Encoding Reactive Chemical Hazards and Incompatibilities in an Alerting System

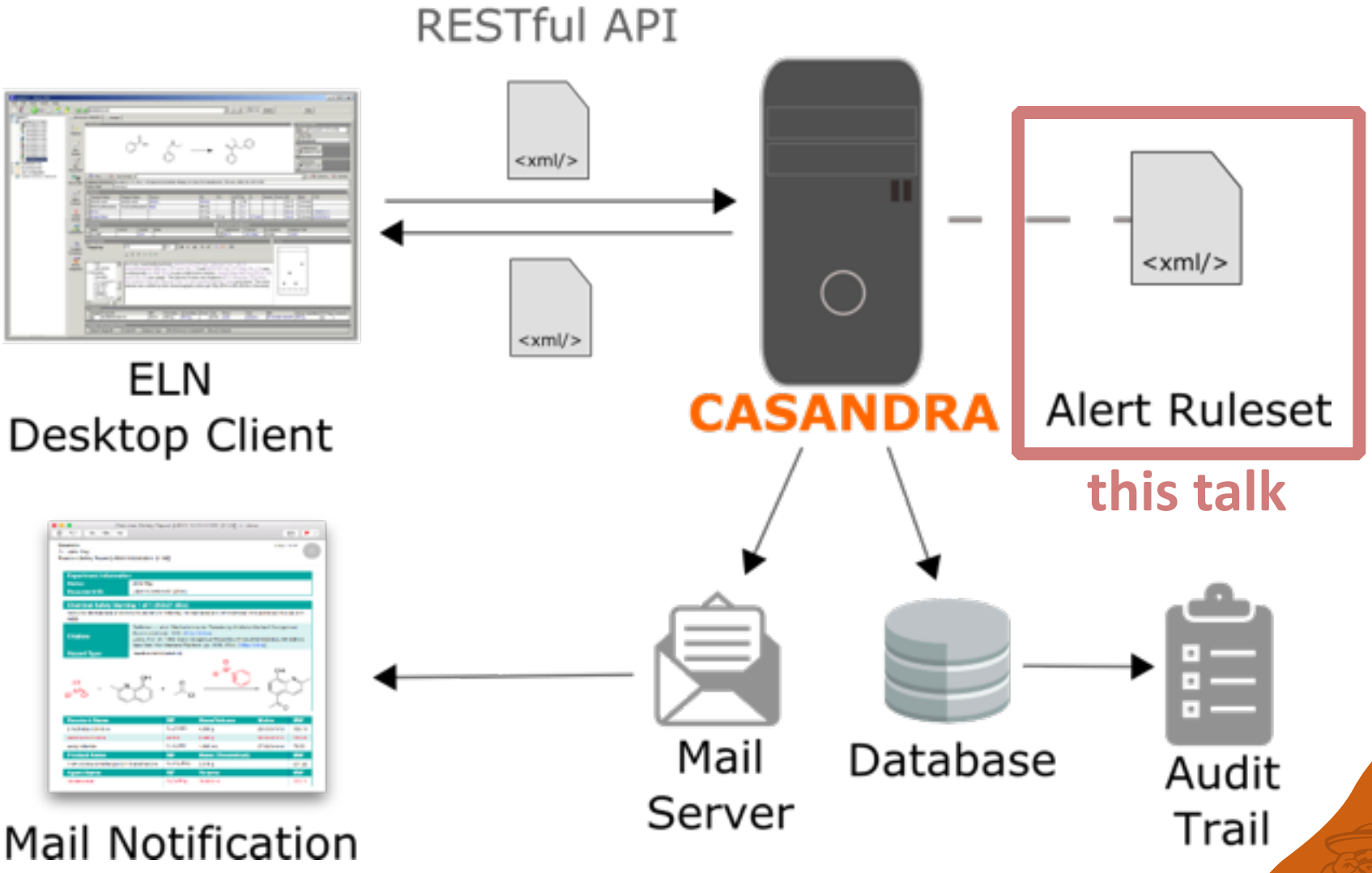
John May and Roger Sayle

NextMove Software

Cambridge, UK

250th American Chemical Society National Meeting & Exposition, Boston MA, Aug 2015

MOTIVATION (THE ALERTING SYSTEM)



Reaction Safety Report [US20110224242A1 [0108]] — Inbox

Casandra
To: John May
Reaction Safety Report [US20110224242A1 [0108]]

Today 14:23

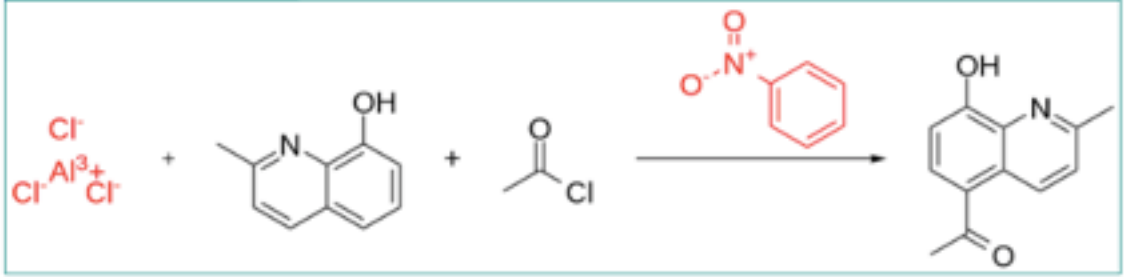
C

Experiment Information	
Name:	John May
Document ID:	US20110224242A1 [0108]

Chemical Safety Warning 1 of 1 [RG:27-38:c]

Contains nitrobenzene and contains aluminium chloride, nitrobenzene and nitromethane form explosive mixures with AlCl3

Citation:	Reithman, J. et al. Mechanismus der Zersetzung nitrobenzolischer Lösungen von Aluminiumchlorid. 1976. (Wiley Online) Lewis, R.J., Sr. 1992. Sax's Dangerous Properties of Industrial Materials, 8th Edition. New York: Van Nostrand Reinhold. pp. 2518, 2544. (Wiley Online)
Hazard Type:	Reactive Incompatability



Reactant Name	MF	Mass/Volume	Moles	MW
2-methylquinolin-8-ol	$C_{10}H_9NO$	4.000 g	25.130 mmol	159.18
aluminium chloride	Al.3Cl	8.380 g	62.820 mmol	133.34
acetyl chloride	C_2H_3ClO	1.960 mL	27.640 mmol	78.50
Product Name	**MF**	**Mass (Theoretical)**		**MW**
1-(8-hydroxy-2-methylquinolin-5-yl)ethanone	$C_{12}H_{11}NO_2$	3.510 g		201.22
Agent Name	**MF**	**Volume**		**MW**
nitrobenzene	$C_6H_5NO_2$	10.000 mL		123.11

