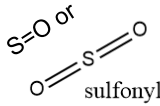


Nitrogen-oxygen bond

halogen-oxygen bond

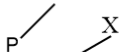


Oxygen-oxygen bond



sulfonyl group

R-SO3
Sulfonate
1



phosphorus-halogen, phosphorus-carbon bond

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

An example

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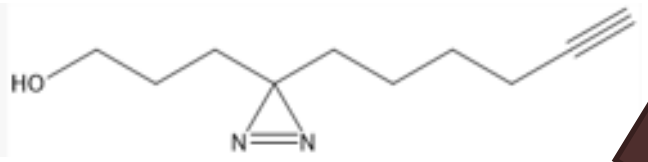
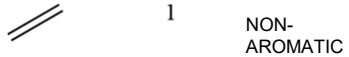


Mw. 194

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



Carbon-carbon double bond

3 member ring, any atoms

Carbon-carbon triple bond

4 member ring, any atoms

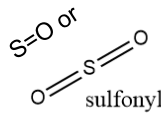
nitrogen-nitrogen bond

halogen-oxygen bond

Nitrogen-oxygen bond

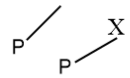
halogen-oxygen bond

Oxygen-oxygen bond



sulfonyl group

R-SO3
Sulfonate
1

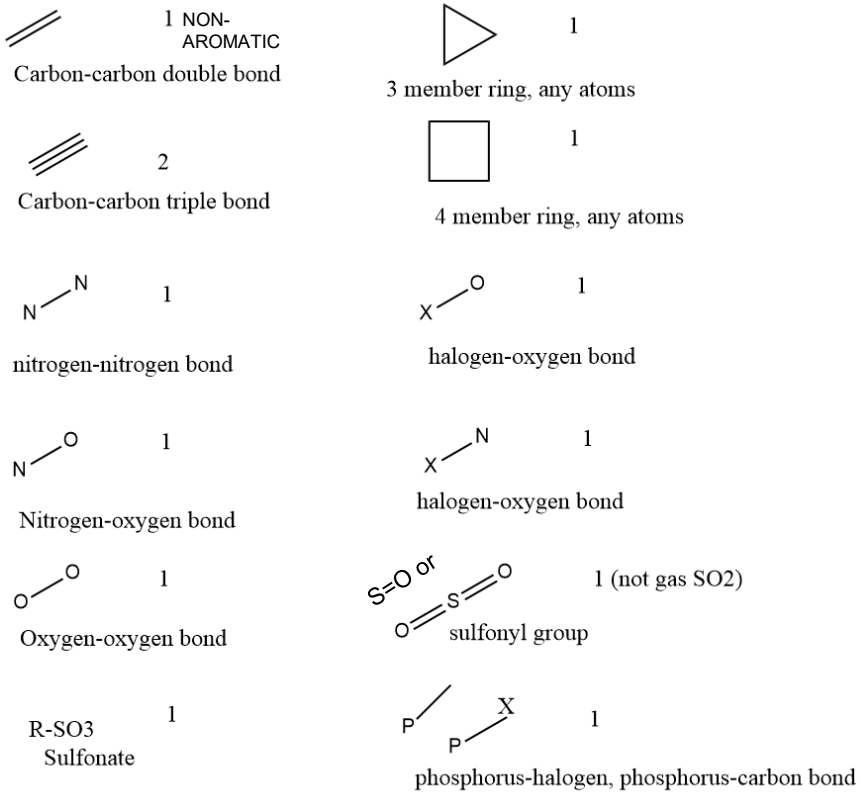


phosphorus-halogen, phosphorus-carbon bond

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				
1-10g				
10-1000g				
1000-10 kg				
>10kg		*	*	*

HEB=high energy bond
CHL= chemical hazard lab



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)

How do we define “trusted vendors”

Current procedure:

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Self-assessment answer

Completed by supplier prior to audit

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

	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 infomation) 2-No, but we work with a 3rd party thermal hazard lab equiped 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

Chemical Hazard Lab

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

Enter SMILES structure

AND

Select the reagent amount

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

Input SMILES string

Results

Medium energy density

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

Not a Yoshida Explosive

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		1.23		
1 - 10g				
10g - 1000g				
1000g - 10kg				
> 10kg				

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				
1 - 10g				
10g - 1000g				
1000g - 10kg			2.98	
> 10kg				

Application example 2

a starting material used by Lilly:

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

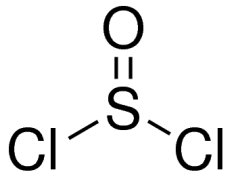
# of high energy bond(HEB) = 2
molecular weight > 200
HEB/mw*100 < 1

