

Mixtures

informatics for formulations and consumer products

Leah R. McEwen & Alex M. Clark

Who

❖ InChI Trust / IUPAC

- ▶ <https://www.inchi-trust.org>
- ▶ Mixtures InChI notation



❖ Collaborative Drug Discovery

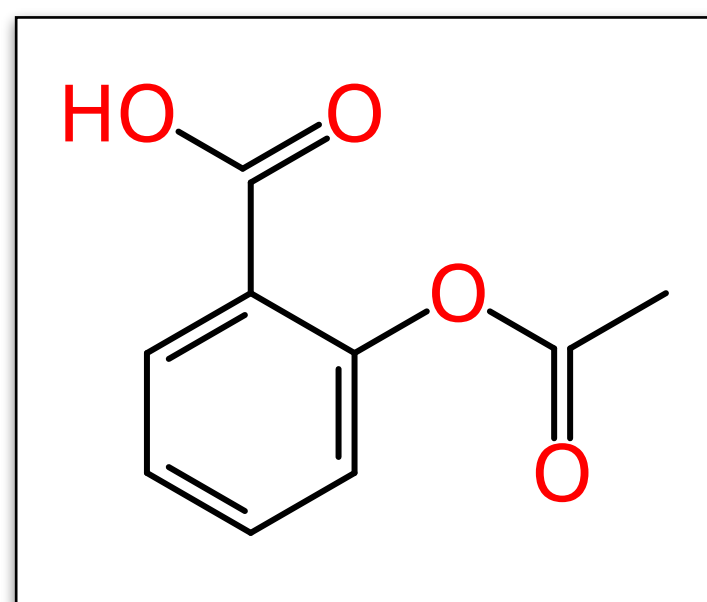
- ▶ <https://collaborativedrug.com>
- ▶ Mixfiles & tools



Introduction

- ❖ Cheminformatics has 40 years of practice representing abstract molecules
- ❖ Very successful applications for pharmaceutical drug discovery

Molfile



```
CC(=O)OC1=CC=CC=C1C(=O)O
```

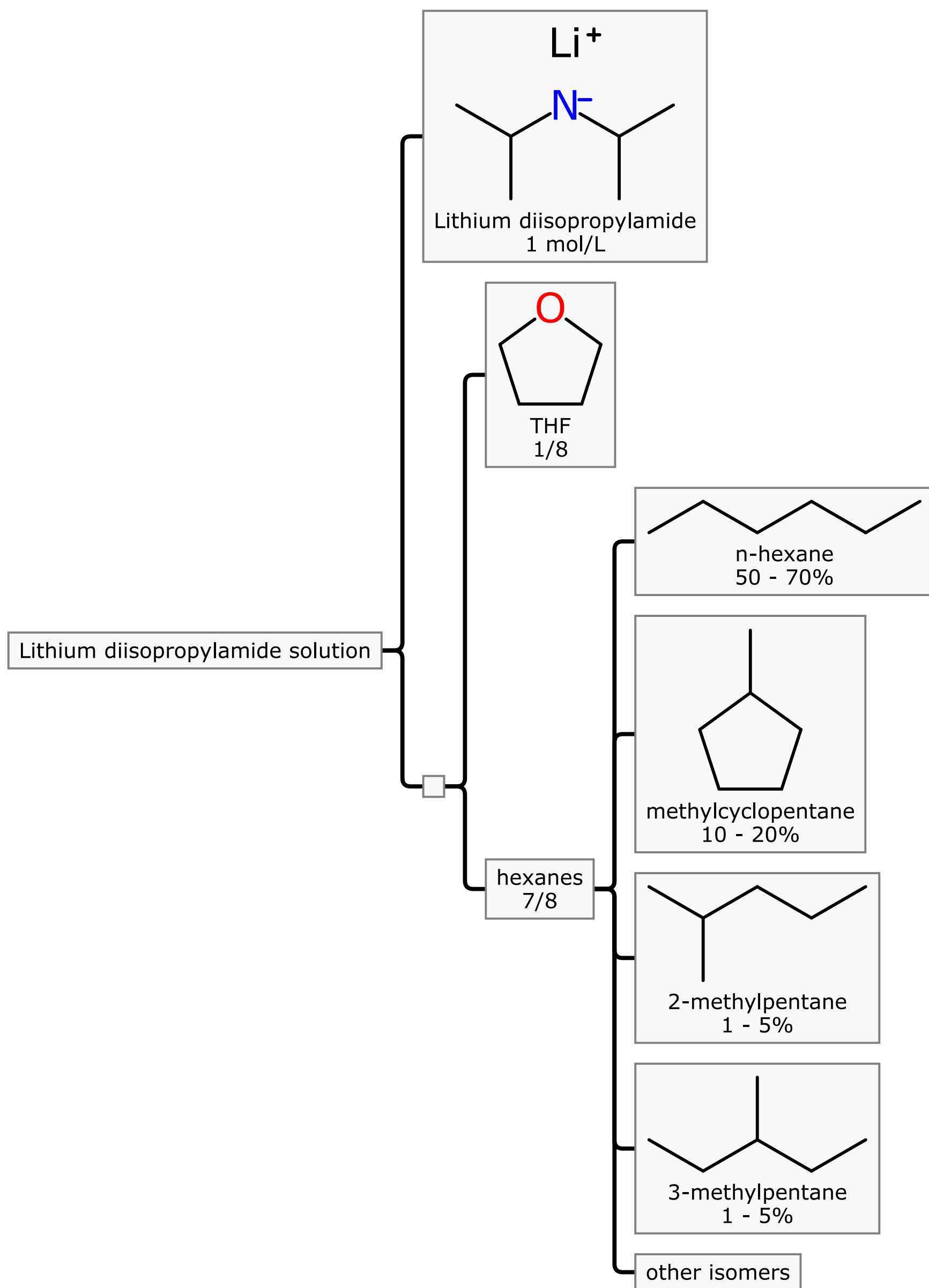
SMILES

```
InChI=1S/C9H8O4/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h2-5H,1H3,(H,11,12)
```

InChI

- ❖ But the reality of chemicals in the lab is that
 - ▶ nothing is ever completely pure
 - ▶ most activities involve explicitly mixing chemicals
 - ▶ mixtures are crafted for specific purposes
- ❖ Yet, there is lack of standard way to describe mixtures

Mixfile/MInChI



❖ Format needs to be:

- ▶ hierarchical
- ▶ embed structures when possible
- ▶ include concentration information
- ▶ tolerate uncertainty

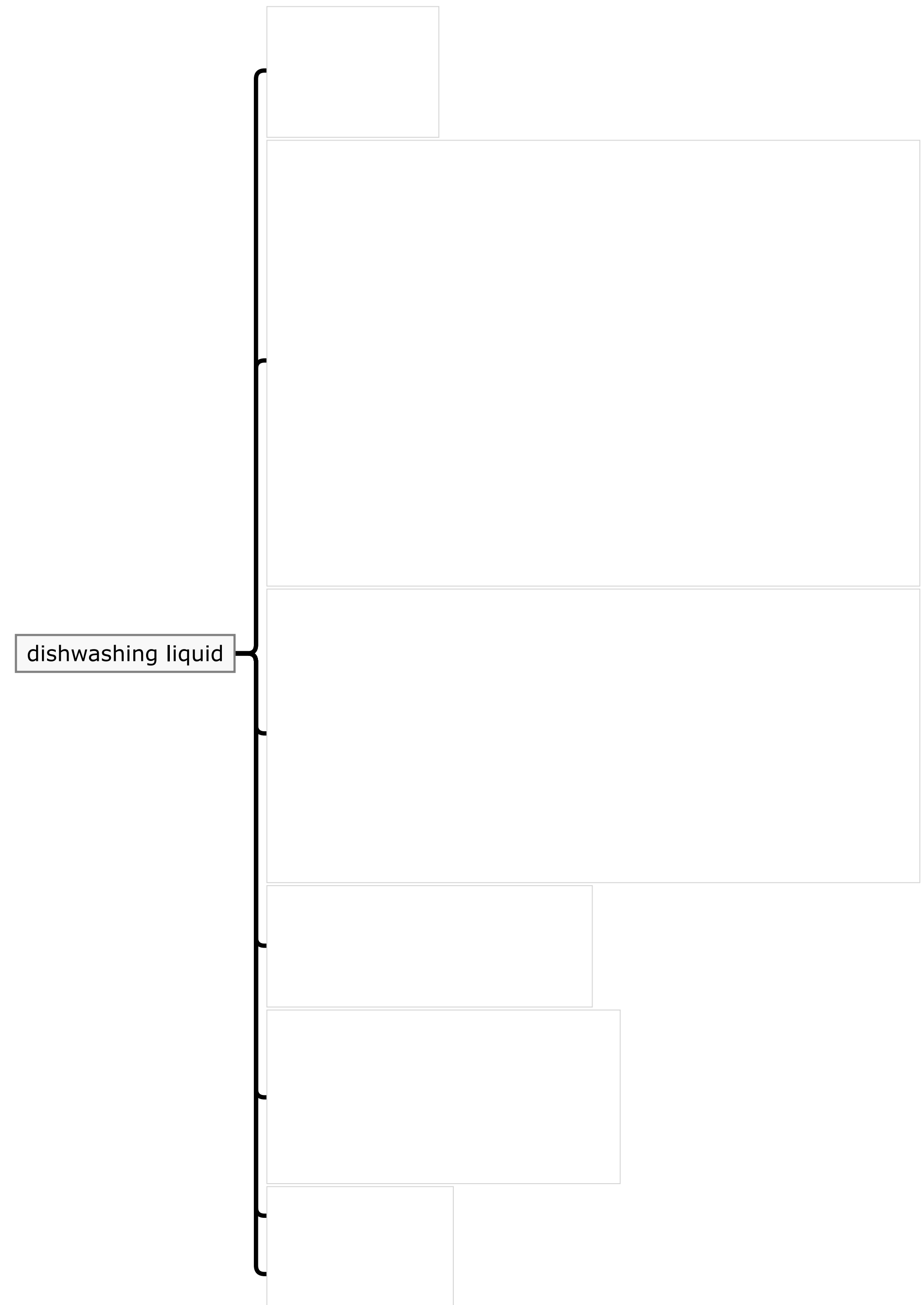
❖ More verbose ELN-friendly form is **Mixfile**

❖ Concise form with canonical components is **MInChI** (*mixtures InChI*)

```
MInChI=0.00.1S/C4H8O/c1-2-4-5-3-1/h1-4H2&C6H12/  
c1-6-4-2-3-5-6/h6H,2-5H2,1H3&C6H14/c1-3-5-6-4-2/  
h3-6H2,1-2H3&C6H14/c1-4-5-6(2)3/h6H,4-5H2,1-3H3&C6H14/  
c1-4-6(3)5-2/h6H,4-5H2,1-3H3&C6H14N.Li/c1-5(2)7-6(3)4;/  
h5-6H,1-4H3;/q-1;+1/n{6&{1&{3&2&4&5}}}/  
g{1mr0&{1vp0&{5:7pp1&1:2pp1&1:5pp0&1:5pp0}7vp0}}
```

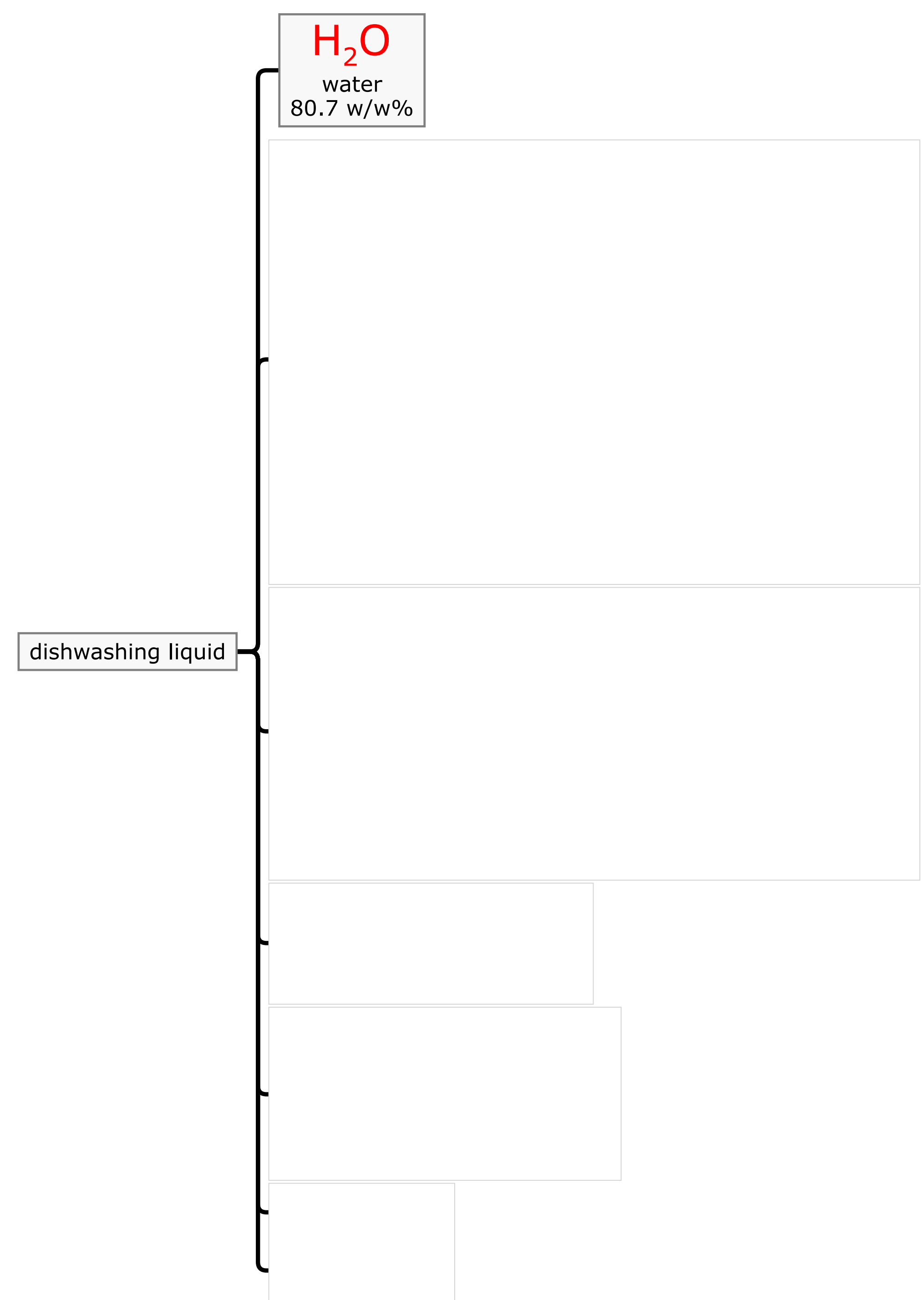
Formulation Example

- ❖ Many consumer products are well described from a chemical perspective
- ❖ Some components are more easily defined than others
- ❖ When structure is not available, can use external identifiers
- ❖ Hierarchy encodes information about the design of the product
- ❖ Concentrations can be expressed with uncertainties