Reason,
Primary Citations,
Category

EVOLUTION OF HAZARD ALERTING

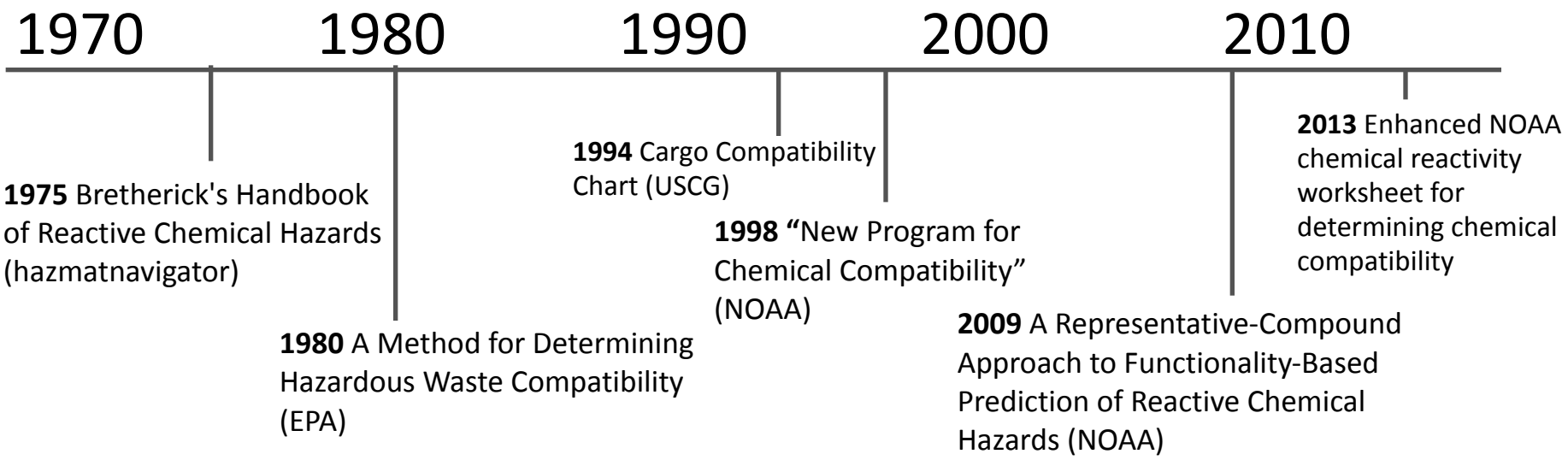
1. Chemical Compound (MSDS) Lookup
   a. Exact name/MFCD/Synonym comparison
   b. Name-to-structure canonical match
   c. Normalised representation (InChI) match
2. Chemical Incompatibility Lookup
3. Substructure Patterns
4. Chemical Class Incompatibility
5. Reaction Mechanism Recognition (+ H2 Gas)
6. Physical Property Thresholds (BP,HoD,VP)

