GHS AND NFPA DIAMONDS: WHERE THEY COME FROM AND HOW THEY CAN BE USEFUL

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NEXTMOVE SOFTWARE, CAMBRIDGE, UK

252nd ACS National Meeting, Philadelphia, PA, Wednesday 24th August 2016

OUR USER USE CASE

- We're interested in analyzing reactions in electronic lab notebooks (ELNs) to identify potential hazards.
- Our typical end-users are medicinal chemists in the pharmaceutical industry.
- This particular use case has some similarities and some differences with iRAMP's academic class room audience, or large-scale process development chemists.

CHALLENGE #1: SIGNIFICANT RISK

- A primary challenge in hazard alerting is identifying the type and severity of risks to report to users.
  - If medical advice is needed, have product container at hand.
  - Keep out of reach of children.
  - Read label before use.
  - Do not pierce or burn, even after use.
  - Do not eat, drink or smoke when using this product.
  - Do not get in eyes, on skin or on clothing.
  - Avoid contact during pregnancy/while nursing.

BRETHERICK'S: 1,3-DINITROBENZENE

- Accidents involving maintenance of railway tankers are probably not relevant at the laboratory scale.

A vessel containing dinitrobenzene for drying, after washing out styphnic and picric acid by products in alkali, retained a heel of some hundreds of litres, with a residue of rust, after emptying. This was cleaned out with low pressure steam at 130°C every two years. During cleaning, the tank burst and burnt out. It was supposed that residual nitrophenol salts had accumulated on the rust, which was shown to thermally sensitise them, and deflagrated, initiating the dinitrobenzene.

DEREK LOWE VS. COMMON SENSE

- "**Ignorance is No Defence:** In A Chemistry Lab, What you don't know really can hurt you", by Derek Lowe, *Chemistry World*, 14th January 2015.

  https://www.chemistryworld.com/opinion/ignorance-is-no-defence/8150.article
- Lists as hazardous both:
  1. Dimethylmercury
  2. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
- The exposure risks of each are not really comparable:
  1. Hazardous when handling even with gloves.
  2. Hazardous if injected intravenously.

GHS PICTOGRAMS ARE NOT ENOUGH

- Unfortunately, GHS labels are insufficient.
- Both methanol and dimethylmercury are labelled with warnings indicating toxic and health hazard if swallowed or exposed to skin respectively.

SOLUTION #1: GHS/NFPA CATEGORY

- The solution adopted by several pharmaceutical customers is to only alert on GHS category 1 or NFPA category 4 hazards (by default).
- These reflect unanticipated hazards.
  - Unstable explosive, and explosive vs. fire hazard/may explode in fire.
  - Extremely flammable gas (H220) vs Flammable gas (H221)
  - Extremely flammable liquid (H224) vs Flammable liquid (H225)
  - Fatal if inhaled (H330)

H280: IRRELEVANT TO PUBCHEM?

- Hazard code H280 is “Contains gas under pressure; may explode if heated”.
- This warning concerns the container that a product may shipped in, and isn’t a fundamental hazard of the chemical itself.
- Any gas at 200 kPa (i.e. in a gas cylinder) has this hazard.
- Currently, 88 PubChem CIDs have this “feature”, including CID 1119 (Sulfur dioxide).

CHALLENGE #2: DATA COVERAGE

- Unfortunately, SDS/MSDS data sheets exist for a very small fraction chemicals.
- Of the 91M compounds in PubChem, Safety information is available for 11487 (~0.01%), and GHS information for 5060 (~0.006%).
- Additionally, unlike high-school and undergraduate practicals, pharmaceutical medicinal chemistry R&D produces previously unsynthesized compounds.
- It's important to check reactants **and** products.