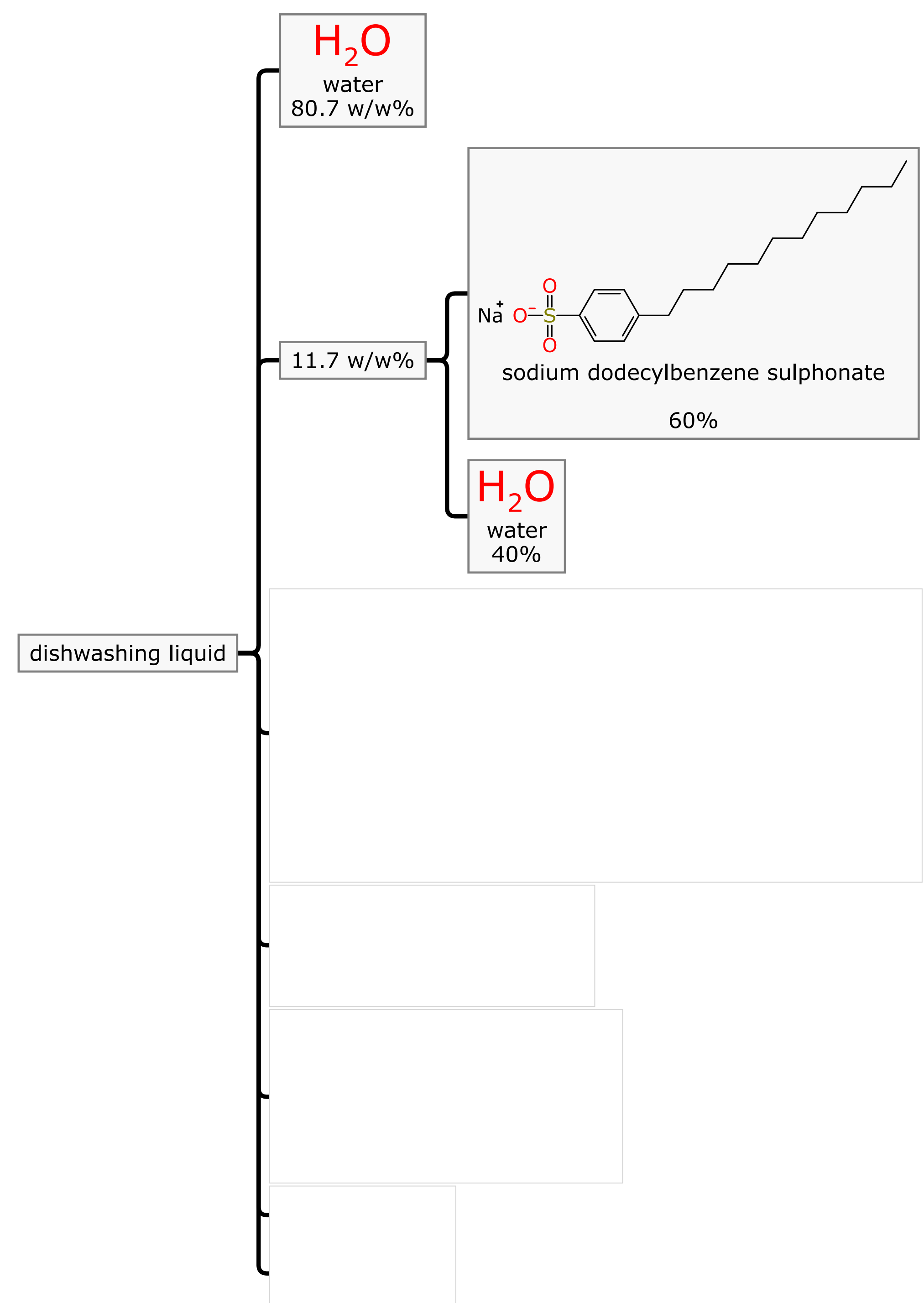
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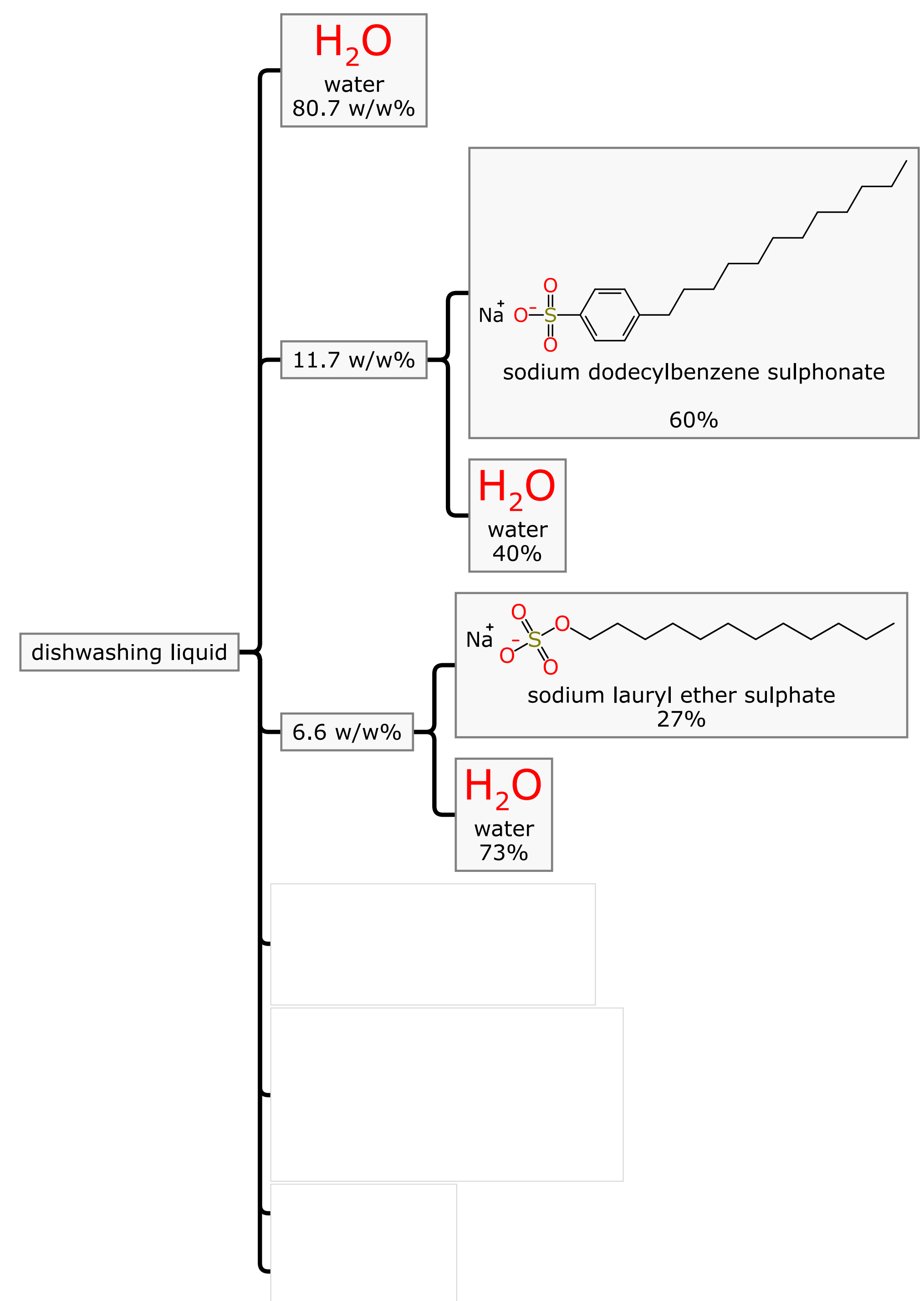
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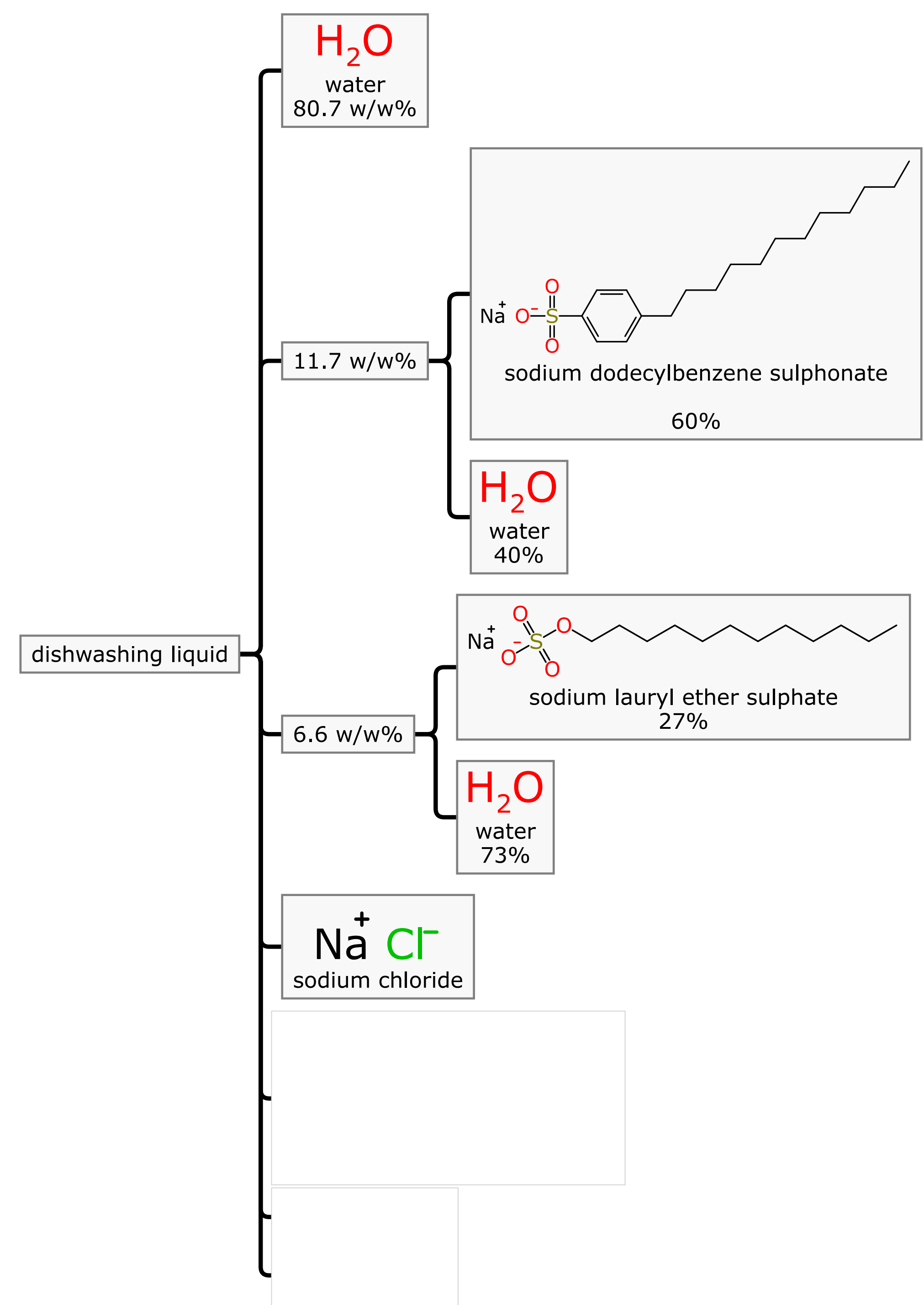
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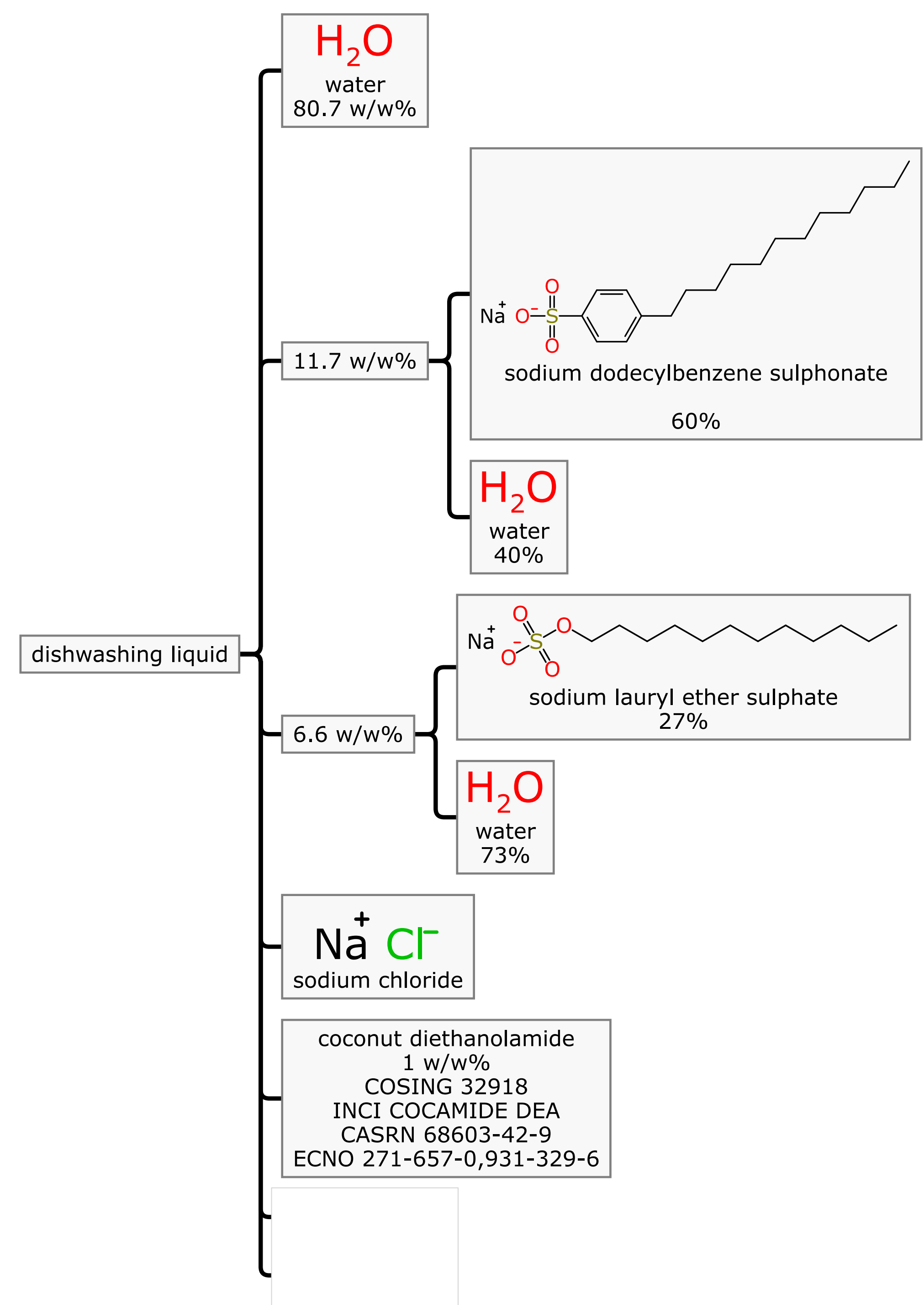
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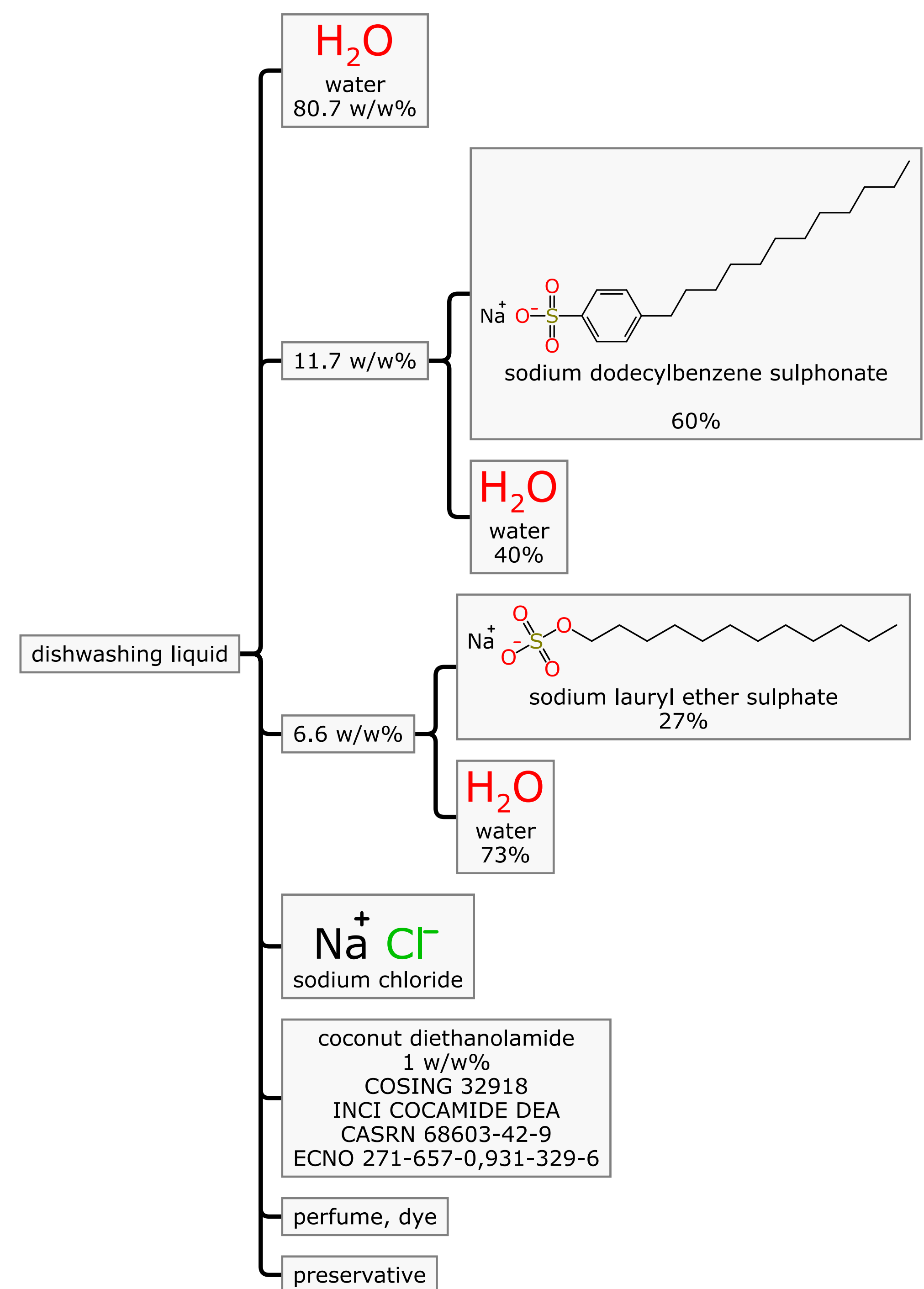
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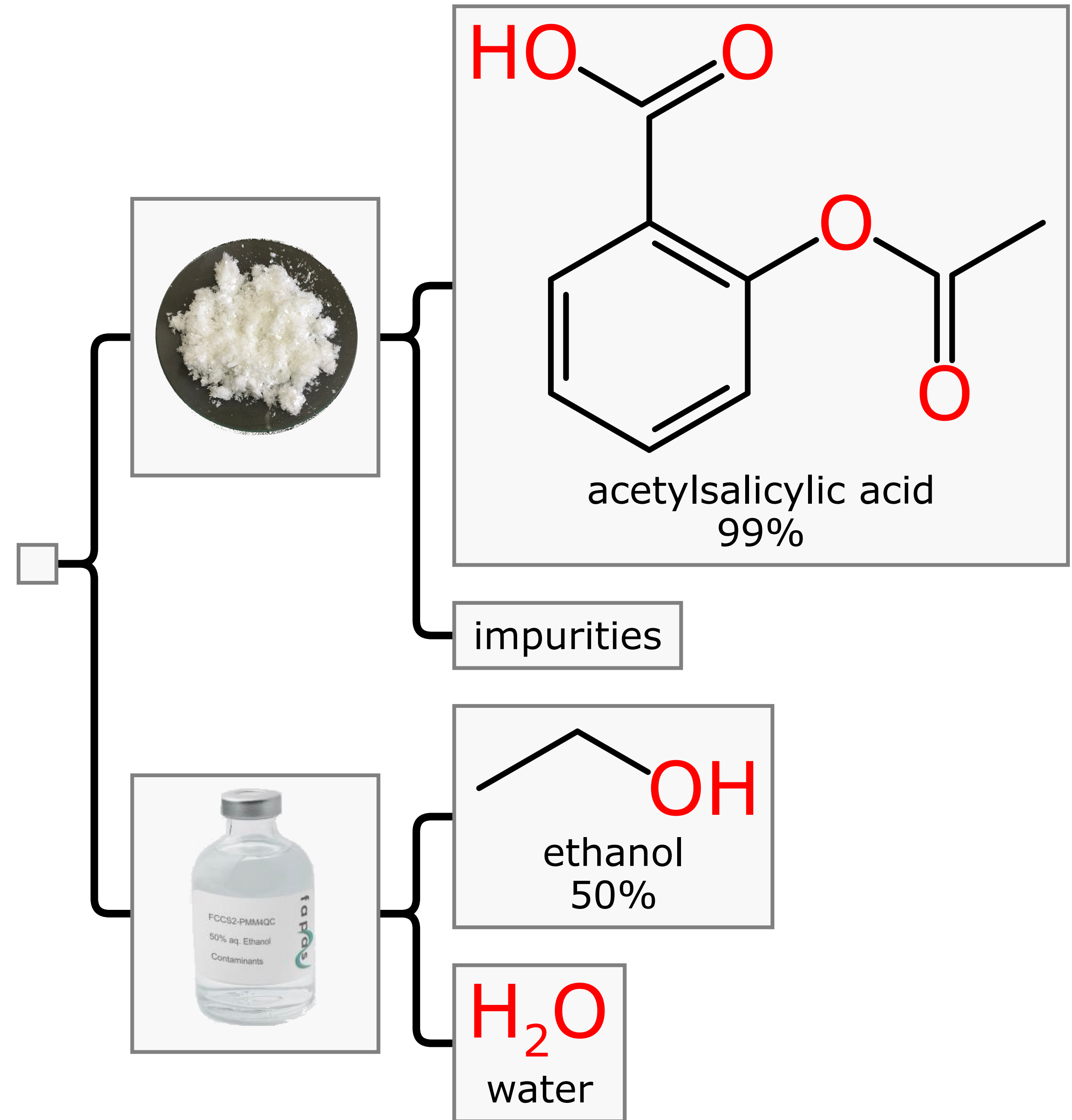
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Design of Mixtures