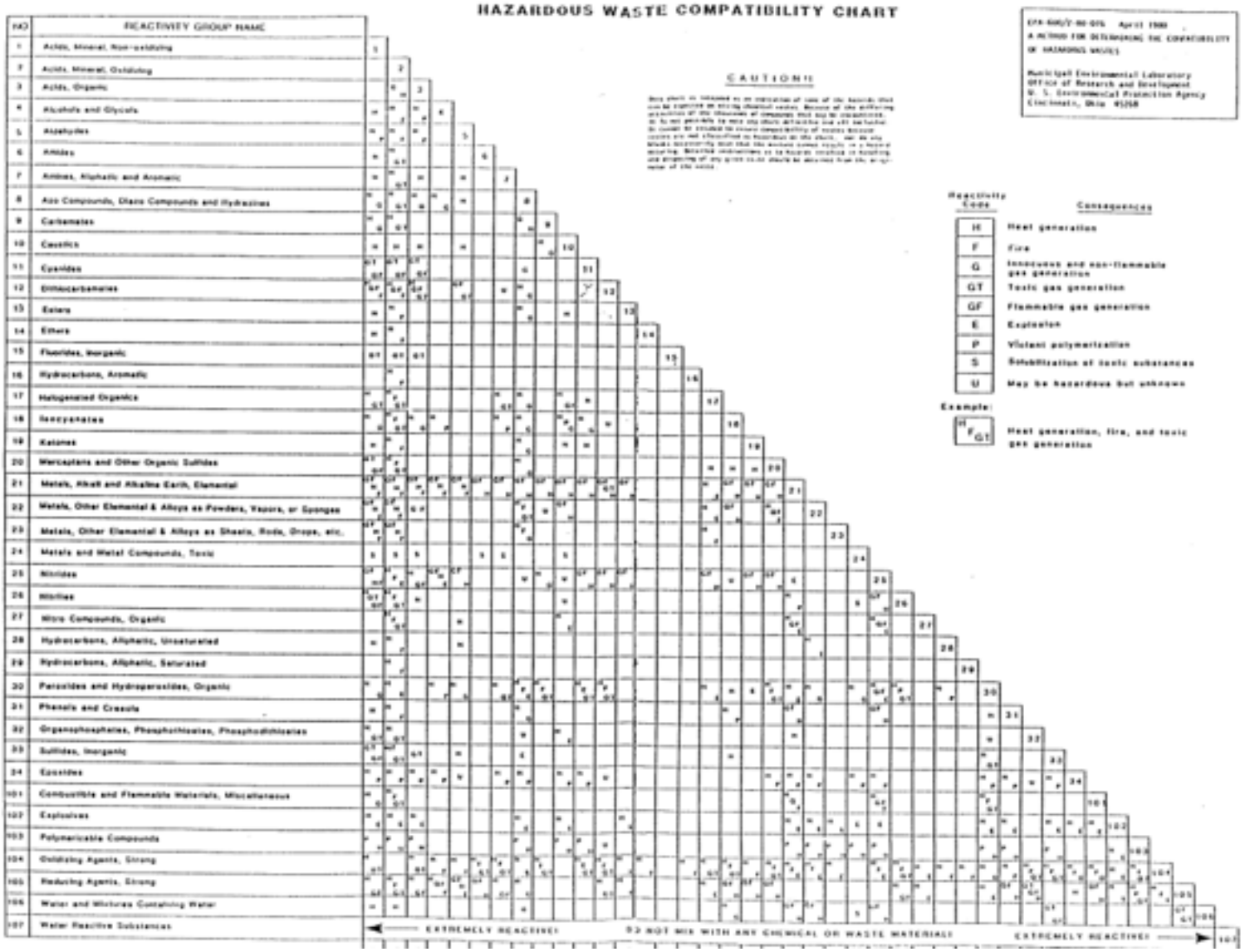
Known Knowns

Known Unknowns

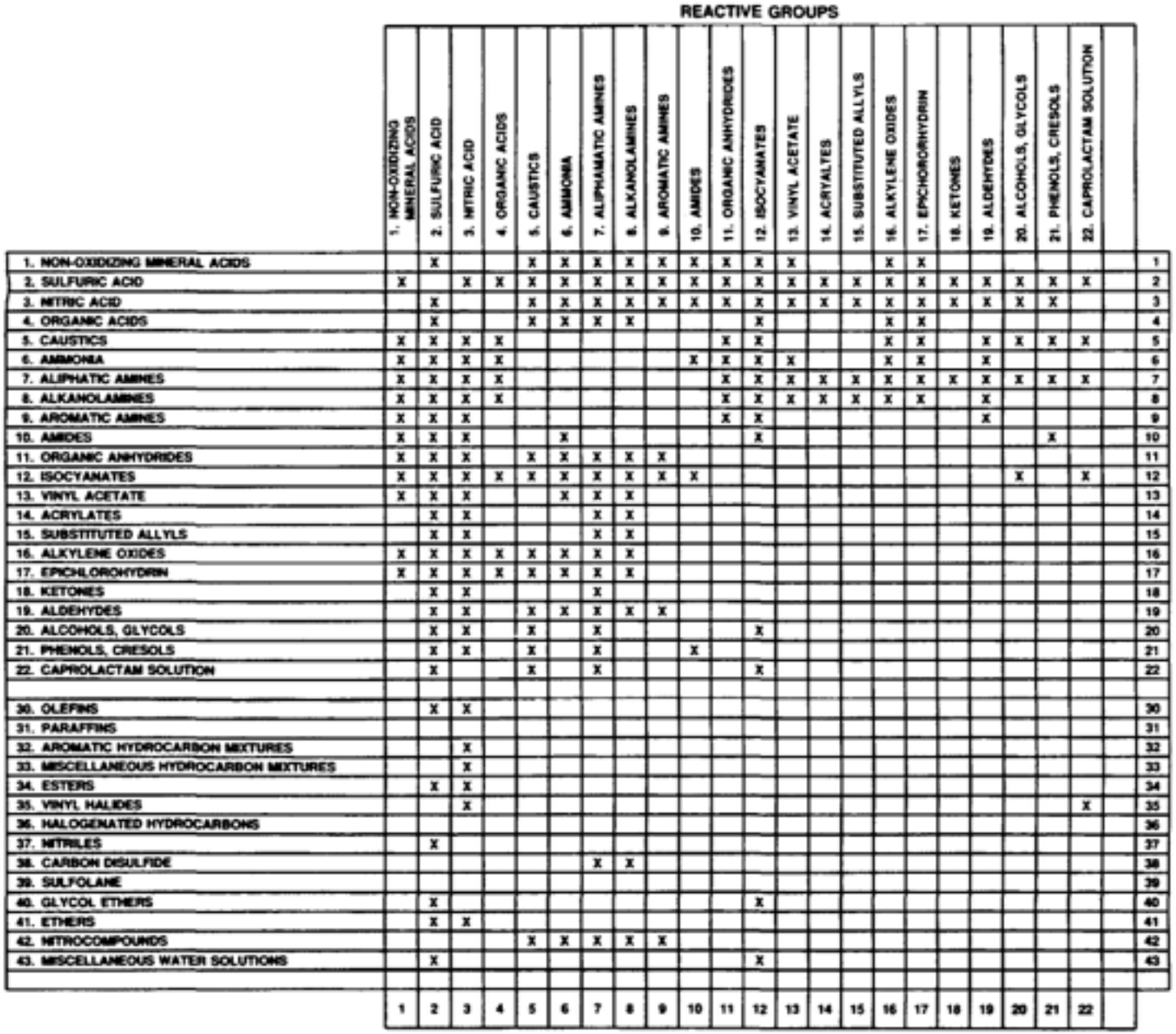
HAZARD COMPATABILITY TIMELINE

(INCOMPLETE)





1980 Hatayama HK *et al.* A Method for Determining Hazardous Waste Compatibility (EPA)



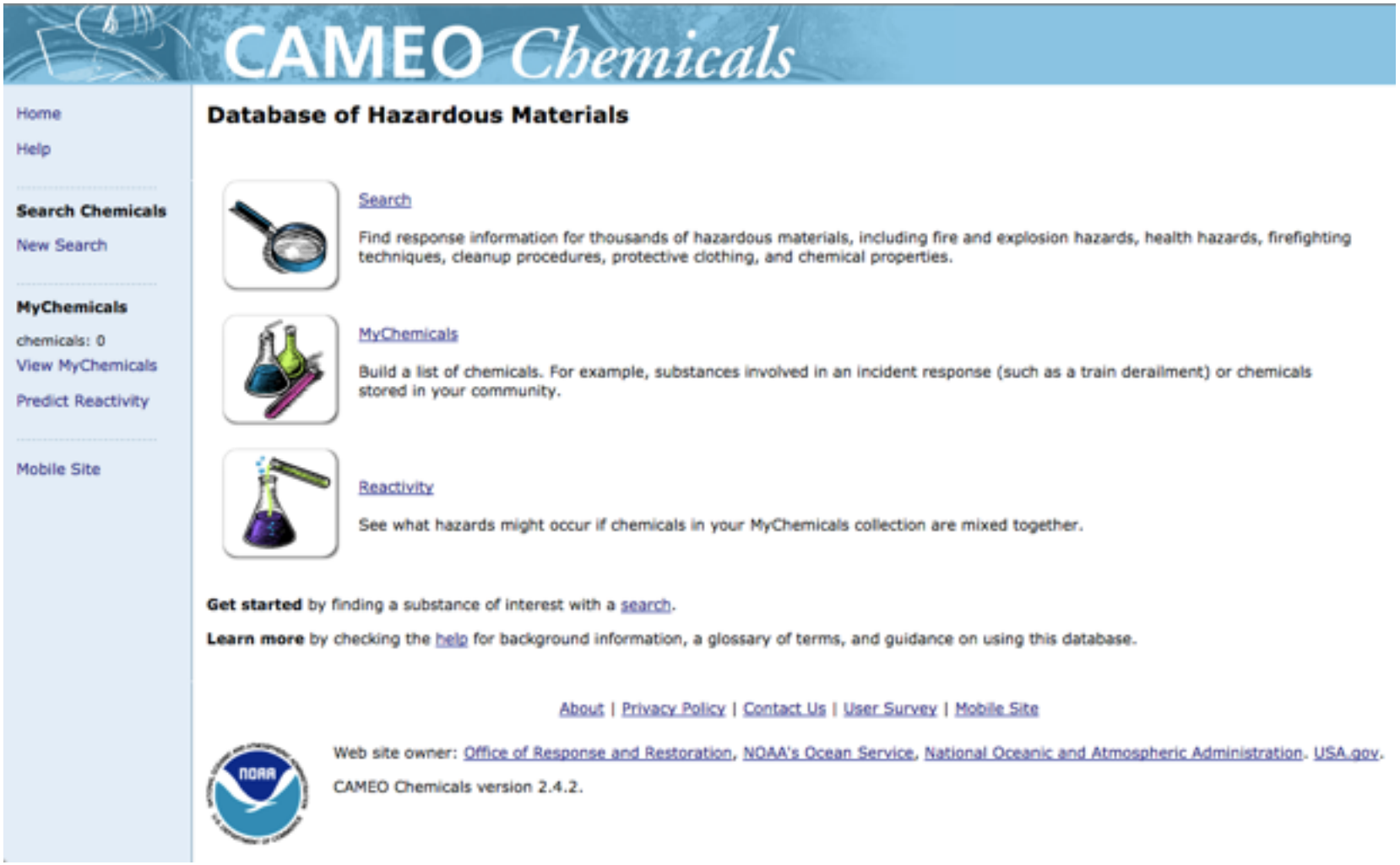
1994 Cargo Compatibility Chart, USCG 46 CFR part 150