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		1.23		
1 - 10g				
10g - 1000g				
1000g - 10kg				
> 10kg				

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:

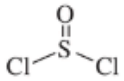
$$SOCl_{2(l)} + H_2O_{(l)} \longrightarrow SO_{2(g)} + 2HCl_{(g)}$$

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

Bretherick's handbook

4090 Sulfinyl chloride (Thionyl chloride)

[7719-09-7] **Cl_2OS**



HCS 1980, 898; *RSC Lab. Hazard Data Sheet No. 26*, 1984

Although many reactions of thionyl chloride appear endothermic, this is because the large volumes of gas evolved are doing work against atmosphere; adiabatically, the situation is very different and spontaneous pressurization highly probable [Ed.]. Violent reaction incidents of thionyl chloride are reviewed [1]. Many more can be found in the subentries below:

Cardillo, P. *Chem. Ind. (Milan)*, 1992, **74**(12), 879

See also Phosphoryl chloride

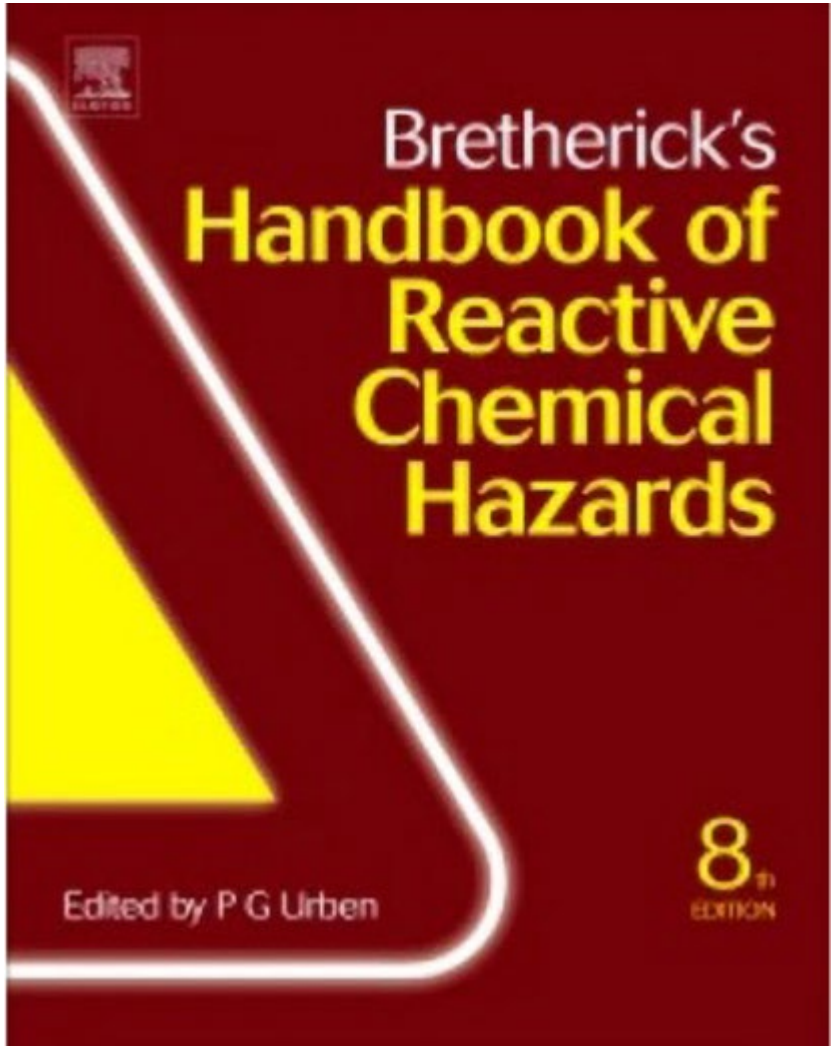
Water

MCA Case History No. 1808

Passage of thionyl chloride through a flexible metal transfer hose which was contaminated with water or sodium hydroxide solution caused the hose to burst. Interaction with water violently decomposes the chloride to hydrogen chloride (2 mol) and sulfur dioxide (1 mol), the total expansion ratio from liquid to gas being 993:1 at 20°C, so very high pressure may be generated.

See other ACYL HALIDES

See other NONMETAL HALIDES



- Chemical incident database with 5000+ chemicals
- Information on reactive hazard/ historical accidents
- All AICHE members/CCPS(center for chemical process safety) member companies have access to this book via AICHE's Knovel database

Automate Brethrick's !