- ❖ Each branch is a *thing*
- ❖ Each leaf is a *concept*
- ❖ Layout can correspond to how the mixture is formulated



Knowledge Capture

- ❖ Capture what we know about the mixture: and nothing more
 - ▶ ideally each leaf node has well defined structure & precise concentration
 - ▶ the closer we get to this, the more analysis we can do
- ❖ Concentrations often variable, unknown, vague, or implied
- ❖ Structure(s) can be hard to pin down...
 - ▶ ... not always a single, well defined, easy to draw molecule

Cerium(IV) and Perchloric acid, Etchant Solution, Ce(IV) concentration 0.22N

1,2-Diphenylcyclopropane, cis + trans, 97%

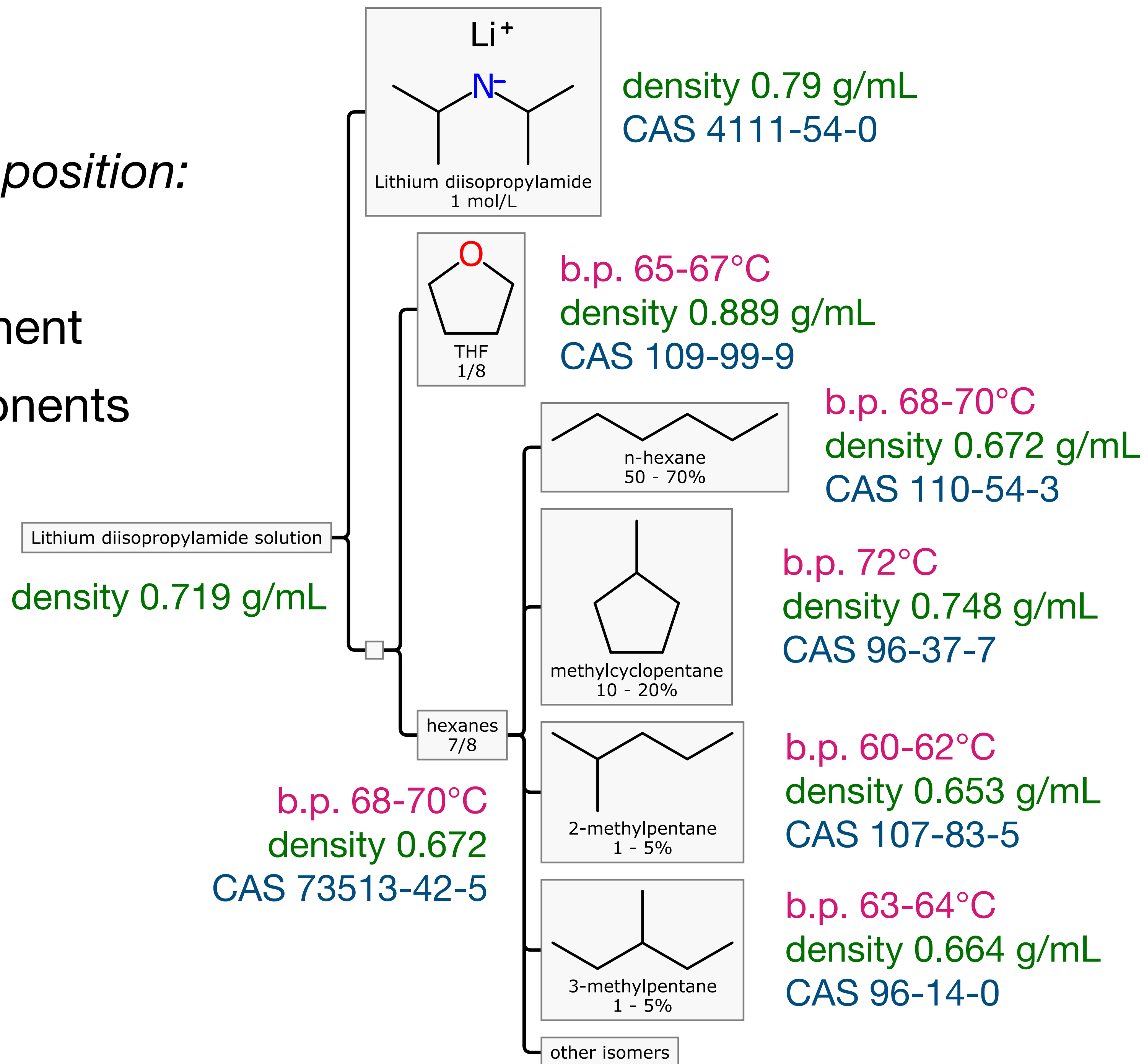
1,3,5,7-Cyclooctatetraene, 98%, stab. with 0.1% Hydroquinone