CRW 3.0/CAMEO

	1. Acetals, Ketals, Hemiacetals, and Hemiketals	2. Acid Halides, Sulfonyl Halides, and Chloroformates	3. Acids, Carboxylic	4. Acids, Strong Non-oxidizing	5. Acids, Strong Oxidizing	6. Acids, Weak
1. Acetals, Ketals, Hemiacetals, and Hemiketals						
2. Acid Halides, Sulfonyl Halides, and Chloroformates	Incompatible					
3. Acids, Carboxylic	Compatible	Incompatible				
4. Acids, Strong Non-oxidizing	Caution	Incompatible	Incompatible			
5. Acids, Strong Oxidizing	Incompatible	Incompatible	Incompatible	Incompatible		
6. Acids, Weak	Compatible	Incompatible	Compatible	Caution	Incompatible	
7. Acrylates and Acrylic Acids	Caution	Caution	Caution	Incompatible	Incompatible	Caution

1998 J. Farr *et al* "New Program for Chemical Compatibility" Chemical Health and Safety 5

CAMEO: Computer-Aided Management of Emergency Operations



http://cameochemicals.noaa.gov/

Hazmat Navigator

Search | Press | Help

Click here to find out more about Hazmat Navigator

QUICK | ADVANCED | STRUCTURE | INDEX

Hazmat Navigator is a chemical safety database based on Bretherick's Handbook of Reactive Chemical Hazards that helps chemists and safety personnel quickly access critical, detailed chemical hazards information.

Enter Chemical Name, CAS# or Molecular Formula

SEARCH

Click here for Search Tips

Hazmat Navigator to Retire

Hazmat Navigator is set to retire and will close on December 31, 2013. To preserve your work, please print it prior to the closing date.

Thank you for your support and patronage of this application. We have enjoyed serving you.
For any questions contact Customer Service.

Sincerely,
The Hazmat Navigator Team

Carcinogenic Potential

Arsenic acid
Arsenic trioxide
Benzene
Lead arsenate
Potassium arsenate
Sodium arsenite

See more...

Warning: Hazmat Navigator has only partial information for some compounds. If a compound is not included or if information is not provided, DO NOT assume that the compound is without hazard. Proceed at your own risk.

http://www.hazmatnavigator.com/search/quick

DESCRIBE COMPABILITIY MATRICES IN XML?

Encode in XML format

ARE THEY APPLICABLE?

Statistics on reaction corpus

CASANDRA 1.0 RULE EXPRESSIONS

`ContainsComponent`

Find a reactant by

name (spelling corrected)

chemical structure (Unique SMILES or InChI)

quantity threshold and normalisation (e.g. > 10 g)

role (e.g. solvent)

`ContainsPattern`

Find reactants that a SMARTS pattern **hits**

`Contains` - enables indirection

```
<alert mesg="...">
  <any>
    <containsComponent name="TNT"/>
    <containsComponent name="trinitrotoluene"/>
  </any>
</alert>

<alert mesg="...">
  <containsPattern name="[NX3](~[OX1])~[OX1]" atLeast="3"/>
</alert>

<alert mesg="...">
  <all>
    <any>
      <containsComponent name="nitrobenzene"/>
      <containsComponent name="nitromethane"/>
    </any>
    <any>
      <containsComponent name="aluminium chloride"/>
      <containsComponent name="aluminum chloride"/>
      <containsComponent name="AlCl3"/>
    </any>
  </all>
</alert>
```

Self Contained

Implementation independent

Facilitate exchange and reuse

Flexible

Arbitrarily complex expressions

Meta-Information

Description/Message

Citation, Links

Category

Hierarchy

ENCODED REACTIVE GROUPS

3 Acids, Carboxylic
5 Aldehydes
6 Amides and Imides
7 Amines, Phosphines, and Pyridines
8 Azo, Diazo, Azido, Hydrazine, and Azide Compounds
9 Carbamates
11 Cyanides, Inorganic
12 Thiocarbamate Esters and Salts/Dithiocarbamate Esters and Salts
13 Esters, Sulfate Esters, Phosphate Esters, Thiophosphate Esters, and Borate Esters
14 Ethers
17 Halogenated Organic Compounds
18 Isocyanates and Isothiocyanates
19 Ketones
20 Sulfides, Organic
21 Metals, Alkali, Very Active
22 Metals, Elemental and Powder, Active
23 Metals, Less Reactive
26 Nitriles
27 Nitro, Nitroso, Nitrate, and Nitrite Compounds, Organic
30 Peroxides, Organic
31 Phenols and Cresols
32 Sulfonates, Phosphonates, and Thiophosphonates, Organic
34 Epoxides
35 Metal Hydrides, Metal Alkyls, Metal Aryls, and Silanes
37 Anhydrides
38 Salts, Acidic (dictionary list)
39 Salts, Basic (dictionary list)
40 Acid Halides, Sulfonyl Halides, and Chloroformates
42 Organometallics
44 Oxidizing Agents (dictionary list)
47 Fluorinated Organic Compounds
55 Chlorosilanes
58 Siloxanes
65 Conjugated Dienes
66 Aryl Halides
68 Amines, Aromatic
69 Nitrate and Nitrite Compounds, Inorganic
70 Acetals, Ketals, Hemiacetals, and Hemiketals
71 Acrylates and Acrylic Acids
72 Phenolic Salts
73 Quaternary Ammonium and Phosphonium Salts
74 Sulfite and Thiosulfate Salts
75 Oximes

REMAINING REACTIVE GROUPS

Planned (17)

1 Acids, Strong Non-oxidizing
2 Acids, Strong Oxidizing
4 Alcohols and Polyols
10 Bases, Strong
16 Hydrocarbons, Aromatic
28 Hydrocarbons, Aliphatic Unsaturated
29 Hydrocarbons, Aliphatic Saturated
33 Sulfides, Inorganic
45 Reducing Agents
46 Non-Redox-Active Inorganic Compounds
51 Nitrides, Phosphides, Carbides, and Silicides
59 Halogenating Agents
60 Acids, Weak
61 Bases, Weak
62 Carbonate Salts
63 Alkynes, with Acetylenic Hydrogen
64 Alkynes, with No Acetylenic Hydrogen

Difficult non-structural categories:

76 Polymerizable Compounds

98 Not Chemically Reactive
99 Insufficient Information for Classification

100 Water and Aqueous Solutions
101 Highly Flammable
102 Explosive
103 Polymerizable
104 Strong Oxidizing Agent
105 Strong Reducing Agent
106 Known Catalytic Activity
107 Water-Reactive
108 Air-Reactive
109 Pyrophoric
110 Decomposes at Elevated Temperatures (<120 deg. C)
111 Peroxidizable Compound

400 Radioactive Material

cameochemicals.noaa.gov/reactivity/documentation/RG5-RG7

Reactivity Predictions (for each pair of reactive groups)

Aldehydes *mixed with*
Amines, Phosphines, and Pyridines

Hazard Predictions

- Exothermic reaction at ambient temperatures (releases heat)
- Reaction may be particularly intense, violent, or explosive

Acetaldehyde reacts violently with amines (MCA Safety Datasheet 43, Manufacturing Chemists' Association, Washington, 1952).