PDF

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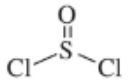
[7719-09-7] **Cl_2OS**



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See also Phosphoryl chloride

Ammonia MRH 0.84/16

Addition of a solution of 4-nitrobenzoyl chloride (1 g) in a large excess (10 ml) of sulfinyl chloride to ice-cold concentrated ammonia solution caused a violent explosion. This may certainly be attributed to the instantaneous hydrolysis of the excess sulfinyl chloride by the aqueous ammonia with production of several liters of unneutralized acid gases in a test tube.

Foote, C. S., private comm., 1965

See Water, below

Bis(dimethylamino) sulfoxide

Interaction of the chloride with the sulfoxide or its higher homologues to form dialkylaminosulfinyl chlorides causes extensive decomposition, possibly explosive above 80°C.

Armitage, D. A. *et al.*, *J. Inorg. Nucl. Chem.*, 1974, **36**, 993

Machine readable metabase

	A	B	C
1	Allyl phosphorodichloridite	[1498-47-1]	Kamler, M. et al., Can. J. Chem., 1985, 63, 825-826 The title compound is formed by reaction of allyl alcohol with phosphorus trichloride and is reported to polymerise explosively if the material, when being purified by distillation, is taken down to less than half its bulk. See other ALLYL COMPOUNDS, PHOSPHORUS ESTERS
2	Potassium 1,1-dinitropropanide	[30533-63-2]	Bisgrove, D. E. et al., Org. Synth., 1963, Coll. Vol. 4, 373 The potassium salt of 1,1-dinitropropane, isolated as a by-product during preparation of 3,4-dinitro-3-hexene, is a hazardous explosive. See NITROALKANES: ALKALI METALS See other POLYNITROALKYL COMPOUNDS
3	Acrylamide (Propenamide)	[79-06-1]	It may polymerise with violence on melting at 86°C [1]. The concentrated aqueous solutions of commerce will crystallise in cool weather. The usual industrial technique for softening raw materials, applying a steam hose to the bottom of the container, to which crystals have fallen, will create domains of molten, unstabilised, monomer, initiating polymerisation of the whole, then rupturing containers through steam pressure. Rather, the liquid at the top should be warmed and circulated. Photoinitiation seems involved, black plastic containers give less problem than trans- lucent ones. Best: do not store below 15°C [2].
4	2,3-Epoxypropionaldehyde oxime (Oxiranecarboxaldehyde oxime)	[67722-96-7]	The residue from distillation at 48-49°C/1.3 mbar polymerised violently, and the distilled material polymerised explosively after 1-2 h at ambient temperature. See 2,3-Epoxypropionaldehyde 2,4-dinitrophenylhydrazone See other 1,2-EPOXIDES, OXIMES, POLYMERISATION INCIDENTS See related ALDEHYDES
5			

Integration with the web interface/app

Chemical Hazard Lab

Thermal Hazard Screening

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

Enter SMILES structure

AND

Select the reagent amount

- <1gm
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- 10 to 1000gm
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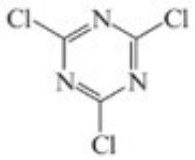
Input SMILES string

Application example 3

Cyanuric chloride (108-77-0)

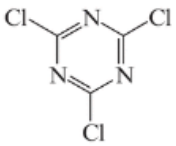


Onset temperature, °C	Heat of decomposition, J/g
360	-36

This is really helpful! Because we were able to identify lots of potential issues with this reagent after the automatic delivery of the process safety information from Brethrick's .

1035 2,4,6-Trichloro-1,3,5-triazine (Cyanuric chloride)

[108-77-0] $C_3Cl_3N_3$



HCS 1980, 925

Of the factors associated with the high reactivity of cyanuric chloride (high exothermicity, rapid hydrolysis in the presence of water-containing solvents, acid catalyzed reactions, liberation of up to 3 mol hydrogen chloride/mol of chloride, formation of methyl chloride gas with methanol, and formation of carbon dioxide from bicarbonates), several were involved in many of the incidents recorded [1] (and given below). The acid catalyzed self-acceleration and high exothermicity are rated highest [2]. It is also a mildly endothermic compound ($\Delta H_f°$ (s) +91.6 kJ/mol, 0.49 kJ/g).

1. Anon., *Loss Prev. Bull.*, 1979, (025), 21–22
2. *See* SELF-ACCELERATING REACTIONS

Methanol

Cyanuric chloride dissolved in methanol reacted violently and uncontrollably with the solvent. This was attributed to the absence of an acid acceptor to prevent the initially acid catalyzed (and later autocatalyzed) exothermic reaction of all three chlorine atoms simultaneously.

Anon., *ABCM Quart. Safety Summ.*, 1960, **31**, 40

Dimethyl sulfoxide

See Dimethyl sulfoxide: Acyl halides

Dimethylformamide

Cyanuric chloride reacts vigorously and exothermically with DMF after a deceptively long induction period. The 1:1 adduct that is initially formed decomposes above 60°C with the evolution of carbon dioxide and formation of a dimeric unsaturated quaternary ammonium salt. Dimethylformamide is appreciably basic and is not a suitable solvent for acyl halides.