Lithium bis(trimethylsilyl) amide, 20% (ca 1.06M) soln. in THF/ethylbenzene, packaged in resealable septum cap bottle

Properties

❖ Metadata is attached to a *position*:

- ▶ root = the whole thing
- ▶ leaf = individual component
- ▶ branch = several components



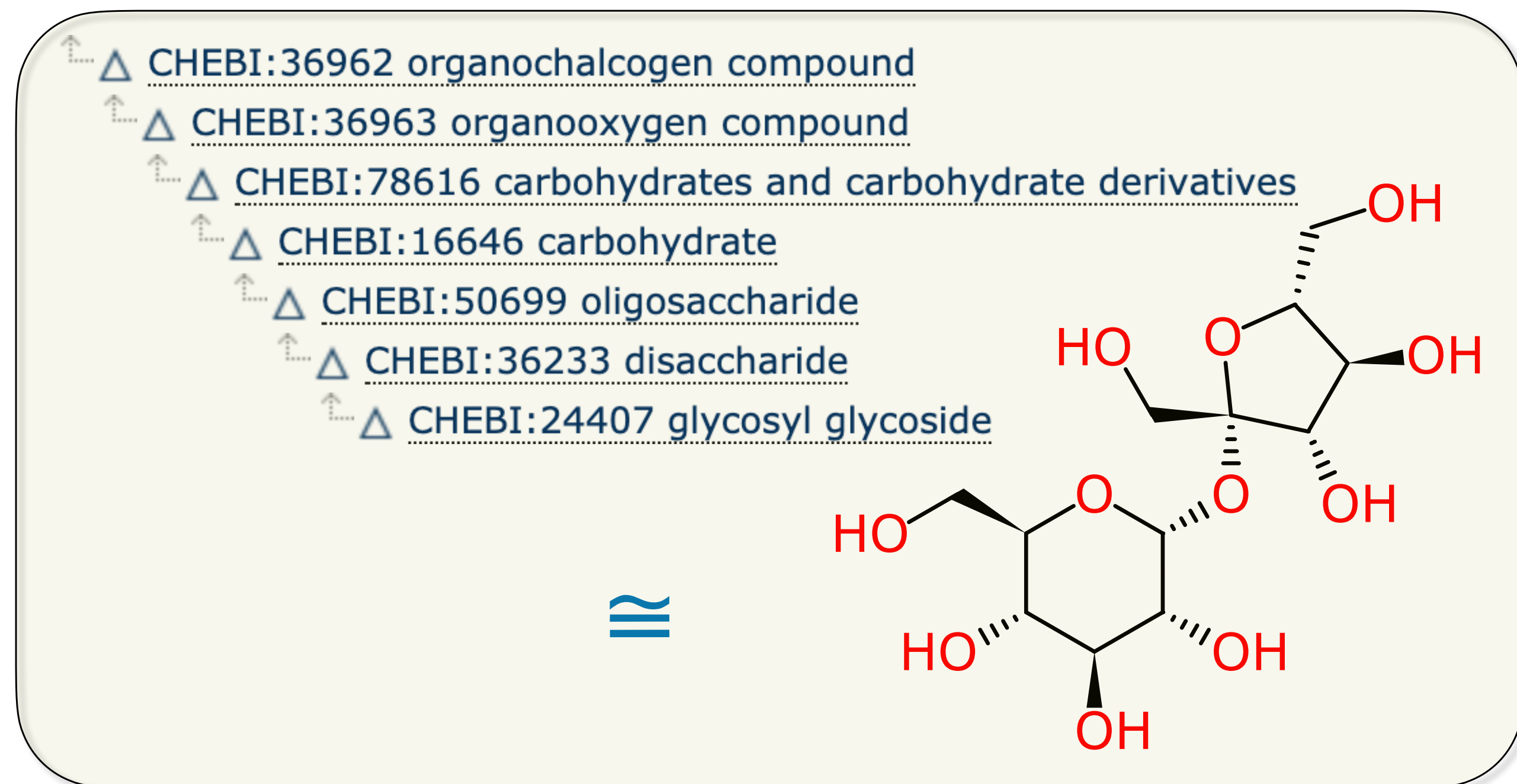
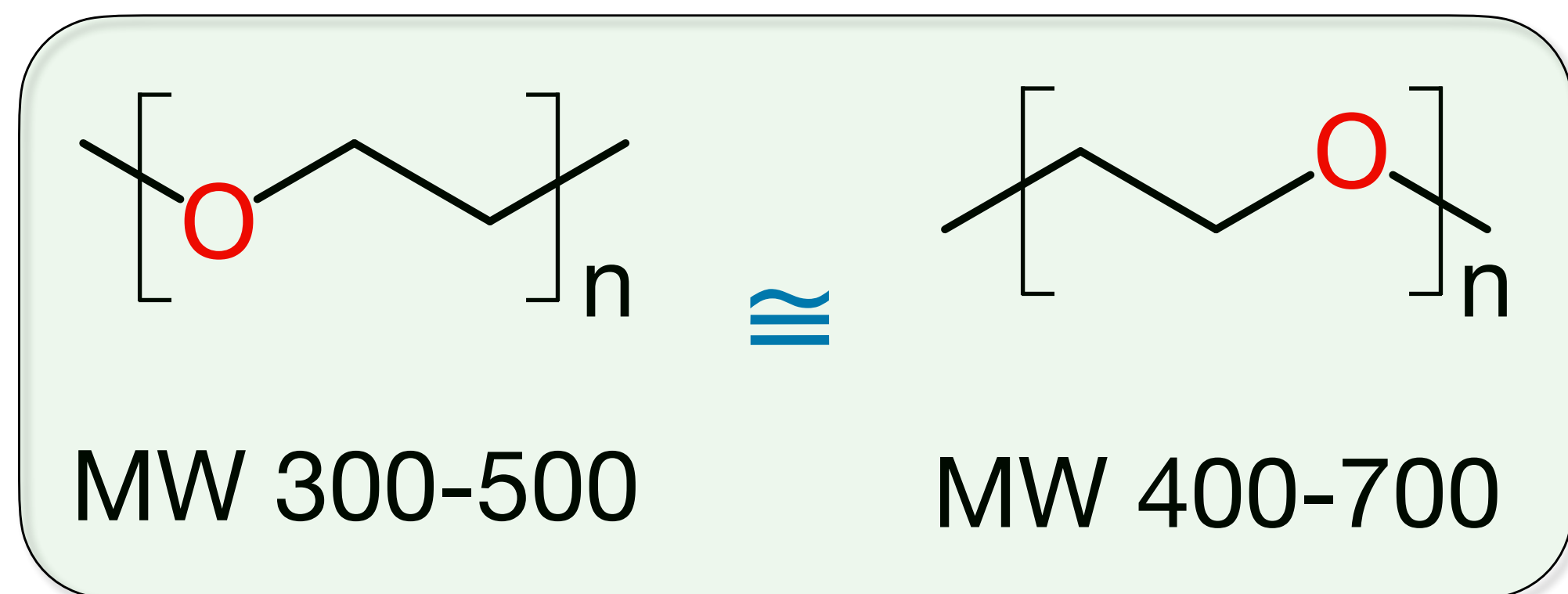
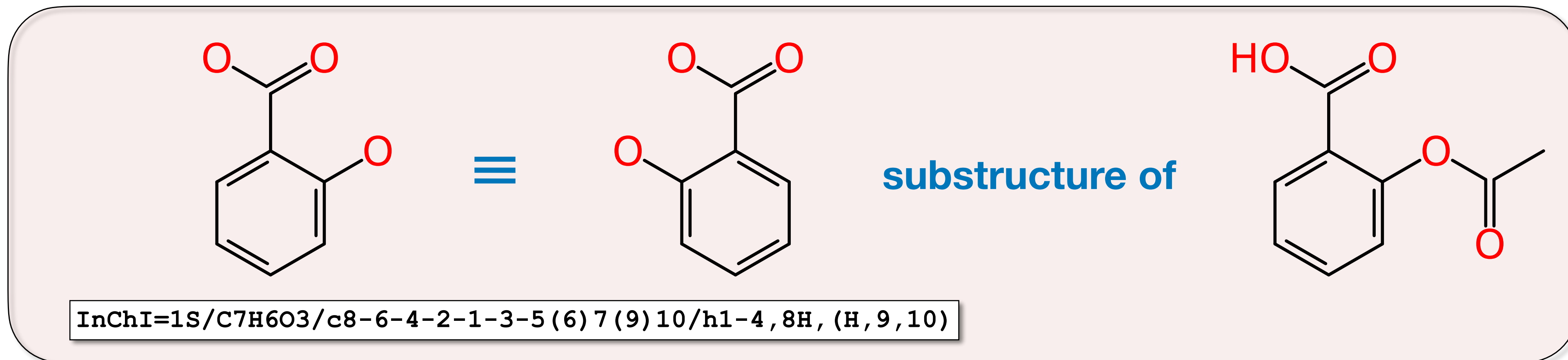
Structures by External Definition

- ❖ Sometimes have to resort to describing a component by method of preparation, means of extraction, measured properties, etc.
- ❖ External database identifiers can be useful:
 - ▶ **CASRN**: Chemical Abstracts literature extraction
 - ▶ **INCI**: International Nomenclature of Cosmetics Ingredients
 - ▶ **UNII**: Food & Drug Administration database
- ❖ Database identifiers are not ideal for machine readability, but they can be used to establish equivalence:

HYDROGENATED COCONUT OIL
COSING 34340
INCI HYDROGENATED COCONUT OIL
CASRN 84836-98-6
ECNO 284-283-8

Coconut oil (hydrogenated)
INCI HYDROGENATED COCONUT OIL

Comparisons with Structures



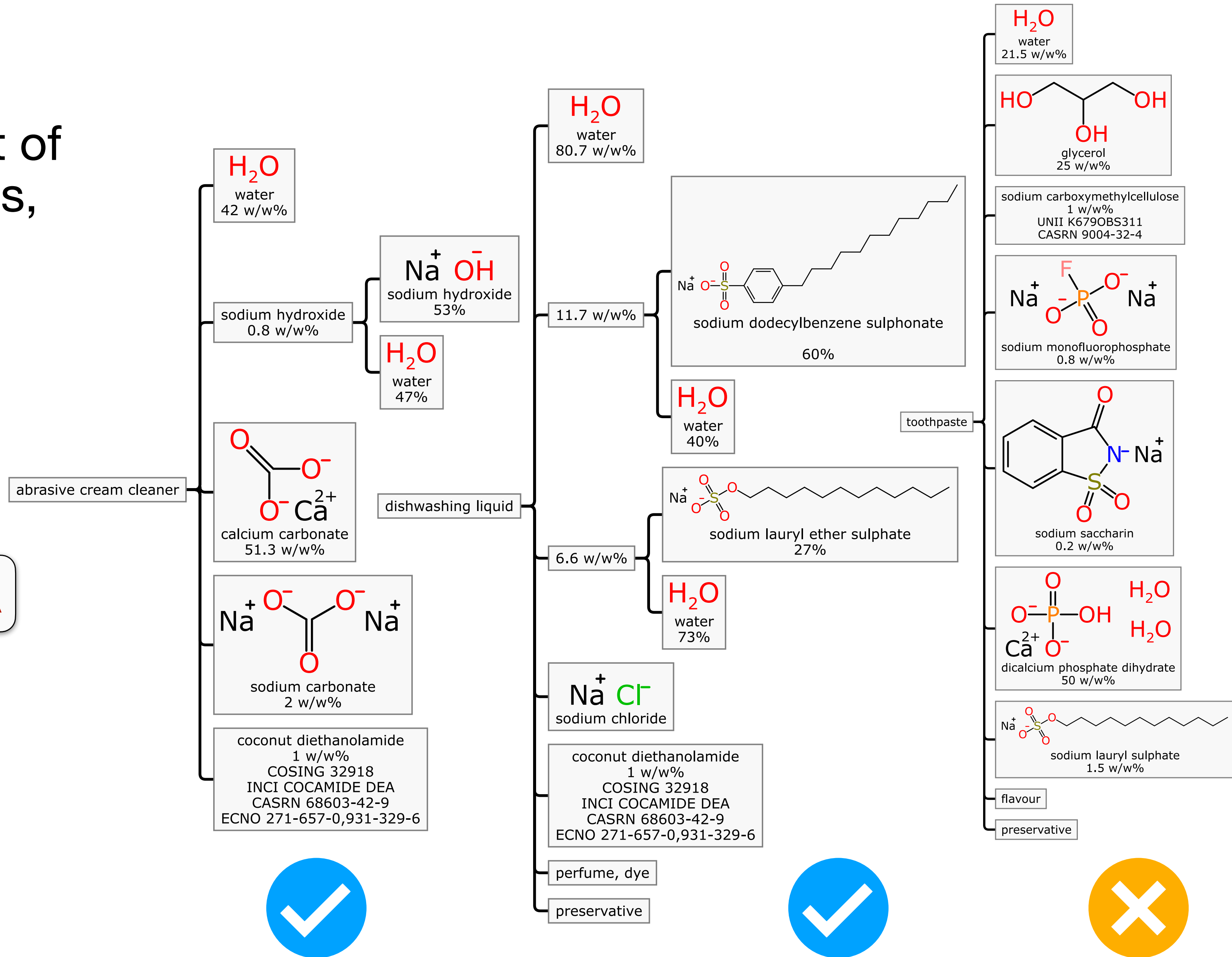
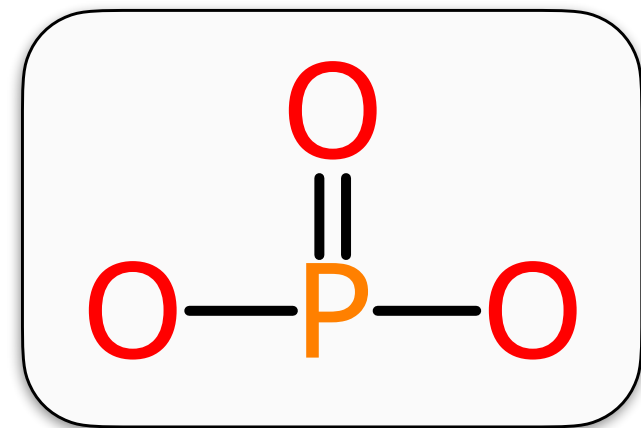
Search Queries