Tertiary amines promote exothermic aldol condensations between aldehydes and/or ketones (Kohlpaintner, C., M. Schulte, J. Falbe, P. Lappe, and J. Weber. 2002. Aldehydes, Aliphatic and Araliphatic. In Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH Verlag GmbH & Co. KGaA. (Online)).

Hazards involving Acrolein (unsaturated aldehyde):

Acrolein polymerizes explosively on contact with amines (Arntz, D., M. Hopp, S. Jacobi, J. Sauer, T. Ohara, T. Sato, N. Shimizu, G. Prescher, H. Schwind, and O. Weiberg. 2002. Acrolein. In Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH Verlag GmbH & Co. KGaA. (Online)).

Ethylenediamine may react violently with acrolein (Lewis, R.J., Sr. 1992. Sax's Dangerous Properties of Industrial Materials, 8th Edition. New York: Van Nostrand Reinhold. pp. 1554.).

Amines such as dimethylamine and triethylamine promote polymerization of acrolein (Urben, P.G. 1995. Bretherick's Handbook of Reactive Chemical Hazards, 5th Edition. Oxford: Butterworth-Heinemann. pp. 417.).

RULE HIERARCHY

rg-5_7 (general)

Aldehydes and **Amines, Phosphines, and Pyridines**

rg-5_7* (specific)

a. **Acetaldehyde** reacts violently with **amines**.
b. **Tertiary amines** promote exothermic aldol condensations between **aldehydes** and/or **ketones**.
c. **Acrolein** polymerizes explosively on contact with **amines**.
    a. **Ethylenediamine** may react violently with **acrolein**.
    b. Amines such as **dimethylamine** and **triethylamine** promote polymerization of **acrolein**.

```
<alert name="rg_5_7" mesg="...">
  <contains ref="aldehydes">
  <contains ref="amines,phosphines,pyridines">
</alert>
...
<alert name="rg_5_7c" mesg="polymerizes explosively on contact"
       parent="rg_5_7">
  <containsComponent name="acrolein">
  <contains ref="amines">
</alert>
<alert name="rg_5_7c_a" mesg="may react violently"
       parent="rg_5_7c">
  <containsComponent name="acrolein">
  <containsComponent name="ethylenediamine">
</alert>
<alert name="rg_5_7c_b" mesg="prompts polymerization"
       parent="rg_5_7c">
  <containsComponent name="acrolein">
  <any>
    <containsComponent name="dimethylamine">
    <containsComponent name="triethylamine">
  </any>
</alert>
```

COMPONENT EXPRESSIONS (2.0)

```
<condition name="trialkylboranes">
  <containsComponent>
    <smarts value="[CX4][BX3]([CX4])[CX4]"/>
    <not>
      <smarts value="([CX4][BX3]([CX4])[CX4].[!#1!C!X4])"/>
    </not>
  </containsComponent>
</condition>
...
<alert name="epa-rg-35_42b"
       mesg="Form strongly basic reducing agents (LiBHR3)."
       cite="Sullivan, E. and Wade, R. 1980. Hydrides...">
    <all>
        <containsComponent name="lithium hydride"/>
        <contains ref="trialkylboranes"/>
    </all>
</alert>
```

1,375 rules (18K lines)

488 GENERAL COMBINATIONS

semi-automatic

297 **incompatible** 191 **caution**

887 SPECIFIC COMBINATIONS

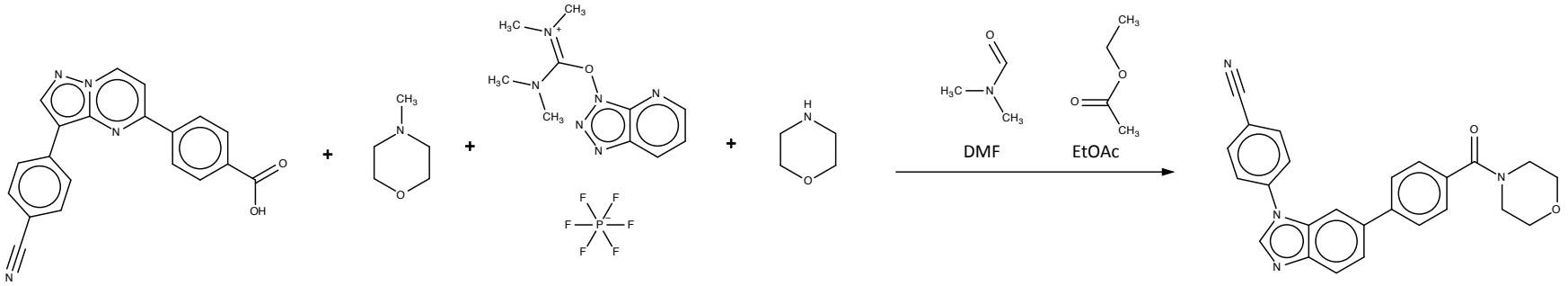
manual

744 **incompatible** 143 **caution**

1,566,049 USPTO REACTIONS

US20150038506A1 [paragraph:943]

[0943] Step 7: To a solution of 4-(1-(4-cyanophenyl)-1H-benzo[d]imidazol-6-yl)benzoic acid 6 (300 mg, 0.88 mmol) in DMF (5 mL) was added NMM (0.178 mL, 1.76 mmol) followed by HATU (501 mg, 1.32 mmol) at rt and the solution was stirred for 30 min. Morpholine (0.84 mL, 0.968 mmol) was added to the reaction mixture and stirring was continued for 16 h. The reaction mixture was diluted with EtOAc and washed with water and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified by preparative HPLC to afford 4-(6-(4-(morpholine-4-carbonyl)phenyl)-1H-benzo[d]imidazol-1-yl)benzonitrile (100 mg, 27%, AUC HPLC 95.9%) as an off-white solid; m.p. 207-210° C.; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.18 (s, 1H), 7.98-7.92 (m, 3H), 7.72 (d, J=6.6 Hz, 3H), 7.66-7.61 (m, 3H), 7.51 (d, J=7.9 Hz, 2H), 3.90-3.40 (m, 8H); MS (ESI) m/z 409.15 $[C_{25}H_{20}N_4O_2+H]^+$.