EVOLUTION OF HAZARD ALERTING

1. Chemical Compound/Substance (MSDS) Lookup
   1a. Exact name/MFCD/Synonym comparison
   1b. Name-to-structure canonical match (spelling correction)
   1c. Normalized representation (InChI) match
2. Chemical Incompatibility Lookup
3. Substructure Patterns
4. Chemical Class Incompatibility
5. Reaction Mechanism Recognition
6. Physical Property Thresholds

SOLUTION #2: DERIVING CATEGORIES

- GHS and NFPA categories are (mostly) derived from physical properties measured by experimental testing and legally mandated thresholds.
- These may also be looked up in a database or calculated algorithmically to categorize/triage compounds.
- Flor A. Quintero, Suhani J. Patel, Felipe Muñoz and M. Sam. Mannan, "**Review of Existing QSAR/QSPR Models Developed for Properties used in Hazardous Chemicals Classification System**", *Industrial and Engineering Chemistry Research*, Vol. 51, pp. 16101-16115, 2012.

EFFECTIVELY ADDING GHS DIAMONDS

CASE STUDY #1: H224

- GHS hazard H224 is “Extremely flammable”.
- The logic for this categorization is:
  - Flash point < 23°C and boiling point ≤ 35°C = H224 (1)
  - Flash point < 23°C and boiling point > 35°C = H225 (2)
  - Flash point ≥ 23°C and ≤ 60°C = H226 (3)
  - Flash point > 60°C = (4)
- Hence trans-2-pentene (SIAL 111260) which has a NIST reported boiling point of 36.25 ± 0.5 °C (NIST Webbook) can’t possibly be H224.

FIGHTING CITY HALL: 2-PENTENE

From: EURMsds@sial.com

Date: 9th July 2015 03:03

Re: Fw: ProdSafety_Request – United Kingdom

Dear Mr Sayle,

Thank you very much for your request. Our classification of CAS 646-04-8 as H224 (extremely flammable) is based on an in house measurement (boiling point/range 35-36°C). Unfortunately this test result was only considered for classification but has not been shown on our SDS / website. I have corrected this with respect to the SDS (new version is attached). I have also forwared a request to the department responsible for our website to change the boiling point range on our website as soon as possible.

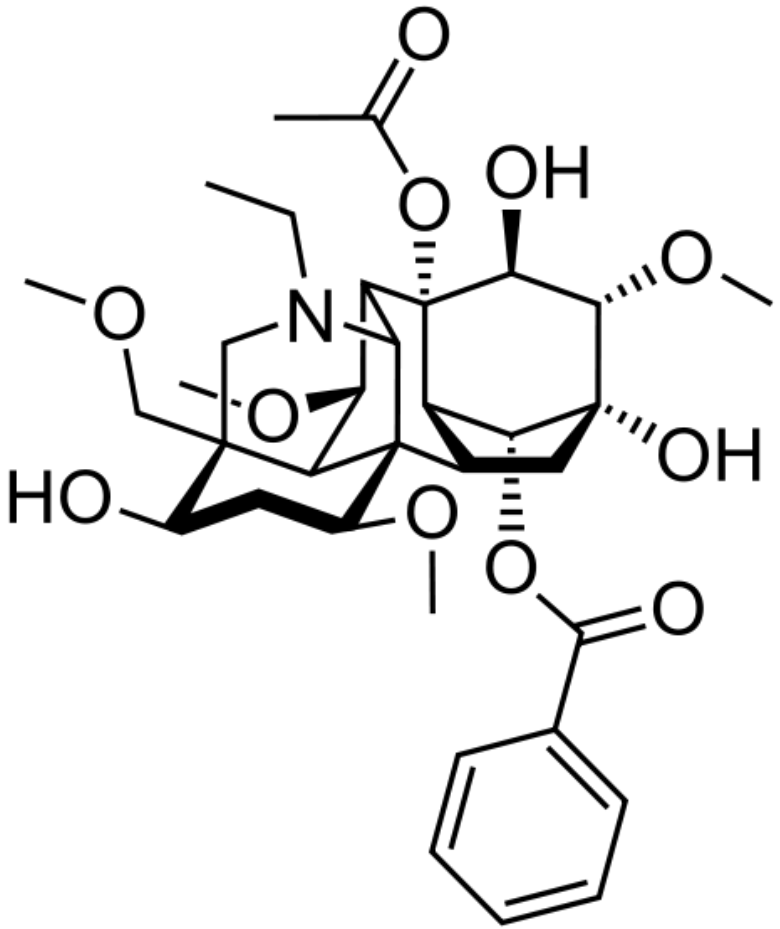
We apologise for any inconveniences caused.