❖ Looking for a certain subset of external cleaning surfactants, phosphate-free

has H_2O >40%

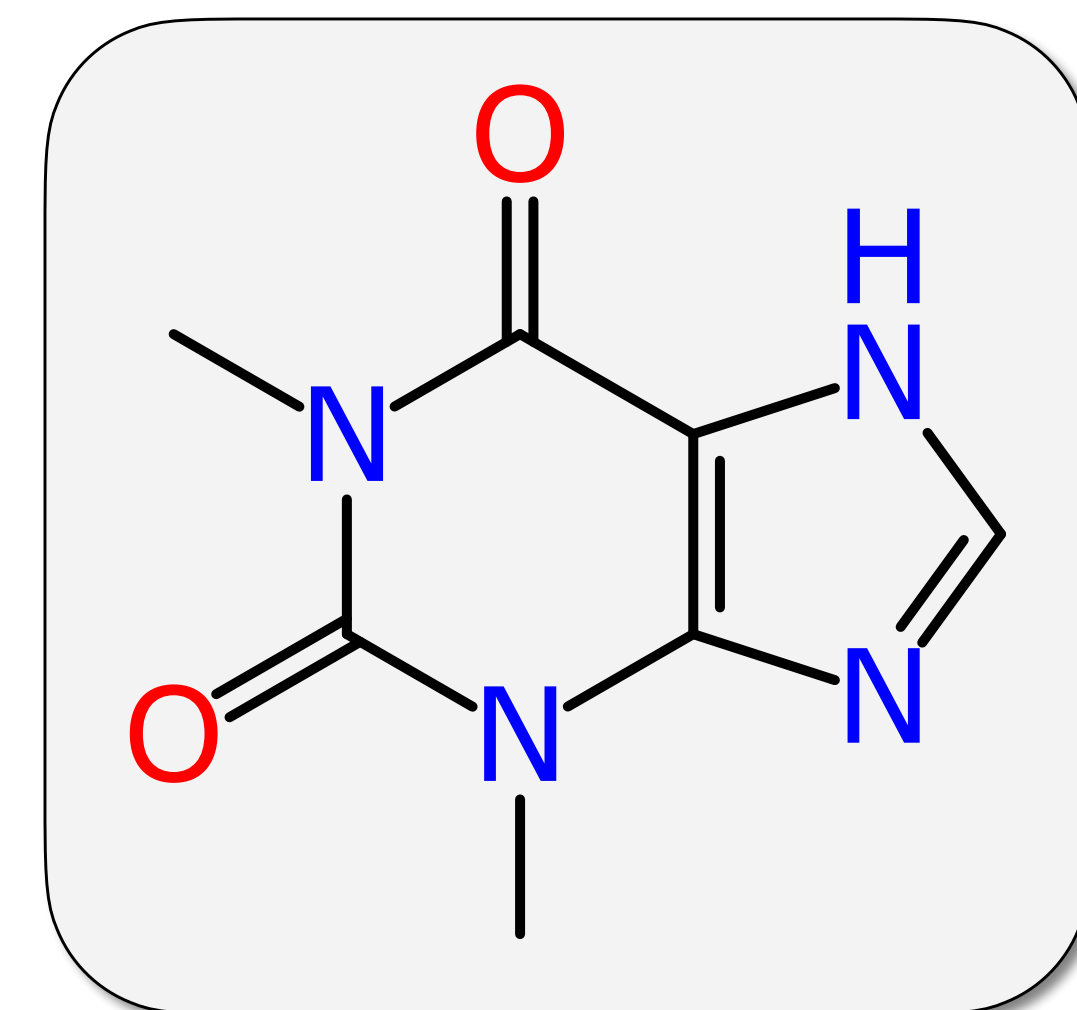
has **INCI: COCAMIDE DEA**

has not substructure



Informatics Example

- ❖ Solubility of theophylline
- ❖ Often delivered in liquid form with mixed solvents: optimising proportion of drug is important
- ❖ Consider a scenario where:
 - all data was provided in *Mixtures InChI* form
 - these data exist in openly available repositories
- ❖ Query:
 - check that *theophylline* is present and has concentration
 - check that other ingredients are *solvents*
- ❖ Consider 4 papers with relevant solubility, published over 20 years...