4-(1-(4-cyanophenyl)-1H-benzo[d]imidazol-6-yl)benzoic acid (300 mg, 0.88 mmol)

NMM (0.178 mL, 1.76 mmol)

HATU (501 mg, 1.32 mmol)

morpholine (0.84 mL, 0.968 mmol)

4-(6-(4-(morpholine-4-carbonyl)phenyl)-1H-benzo[d]imidazol-1-yl)benzonitrile (100 mg)

nextmovesoftware.com/leadmine.html
nextmovesoftware.com/blog/2014/02/

WARNINGS OVERVIEW

1,431,165 (91%) reactions flagged in **3h3m12s**

7 ms avg per reactions (**142 s^{-1}**)

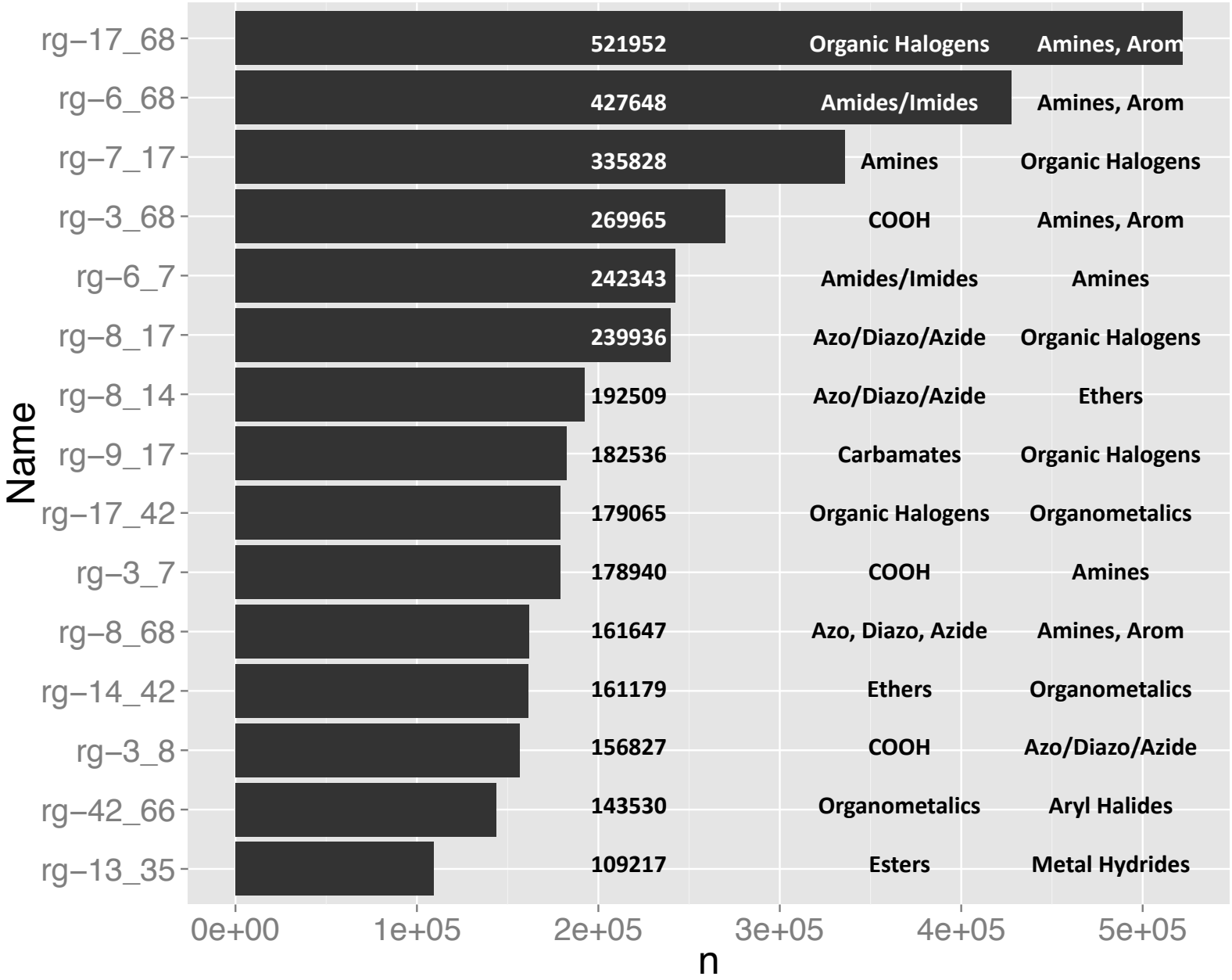
6,200,046 incompatibles

1,477,142 specific in 642,649 (41%) reactions

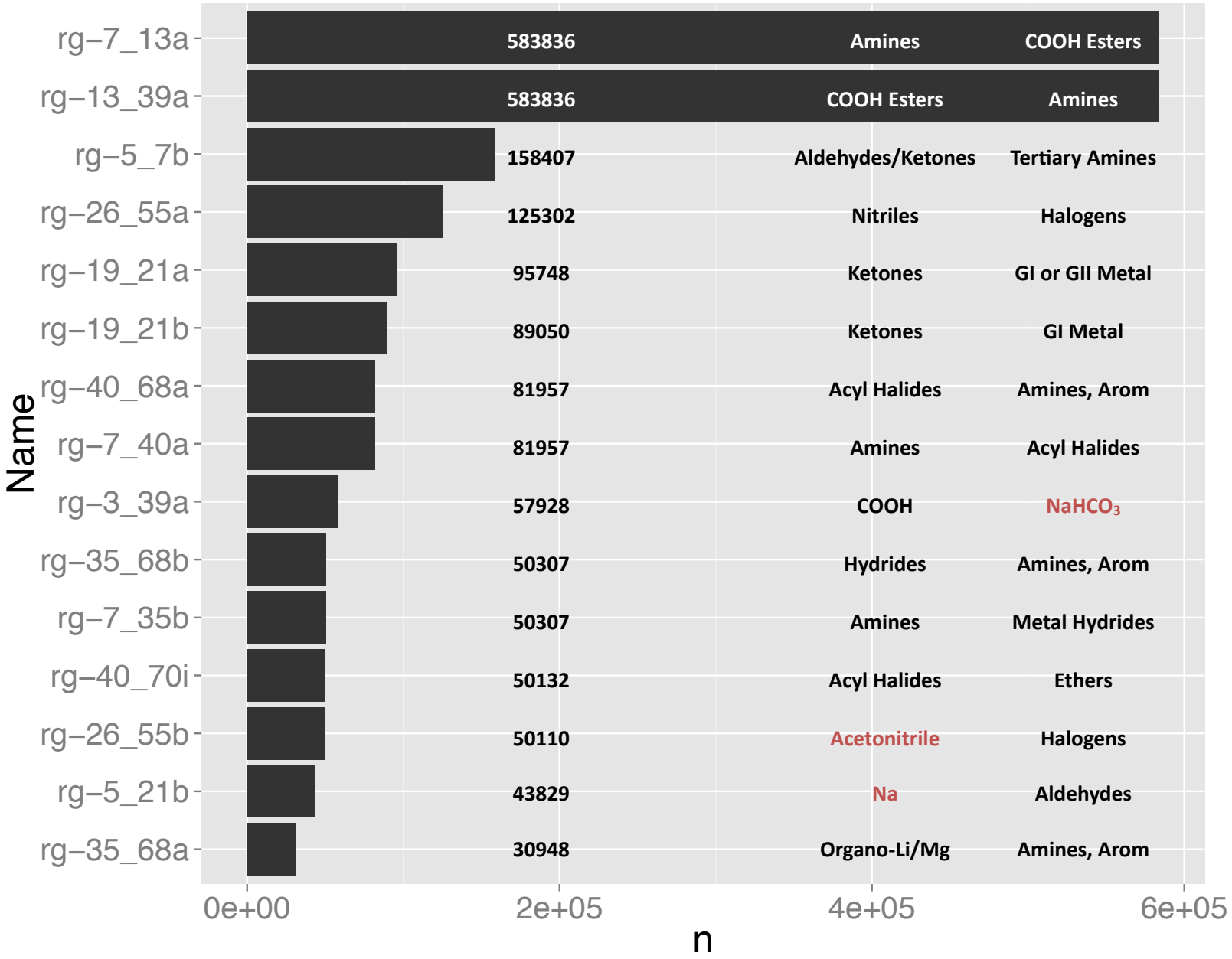
3,247,847 cautions

1,194,938 specific in 600,209 (38%) reactions

TOP 15 GENERAL INCOMPATIBILITIES



TOP 15 SPECIFIC INCOMPATIBILITIES



INFORMATION OVERLOAD

1. Scope/Structure of CRW/CAMEO

for emergency responders rather than experimentalists

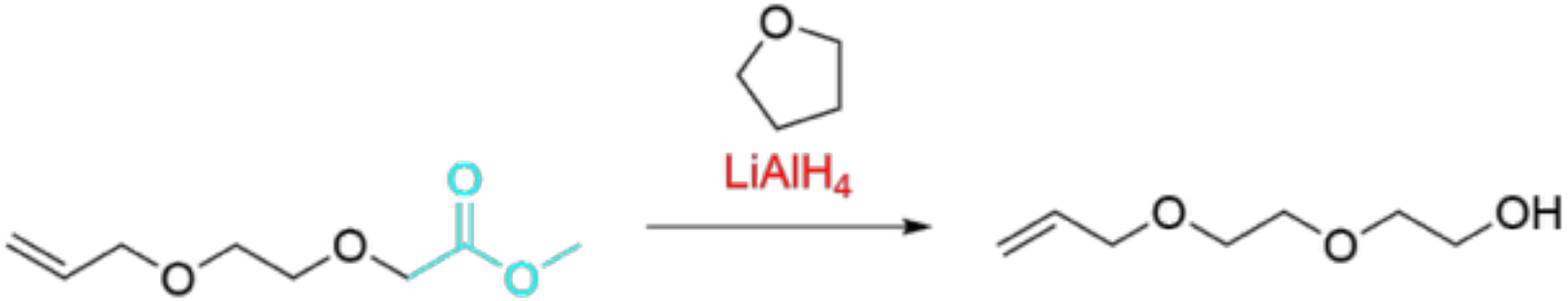
2. Coarse Hazard Level

dimethylmercury and methanol pictograms:

3. Classification accuracy