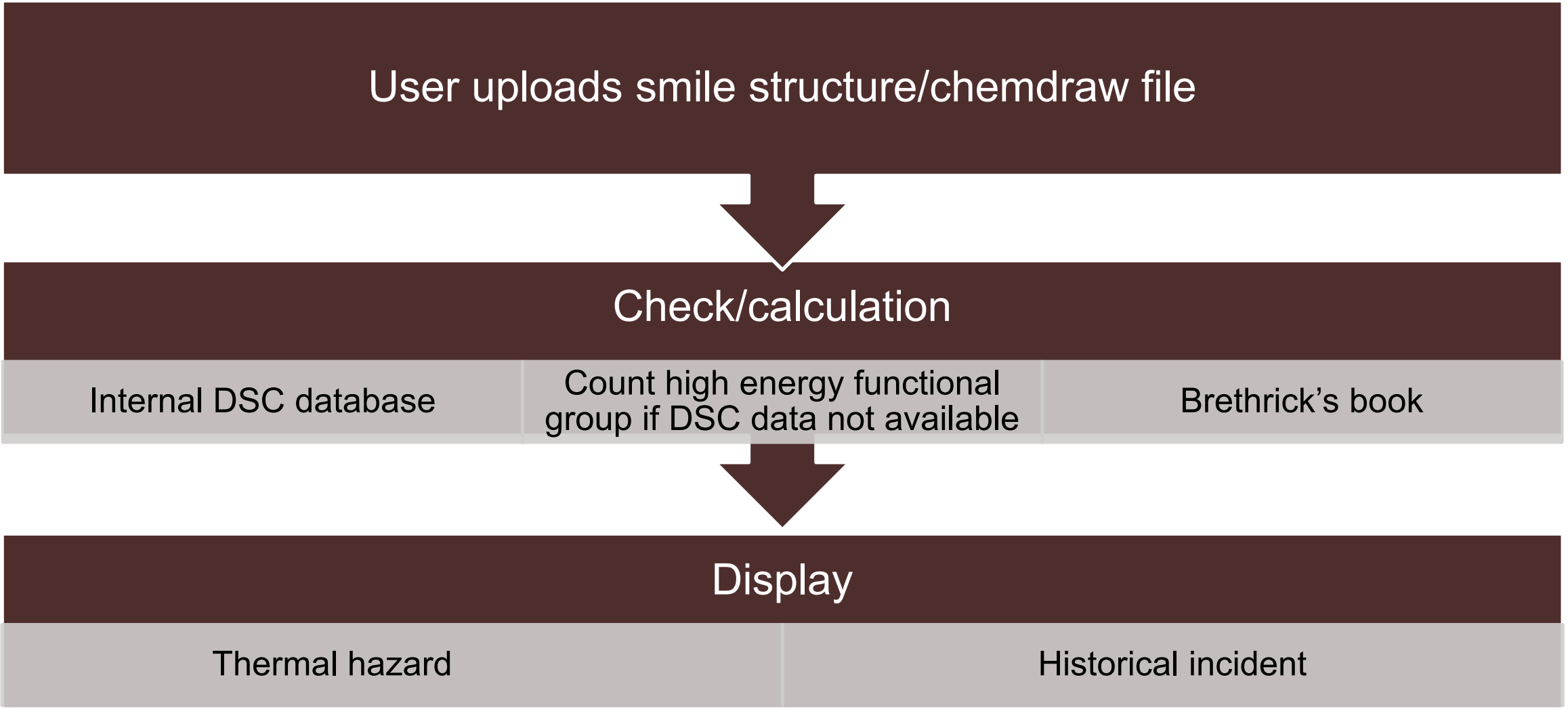
Anon., *BCISC Quart. Safety Summ.*, 1960, **35**, 24
See other INDUCTION PERIOD INCIDENTS

Acetone, Water

The chloride was to be purified by dissolution in dry acetone, but in error, acetone containing 40% of water was used. The acid-catalyzed exothermic hydrolysis reaction of the chloride accelerated to runaway, and gas and vapor evolution ruptured the vessel, leading to fire and explosion.

Anon., *Loss Prev. Bull.*, 1979, (025), 20
See Methanol below
See also Water, below
See other GAS EVOLUTION INCIDENTS
See other SELF-ACCELERATING REACTIONS

Flow chart


User uploads smile structure/chemdraw file
Check/calculation
Internal DSC database
Count high energy functional group if DSC data not available
Brethrick's book
Display
Thermal hazard
Historical incident

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