Kind regards,

CASE STUDY #2: H330

- GHS hazard H330 is “Fatal if inhaled”.
- Applicable to poison gasses such as phosgene.
- The set of gasses is finite, but this categorization is also to vapours, dusts and mists.
- This categorization is based on LC_{50} in ppm/V.
- A surprise discovery was that the natural product Aconitine (MW ~646) is categorized as H330, even though used therapeutically, and no reported LC_{50}.
- It turns out this categorization is required by law!?

ACONITINE



ENERGETIC SUBSTRUCTURES

- UN recommendations on "Transport of Dangerous Goods" lists the following function groups as being associated with explosive properties:
  - **C-C unsaturation**: Acetylenes, acetylides, 1,2-dienes.
  - **C-Metal, N-Metal**: Grignard reagents, organo-lithium compounds.
  - **N-N**: Azides, aliphatic azo compounds, diazonium salts, hydrazines, sulfonylhydrazides.
  - **O-O**: Peroxides, ozonides.
  - **N-O**: Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles.
  - **N-Halogen**: Chloramines, fluoramines.
  - **O-Halogen**: Chlorates, perchlorates, iodosyl compounds.

OXYGEN BALANCE

- Oxygen Balance (OB%) is used to indicate the degree to which an explosive can be oxidized.
- $$OB\% = \frac{-1600}{Mol.wt.of\ compound} \times \left(2X + \left(\frac{Y}{2}\right) + M - Z\right)$$
  - X = number of carbon atoms
  - Y = number of hydrogen atoms
  - Z = number of oxygen atoms
  - M = number of metallic atoms
- TNT ($C_7H_5N_3O_6$) has MW of 227.1 and OB of -74%.

EXAMPLE: TRINITROTOLUENE (TNT)

- Decomposition
  - $C_7H_5N_3O_6 \rightarrow 2.5H_2O + 1.75CO_2 + 5.25C + 1.5N_2$

    H_f=-63.2 →H_f=2.5*-240.6 + 1.75*-393.5 = -1290.12kJ/mol

    ΔH_d = -1226.92 kJ/mol
- Combustion
  - $C_7H_5N_3O_6 + 5.25O_2 \rightarrow 2.5H_2O + 7CO_2 + 1.5N_2$

    H_f=-63.2 →H_f=2.5*-240.6 + 7*-393.5 = -3356kJ/mol

    ΔH_c = -3292.8 kJ/mol

SETTING THRESHOLDS

- The "Guidelines for Chemical Reactivity Evaluation and Application to Process Design" by the Center for Chemical Process Safety (CCPS) advises
  - above 2.93 kJ/g heat of decomposition → High hazard
  - 1.26 to 2.93 kJ/g heat of decomposition → Medium hazard
  - 0.42 to 1.26 kJ/g heat of decomposition → Low hazard
  - Below 0.42 kJ/g heat of decomposition → Very low hazard

- Original limits in Kcal/g [1Kcal/mol = 4.184kJ/mol]
- Use molecular weight (g/mol) to covert from kJ/mol.