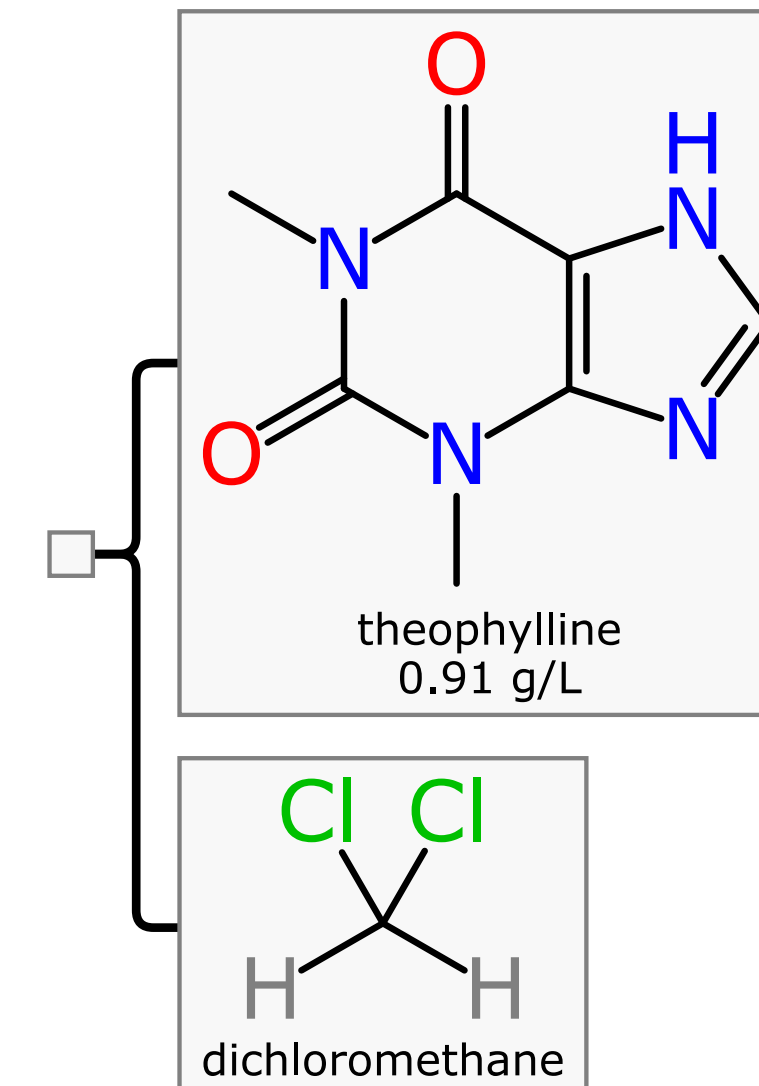
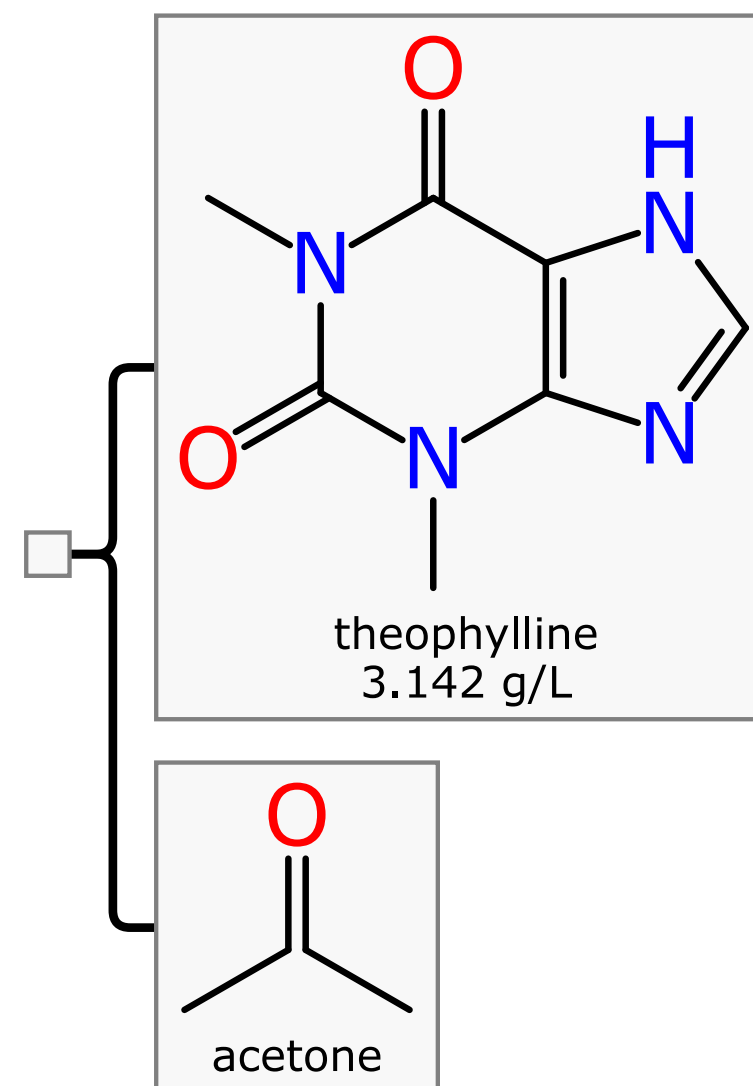
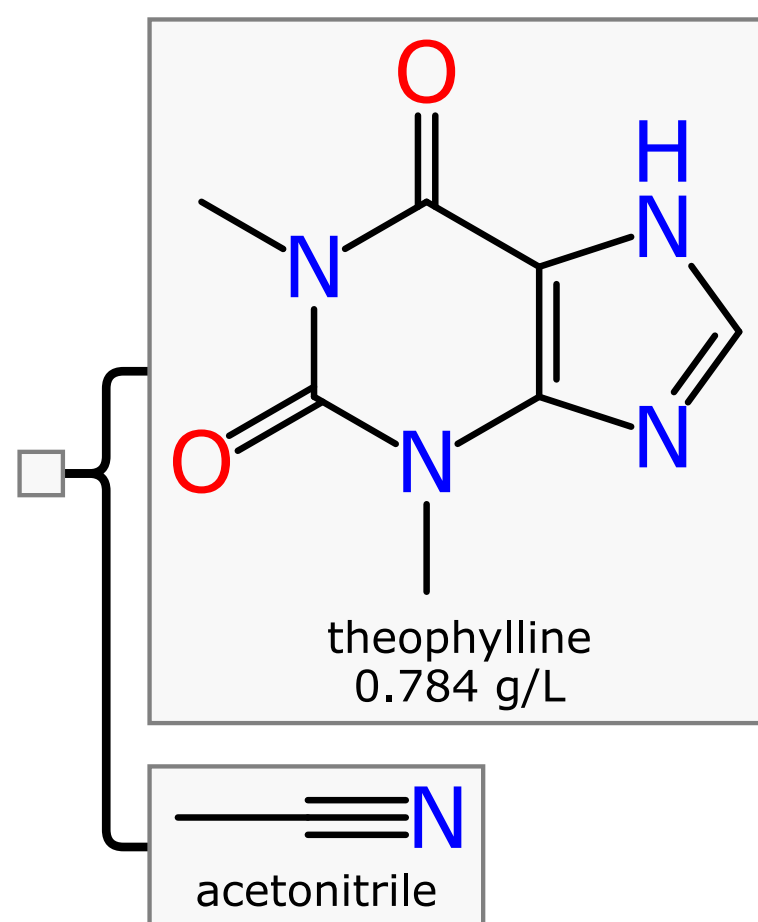
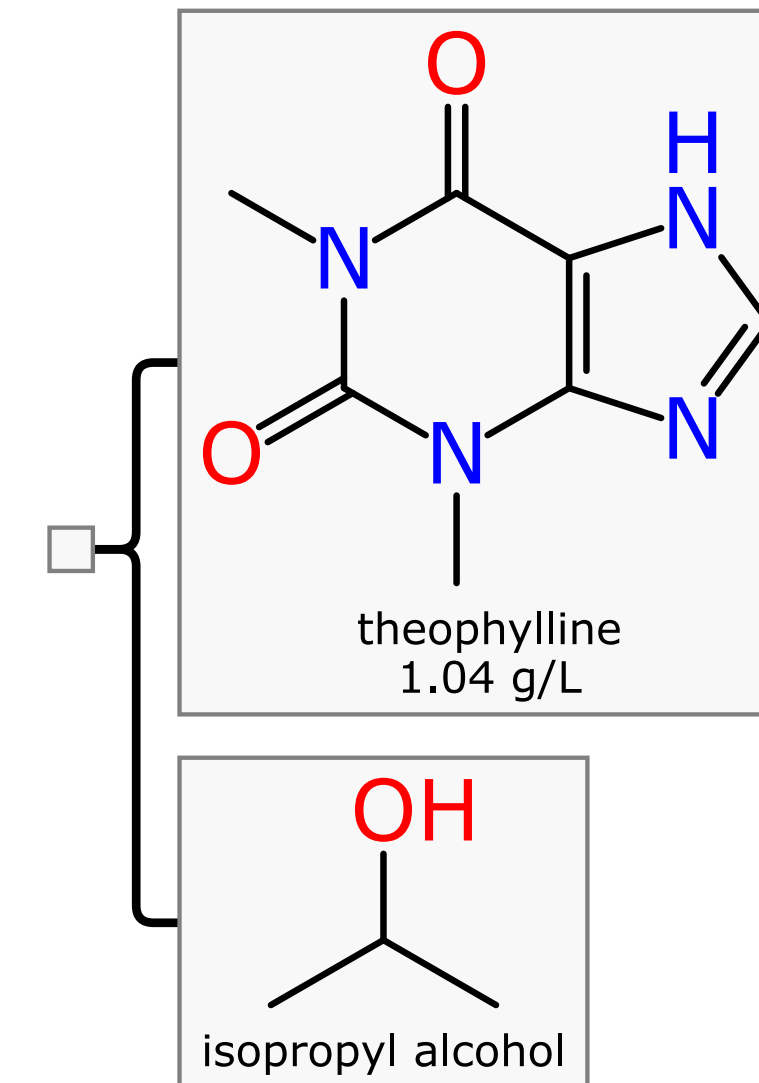
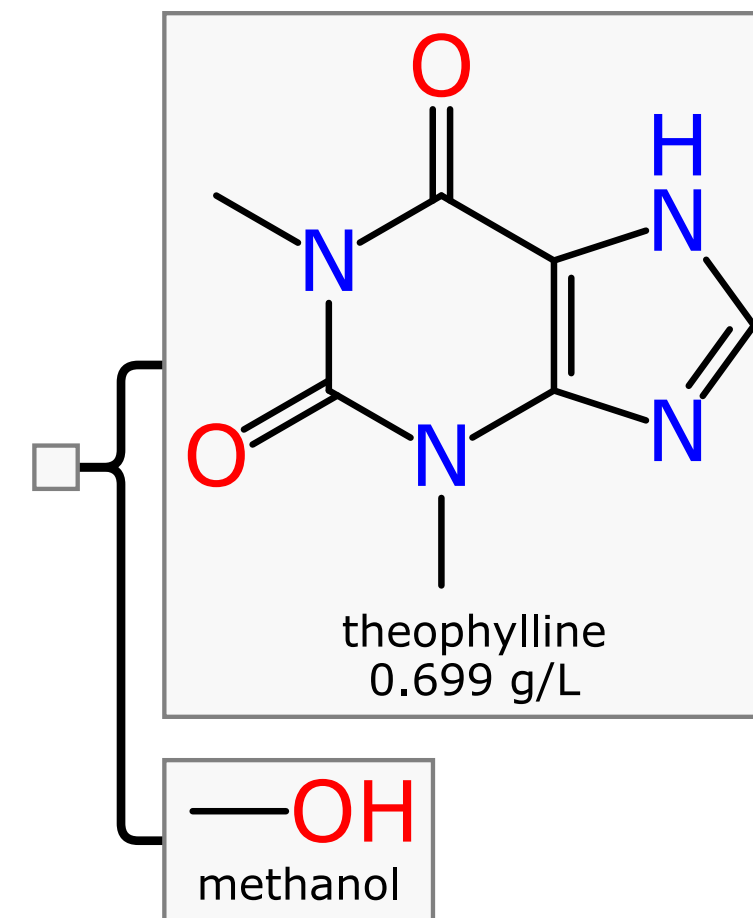
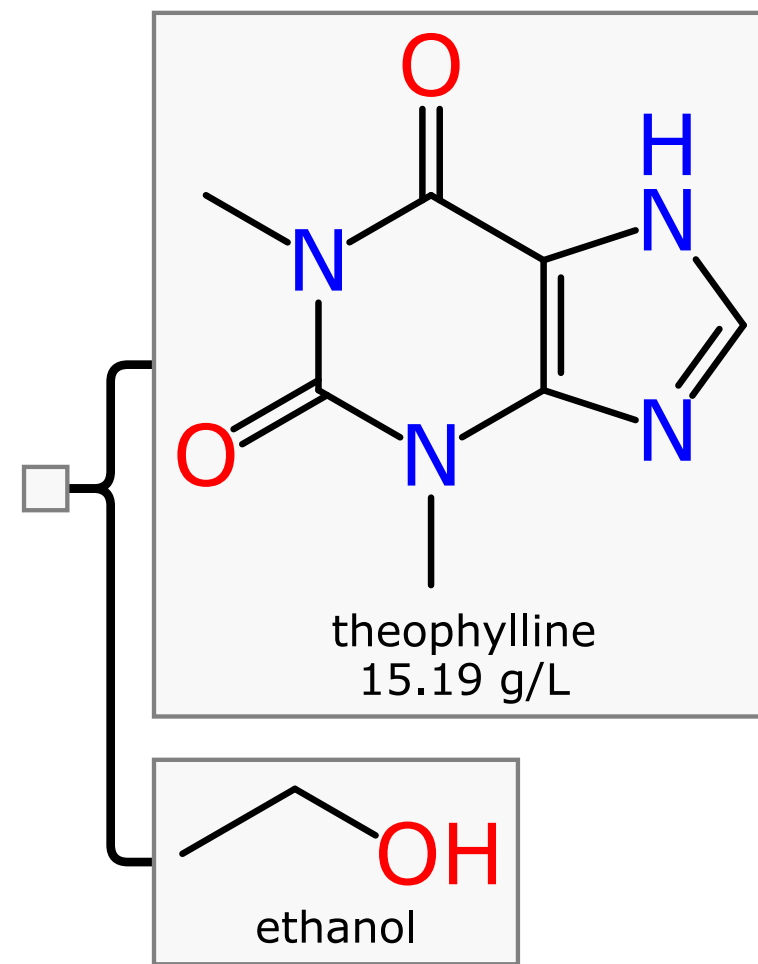