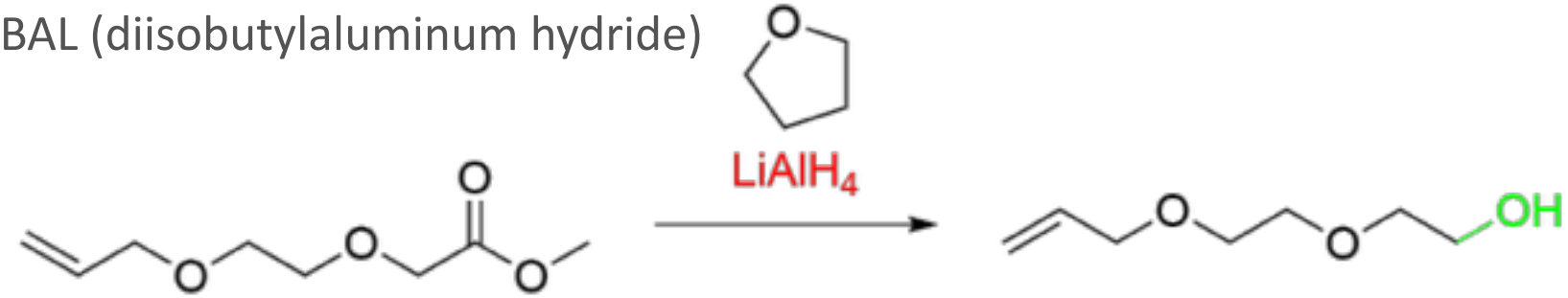
Loose structural patterns

US20110306771A1 [paragraph:0056]



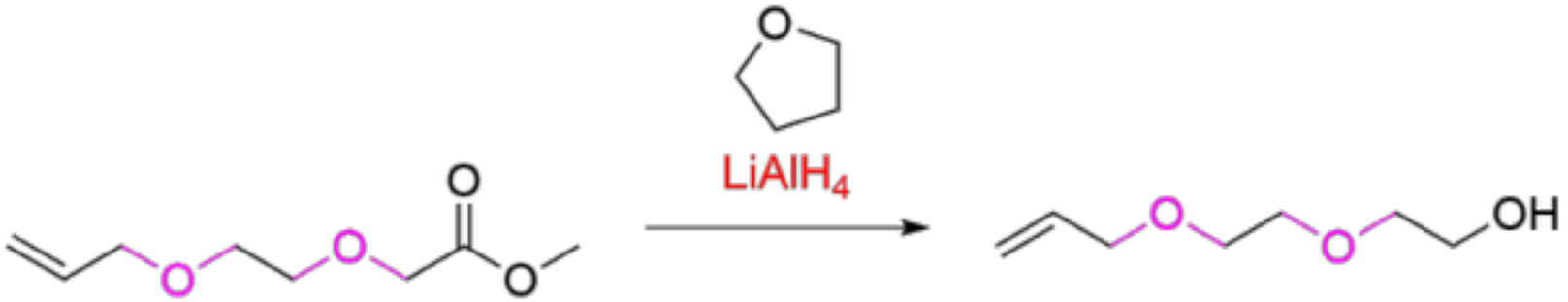
rg-13_35e **esters** can be reduced to alcohols with complex metal hydrides, especially **lithium aluminum hydride**.

rg-13_35b **carboxylic acid esters** can be reduced to aldehydes or alcohols, depending on conditions, by complex hydrides such as **LiAlH4**, LiBH4, NaAlH4, or DIBAL (diisobutylaluminum hydride)



rg-35_70d **hydrides** react spontaneously and irreversibly with proton donors, including **alcohols**, evolving flammable H2 gas

US20110306771A1 [paragraph:0056]



rg-14_42 solutions of molybdenum hexacarbonyl **(42?)** in diethylether **(14)** can explode after standing in air for an extended period. Chromium hexacarbonyl in diethylether may behave the same way

rg-35_42 the interaction between tetravinyllead **(42?)** and diborane **(35)** is explosively violent at ambient temperature.