ASTM CHETAH CLASSIFICATIONS

Name	MW	Hf	Hd	Hc	Hazard
Hexane	86.18	-199.4	2.31	-44.63	Very low
Acetone	58.08	-250.0	0.16	-28.45	Very low
Acetic acid	60.05	-483.9	0.04	-13.06	Very low
p-Nitroaniline	138.12	-5.6	-3.44	22.28	Medium*
2,4-Dinitrophenol	184.11	-235.5	-4.54	-14.16	High
2,4,6-Trinitrotoluene	227.13	-63.2	-5.40	-14.50	High
Picric acid	229.10	-217.9	-5.35	-10.93	High
Nitroglycerin	227.09	-370.0	-6.22	-6.22	High

H_f Heat of Formation (kJ/mol)
H_d Heat of Decomposition (kJ/g)
H_c Heat of Combustion (kJ/g)

ACCOUNTING FOR SCALE

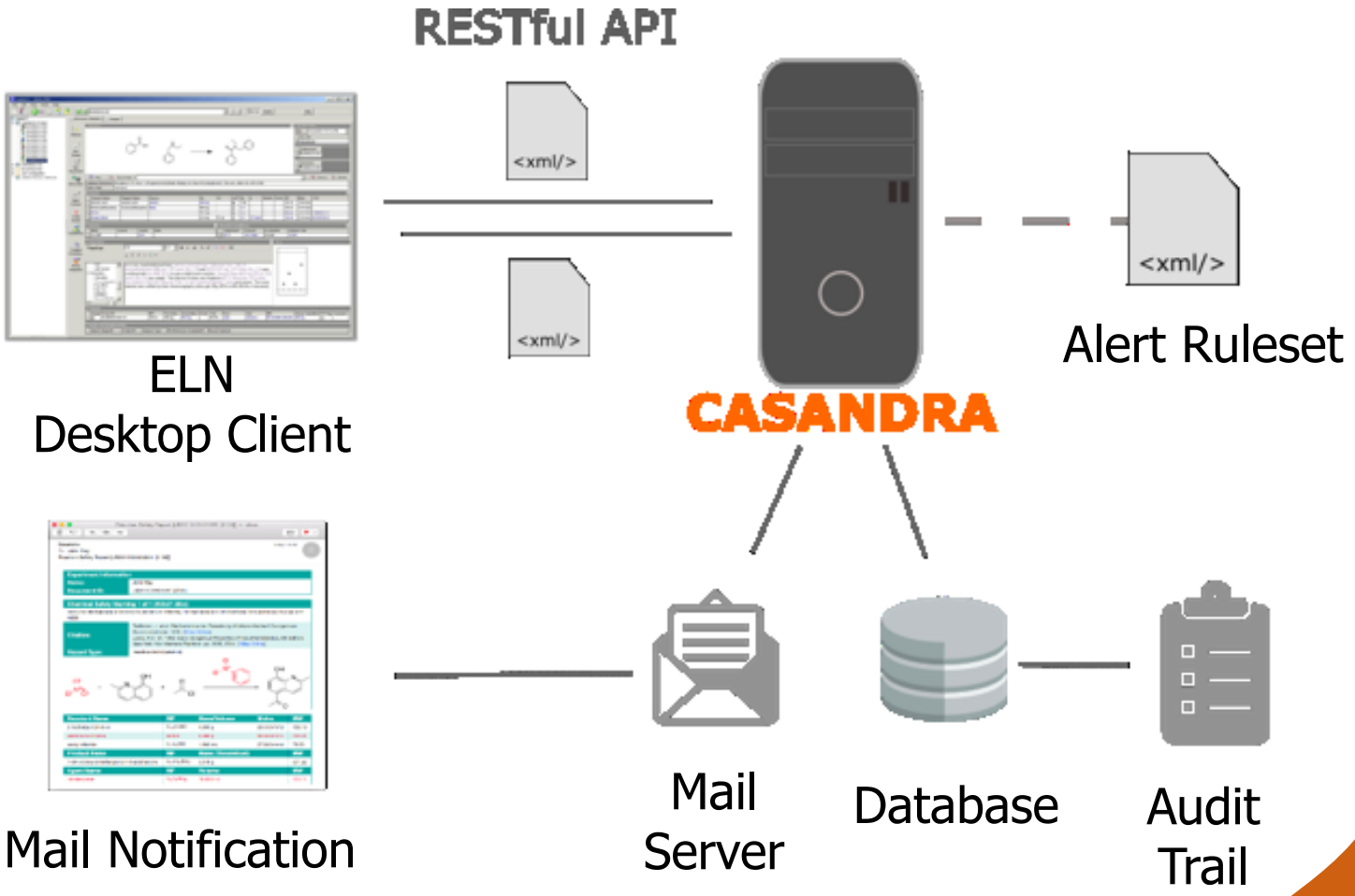
- Clearly the scale of a reaction influences the chemical hazard associated with a reaction.
- This also allows us to unify safety thresholds between process development and MedChem R&D.
- Fortunately, having thresholds specified in kJ/mol or kJ/g allows us to account for quantities.
- Hence, safety thresholds are in energy (Joules).