theophylline

nasal anti-inflammatory

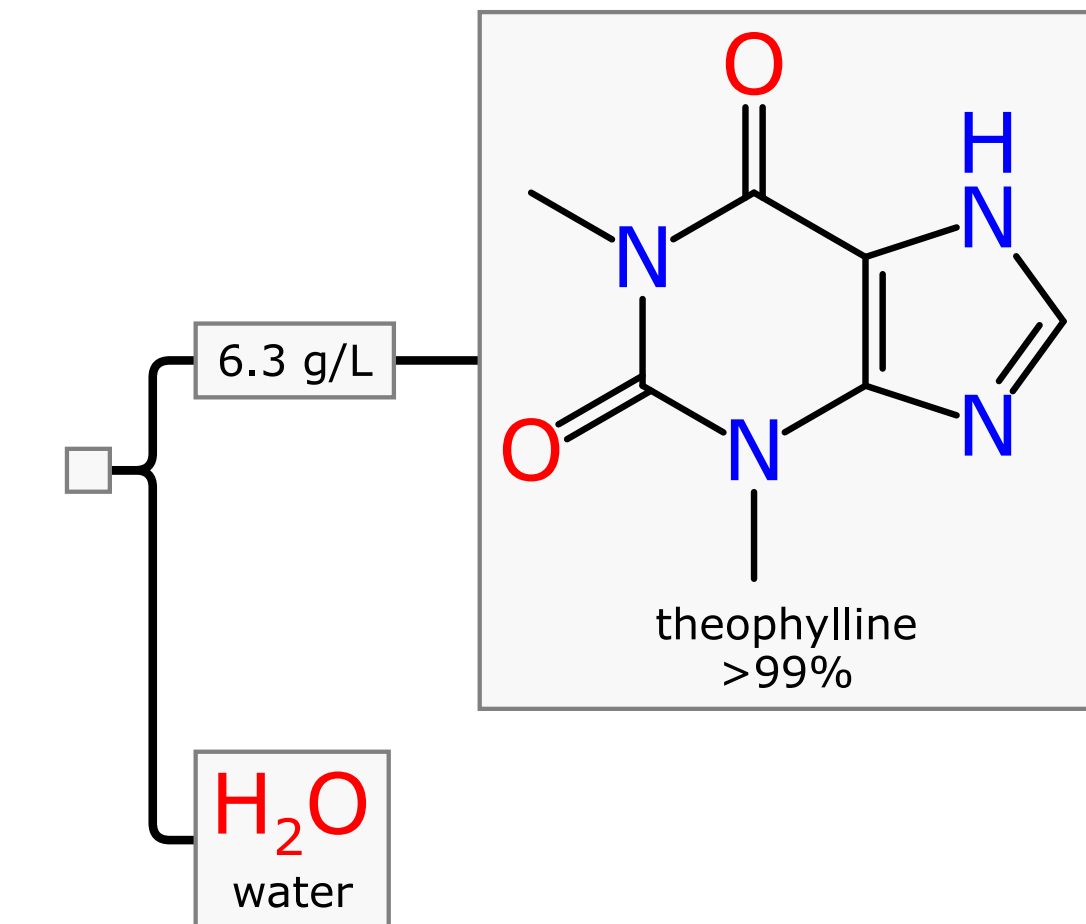
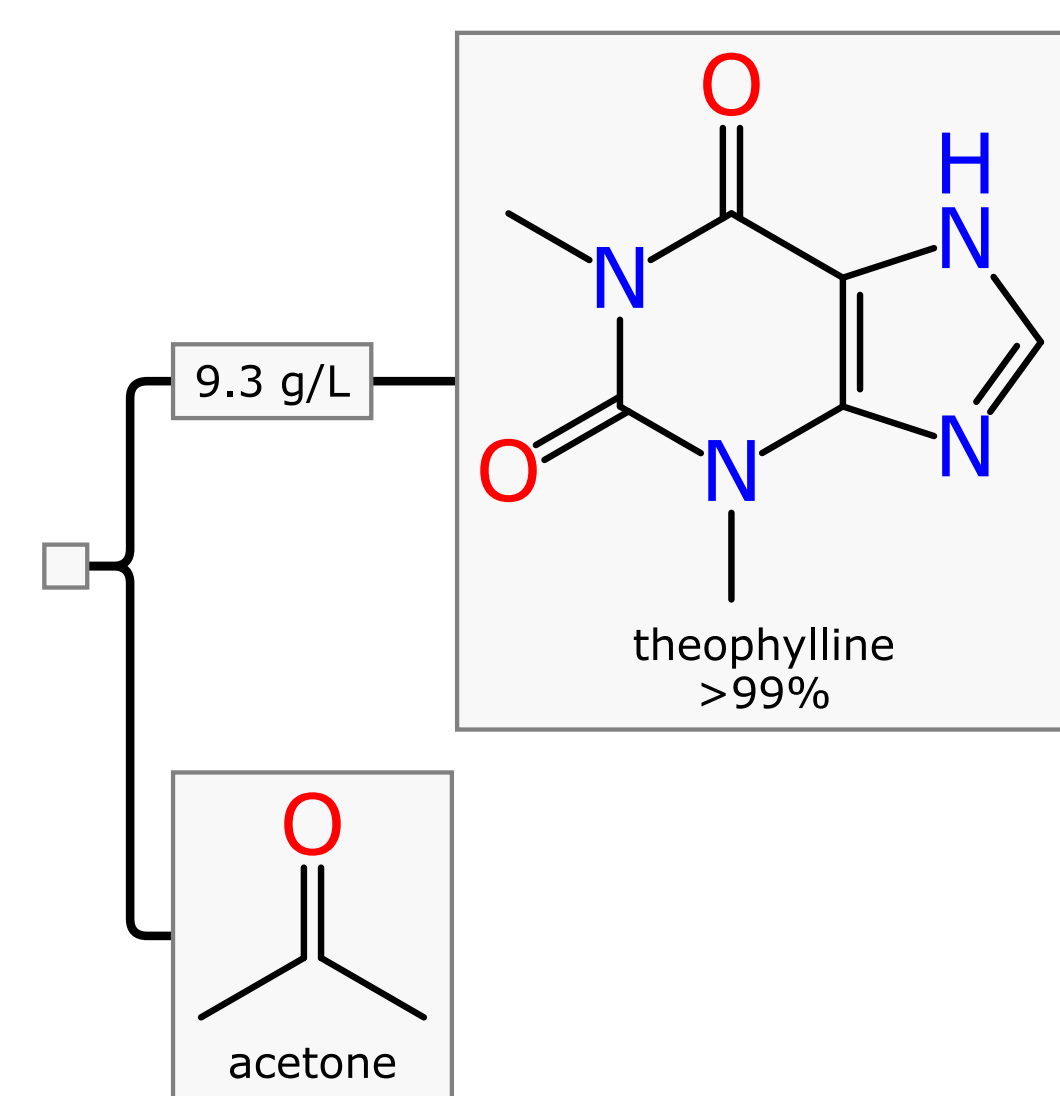
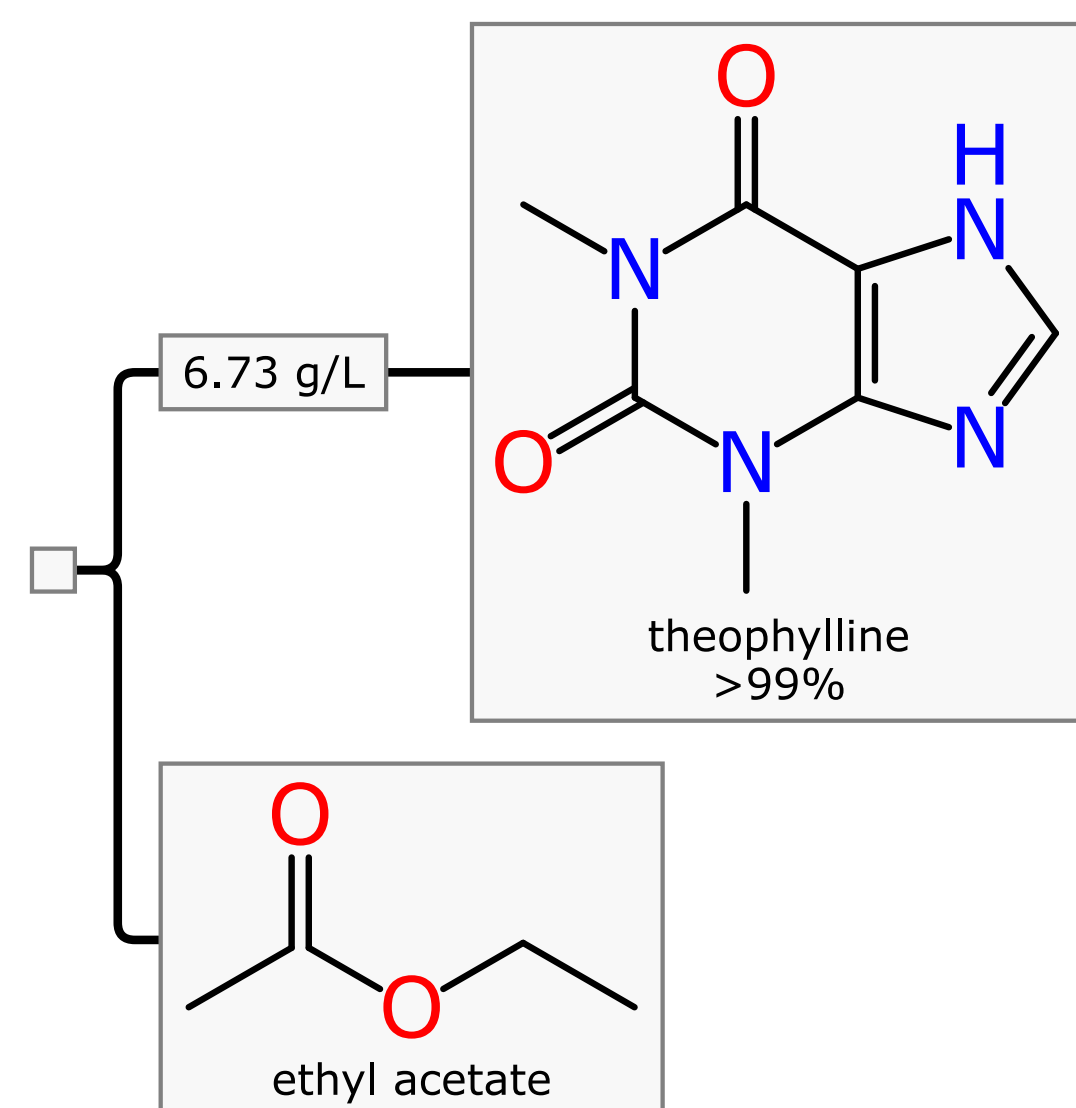
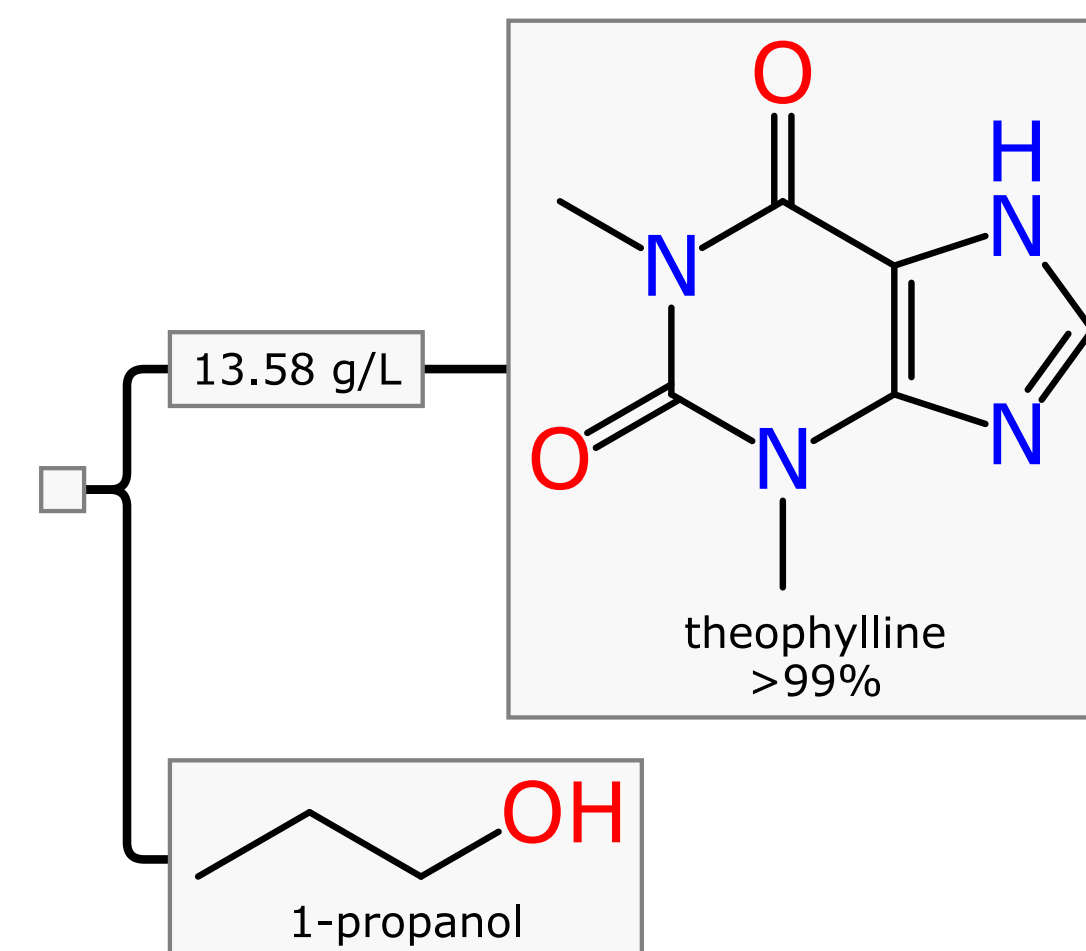
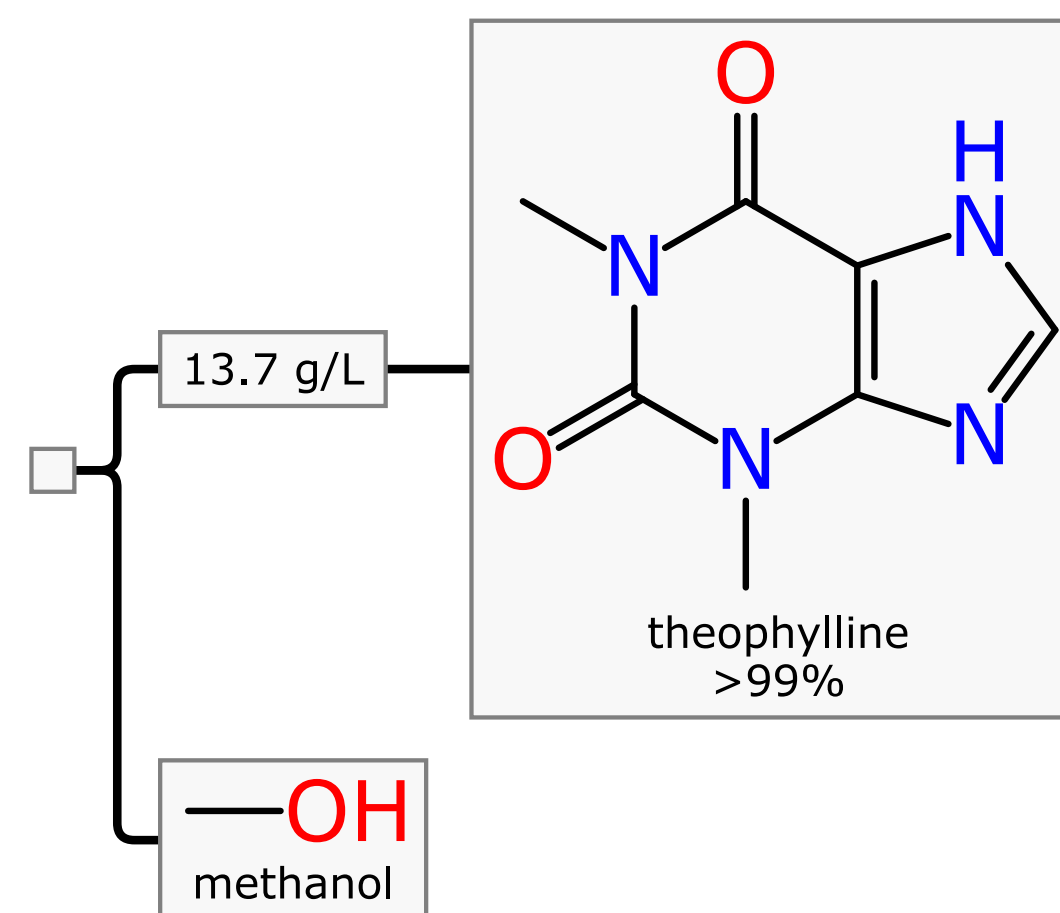
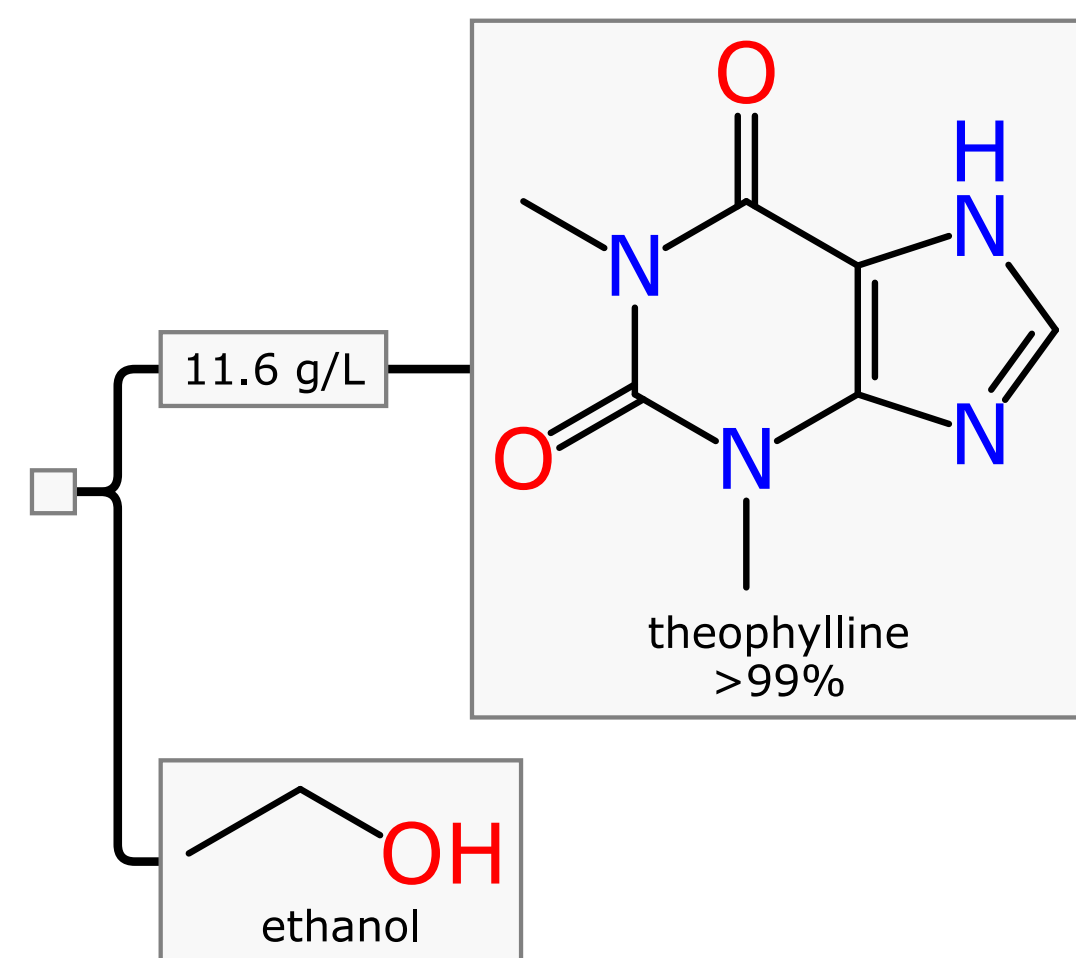
Paper #1