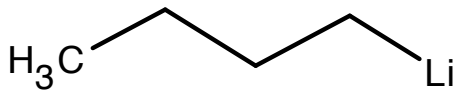
14: Ethers

35: Metal Hydrides, Metal Alkyls, Metal Aryls, and Silanes

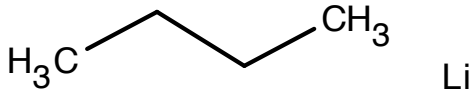
42: Organometallics (previously just matched as 'has metal')

ORGANOMETALIC STRUCTURAL PATTERN

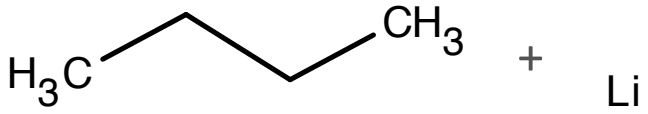
`[#6]-[#M]` carbon–metal bond



`[#6].[#M]` carbon and metal



`[#M]` metal




```
[#M] = [!#1!#2!#5!#6!#7!#8!#9!#10!#14!#15!#16!#17!
#18!#35!#36!#53!#54!#85!#86!#117!#118]
```

CAMEO COMPLETENESS

Reactivity Predictions (for each pair of reactive groups)

Amides and Imides *mixed with*
Amines, Aromatic

Hazard Predictions

- Reaction products may be flammable
- Reaction liberates gaseous products and may cause pressurization
- Reaction products may be toxic

Thionamides may react with amines, anilines, hydrazine, and ammonium hydroxide to liberate toxic and flammable H2S gas (Smith, P. A. S., Open-Chain Nitrogen Compounds, Vol. I. New York: W. A. Benjamin, Inc., 1965, pp. 162).

Potential Gas Byproducts

- Hydrogen Sulfide (H2S)

http://cameochemicals.noaa.gov/reactivity/documentation/RG6-RG68

CAMEO INCONSISTENCIES

Reactivity Predictions (for each pair of reactive groups)

Nitriles *mixed with*
Chlorosilanes

Hazard Predictions

- Reaction liberates gaseous products and may cause pressurization
- Exothermic reaction at ambient temperatures (releases heat)
- Polymerization reaction may become intense and may cause pressurization
- Reaction products may be toxic

Halogens may initiate polymerization of acrylonitrile, even at reduced temperatures (MCA Case History No. 1214, Case Histories of Accidents in the Chemical Industry, Manufacturing Chemists' Association, Washington.).

Nitriles may react with the halogens to liberate toxic HX gases (Smith, P. A. S., Open-Chain Nitrogen Compounds, Vol. I. New York: W. A. Benjamin, Inc., 1965, pp. 218).

Potential Gas Byproducts

- Hydrogen Halide (HX)

http://cameochemicals.noaa.gov/reactivity/documentation/RG26-RG55

Reactivity Predictions (for each pair of reactive groups)

Amines, Phosphines, and Pyridines *mixed with*
Halogenated Organic Compounds

Hazard Predictions

- Reaction liberates gaseous products and may cause pressurization
- Exothermic reaction at ambient temperatures (releases heat)
- Reaction may be particularly intense, violent, or explosive
- Reaction products may be toxic

Ethylenediamine reacts violently with ethylene chlorohydrin (Lewis, R.J., Sr. 1992. Sax's Dangerous Properties of Industrial Materials, 8th Edition. New York: Van Nostrand Reinhold. pp. 1554.).

Trimethylamine may react with RX compounds to form (CH2)NR and halogenated methanes (Rodd, E. H, Ed. Chemistry of Organic Compounds. New York: Elsevier Publishing Company, 1951. Vol. I pp. 380).

Ethylphosphine explodes on contact with chlorine, bromine or fuming nitric acid, and inflames with conc. acid. (Fire and Explosion Risks, von Schwartz, E., London, Griffin, 1918, p. 324-325)

Aniline, dimethyl amine and pyridine incandesce on contact with fluorine. (Hoffman, C. J., Chem. Rev., 1962, 62, 12)

Common halogenated hydrocarbons (CH2Cl2, CHCl3, etc.) incompatibility with amines is a well-known reactivity issue in the chemical industry.

Common halogenated hydrocarbons (CH2Cl2, CHCl3, etc.) incompatibility with amines is a well known reactivity issue in the chemical industry.

Potential Gas Byproducts

- Halocarbons

http://cameochemicals.noaa.gov/reactivity/documentation/RG17-RG7

Reactivity Predictions (for each pair of reactive groups)

Metal Hydrides, Metal Alkyls, Metal Aryls, and Silanes *mixed with* Amines, Aromatic

Hazard Predictions

- Reaction products may be corrosive
- Reaction products may be explosive or sensitive to shock or friction
- Reaction products may be flammable
- Reaction liberates gaseous products and may cause pressurization
- Exothermic reaction at ambient temperatures (releases heat)

1) Amines may react with organolithium and organomagnesium reagents to liberate flammable hydrocarbon gases.

- Carey, Francis. "Organic Chemistry", 5th Edition, Chpt. 14. Accessed at: http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch14/ch14-1.html#Reactivity

2) Hydrides react spontaneously and irreversibly with amines, evolving flammable H2 gas.

- Rittmeyer, P., U. Wietelmann. 2002. Hydrides. In Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH Verlag GmbH & Co. KGaA. (Online) - Sullivan, E. and Wade, R. 1980. Hydrides. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley & Sons, Inc.

3) Aromatic amines react with lithium aluminum hydride to form azo compounds, which are potentially explosive.

- Cartolano, A. R. and Vedage, G. A. 2004. Amines by Reduction. Kirk-Othmer Encyclopedia of Chemical Technology. (Online)

4) Sodium hydride reacts with amines to form corrosive and strongly basic sodium amide salts.

- Klemm, A., Hartmann, G. and Lange, L. 2000. Sodium and Sodium Alloys. Ullmann's Encyclopedia of Industrial Chemistry. (Online)

Potential Gas Byproducts

- Hydrogen (H2)
- Hydrocarbons

http://cameochemicals.noaa.gov/reactivity/documentation/RG68-RG35

CONCLUSIONS

Able to encode many chemical incompatibility matrices in **Casandra's** self contained XML rule format

- **real-time** alerting (ELN interaction) even with the moderately large rule set
- **v2.0**: Markush like queries, Custom properties

CAMEO is an **excellent** resources for hazard information

- Still room for improvement and reorganisation:
  - wiki, ontology, self-organising hierarchy, citations
- Repurposing for experimentalist is feasible given dedicate manual curation
- Validation ***corpus*** are relevant hazards identified/missed

FUTURES

Classification And Labelling Requirements For Hazardous Substances And Mixtures

Table 2.6.1

Category	Flash Point	Initial Boiling Point
GHS 1 Flammable Liquids	< 23 °C	≤ 35 °C
GHS 2 Flammable Liquids	< 23 °C	> 35 °C
GHS 3 Flammable Liquids	≥ 23 °C ≤ 60 °C	

Liquid:

i. vapour pressure ≤ 300 kPa at 50 °C
ii. not completely gaseous at 20 °C at a standard pressure 101,3 kPA
iii. (initial) melting point ≤ 20 °C at a standard pressure 101,3 kPA

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NextMove Software

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Booth #643 (too late)

http://nextmovesoftware.com

Slides will be available:

http://www.slideshare.net/NextMoveSoftware