STRUCTURES AREN'T ENOUGH

Material Properties					Chemistry		Planned Amount		Actual Amount		Density		Strength		Calculated Amounts (Planned)					Calculated Amounts (Actual)					Actual Yield
Name	Class	Phase	MW	Lot Number	LR	SC	Value	Units	Value	Units	Value	Units	Value	Units	g	mL	mmoles	equiv	moles/mol-pure-LR	g	mL	mmoles	equiv	moles/mol-pure-LR	%
Acetic Acid	Chemical	Liquid	60.05	61780705001730			5	equiv (molar)	5	equiv (molar)	1.048	g/mL	100.00	wt/wt%	1.26	1.20	20.99	5.00	5.00	1.26	1.20	20.99	5.00	5.00	n/a
30% Hydrogen Peroxide in water	Chemical	Liquid	34.01				10	equiv (molar)	10	equiv (molar)	1.105	g/mL	30.00	wt/wt%	4.76	4.31	41.97	10.00	10.00	4.76	4.31	41.97	10.00	10.00	n/a
Sodium Iodide	Chemical	Solid	149.89				0.05	equiv (molar)	0.05	equiv (molar)	1	g/mL	100.00	wt/wt%	0.03	0.03	0.21	0.05	0.05	0.03	0.03	0.21	0.05	0.05	n/a
Piperidine	Chemical	Liquid	85.15				3	equiv (molar)	0	mL	0.8608	g/mL	100.00	wt/wt%	1.07	1.25	12.59	3.00	3.00	0.00	0.00	0.00	0.00	0.00	n/a
Benxoxazole	Reactant	Solid	119.12		☑	1	500	mg	500	mg	1	g/mL	100.00	wt/wt%	0.50	0.50	4.20	1.00	1.00	0.50	0.50	4.20	1.00	1.00	n/a
Morpholino benzoxazole	Product	Solid	204.23			1	0.86	g	0.7	g	1	g/mL	100.00	wt/wt%	0.86	0.86	4.20	1.00	1.00	0.70	0.70	3.43	0.82	0.82	81.66

Material Properties				
Name	Class	Phase	MW	Lot Number
Acetic Acid	Chemical	Liquid	60.05	61780705001730
30% Hydrogen Peroxide in water	Chemical	Liquid	34.01	
Sodium Iodide	Chemical	Solid	149.89	
Piperidine	Chemical	Liquid	85.15	
Benxoxazole	Reactant	Solid	119.12	
Morpholino benzoxazole	Product	Solid	204.23	

CASANDRA 2.0 ARCHITECTURE



CONCLUSIONS/INSIGHTS

- Currently reviewing algorithms for predicting compound properties (QSAR models).
- However, early results show that the classification of hazardous materials is relatively insensitive to heat of formation of the starting material.
- The chemical hazard reflects the elemental composition rather than it's functional groups.

ACKNOWLEDGEMENTS

- Dana Vanderwall, Ramesh Durvasula, Dong Li and Carol Mcnab from Bristol-Myers Squibb.
- Bharath Ramandran and Jen Sonnenberg-Rhim at Amgen (Thousand Oaks and South San Fran, CA).
- Leah McEwen, Evan Bolton and Ralph Stuart at iRAMP.
- Chemical Safety Library (CSL) project, Pistoia Alliance.
- The rest of the team at NextMove Software.