❖ Valizadeh et al, *Adv. Pharm. Bull.* (2011), DOI 10.5681/apb.2011.003



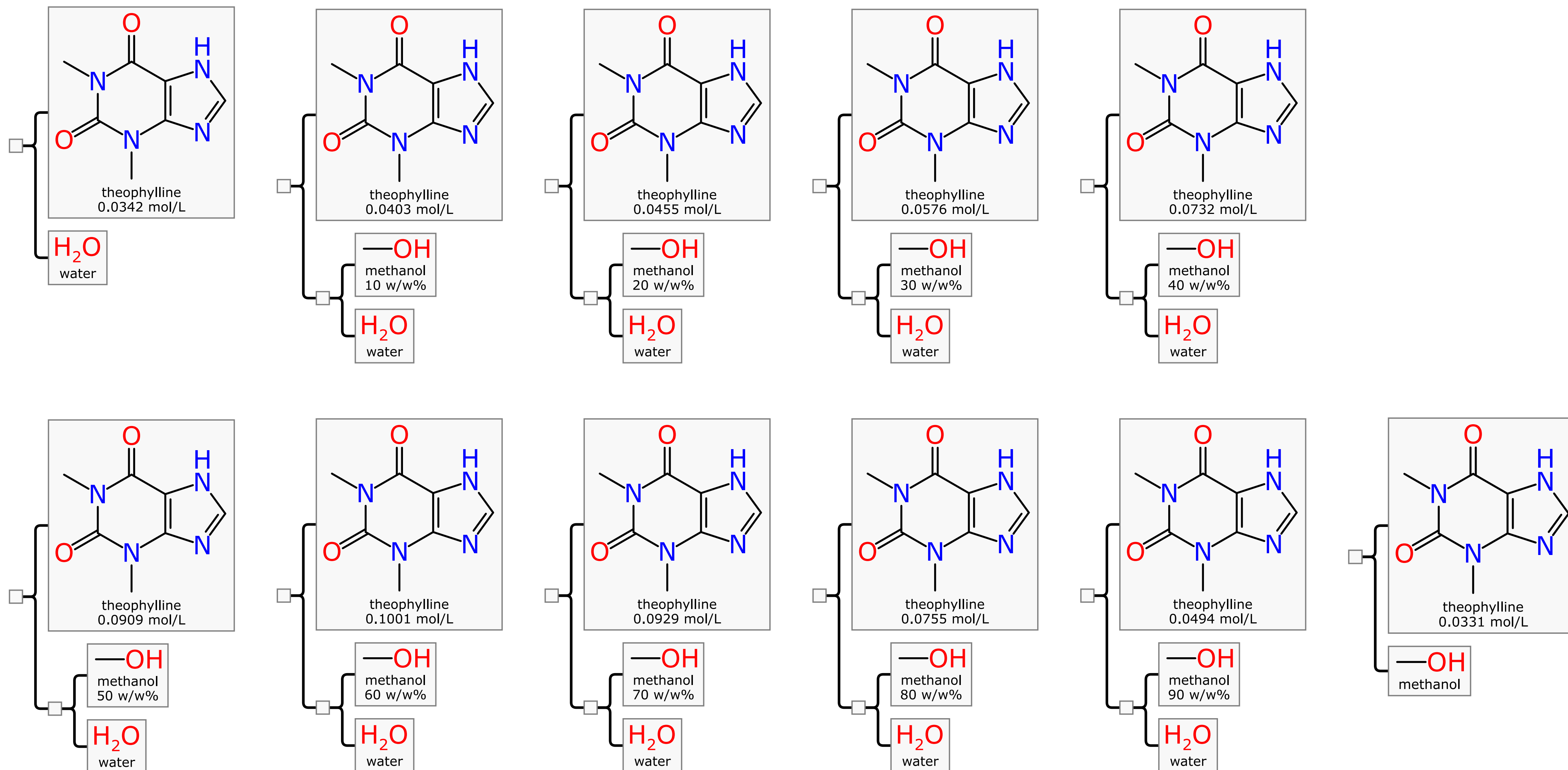
Paper #2

❖ Yan et al, *J. Chem. Eng. Data* (2017), DOI 10.1021/acs.jced.7b00065



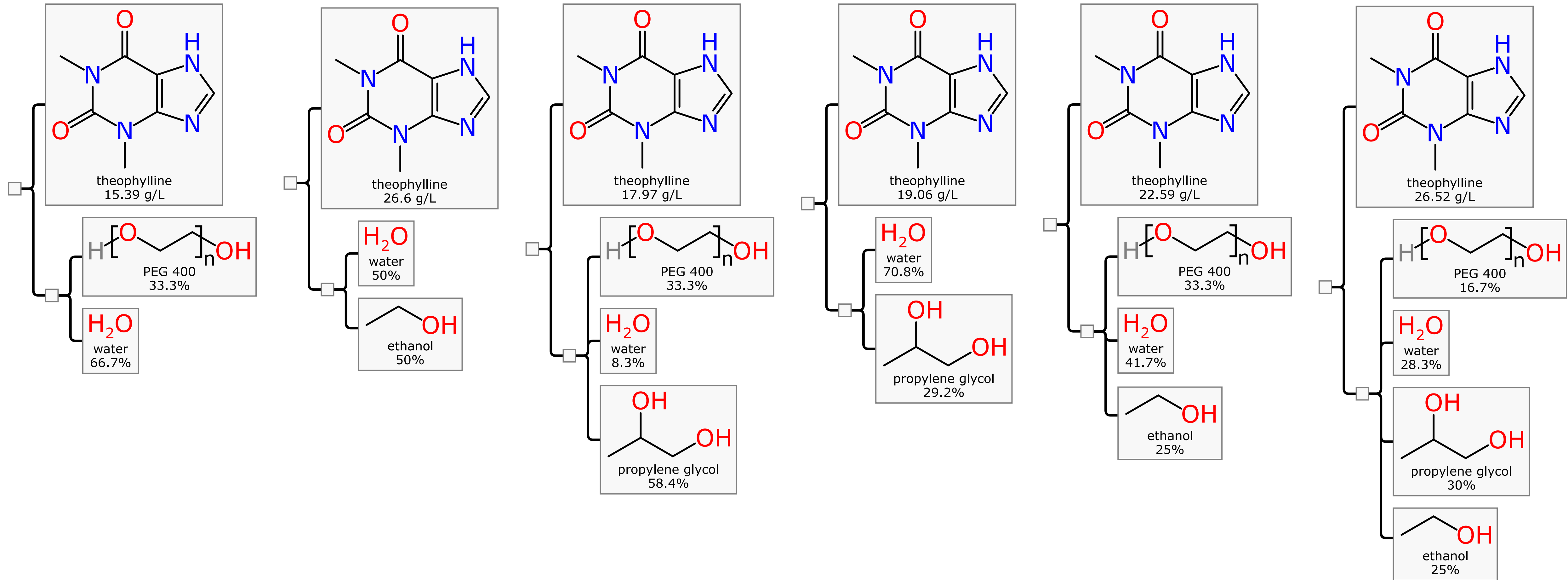
Paper #3

❖ Martínez et al, *J. Solution Chem.* (2017), DOI 10.1007/s10953-017-0666-z



Paper #4

❖ Campisi et al, *J. Pharm. Biomed.* (1998), DOI 10.1016/S0731-7085(98)00175-7



+ 14 more measurements

All Together for QSAR

Solubility	<chem>H2O</chem>	<chem>—OH</chem>	<chem>CCO</chem>	<chem>CCCO</chem>	<chem>CC(O)C</chem>	<chem>CC(O)CO</chem>	<chem>H[OCH2]nOH</chem>	<chem>CC(=O)C</chem>	<chem>CC(=O)OCC</chem>	<chem>C#N</chem>	<chem>CCl(Cl)C</chem>
0.699		1									
15.19			1								
1.04					1						
3.142								1			
0.784										1	
0.91											1
6.3	1										
13.7		1									
11.6			1								
13.58				1							
6.73									1		
9.3								1			
8.20	0.8	0.2									
16.38	0.5	0.5									
13.60	0.2	0.8									
	(+8 more similar)										
15.39	0.333						0.667				
26.6	0.5		0.5								
17.97	0.083					0.584	0.333				
19.06	0.708					0.292					
22.59	0.417		0.25				0.333				
26.52	0.283		0.25			0.3	0.167				
	(+14 more similar)										

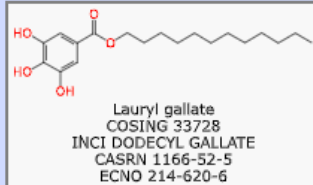

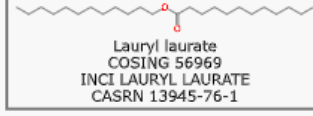
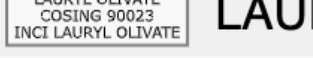
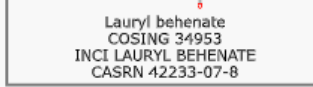
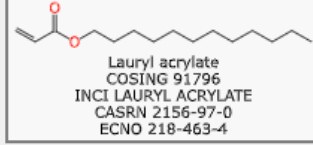

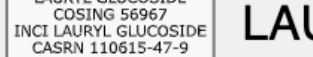
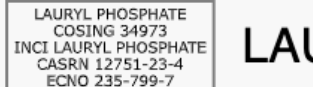
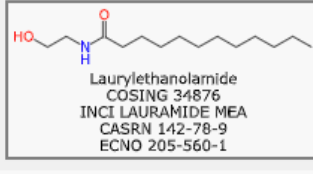
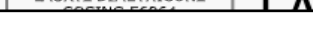
Source Data & Inventory

❖ Gather public content like INCI and UNII:

Lookup Component Close Use

lauryl

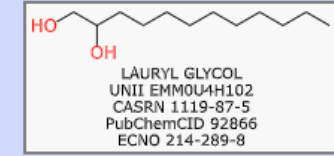
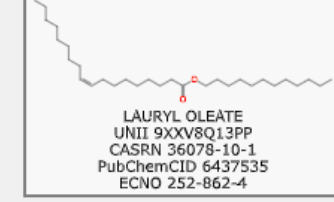
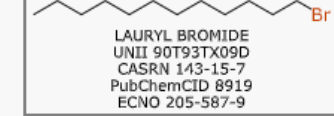
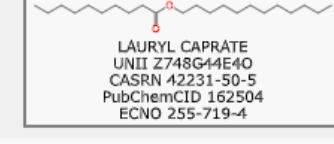
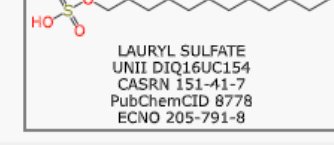
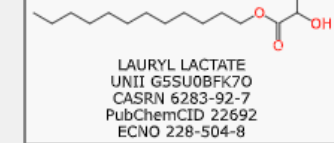
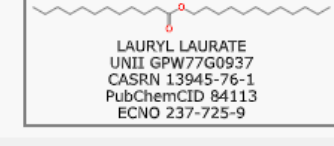
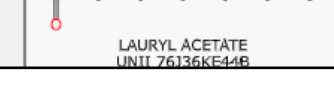
Fine Chemicals FDA Substances **Cosmetic Ingredients**

 <p>Lauryl gallate COSING 33728 INCI DODECYL GALLATE CASRN 1166-52-5 ECNO 214-620-6</p>	Lauryl gallate
 <p>LAURYL COCOATE COSING 34955 INCI LAURYL COCOATE</p>	LAURYL COCOATE
 <p>Lauryl laurate COSING 56969 INCI LAURYL LAURATE CASRN 13945-76-1</p>	Lauryl laurate
 <p>LAURYL OLIVATE COSING 90023 INCI LAURYL OLIVATE</p>	LAURYL OLIVATE
 <p>Lauryl behenate COSING 34953 INCI LAURYL BEHENATE CASRN 42233-07-8</p>	Lauryl behenate
 <p>Lauryl acrylate COSING 91796 INCI LAURYL ACRYLATE CASRN 2156-97-0 ECNO 218-463-4</p>	Lauryl acrylate
 <p>LAURYL MALAMIDE COSING 56970 INCI LAURYL MALAMIDE</p>	LAURYL MALAMIDE
 <p>LAURYL GLUCOSIDE COSING 56967 INCI LAURYL GLUCOSIDE CASRN 110615-47-9</p>	LAURYL GLUCOSIDE
 <p>LAURYL PHOSPHATE COSING 34973 INCI LAURYL PHOSPHATE CASRN 12751-23-4 ECNO 235-799-7</p>	LAURYL PHOSPHATE
 <p>Laurylethanolamide COSING 34876 INCI LAURAMIDE MEA CASRN 142-78-9 ECNO 205-560-1</p>	Laurylethanolamide
 <p>LAURYL DIMETHICONE</p>	LAURYL DIMETHICONE

Lookup Component Close Use

lauryl

Fine Chemicals FDA Substances **Cosmetic Ingredients**

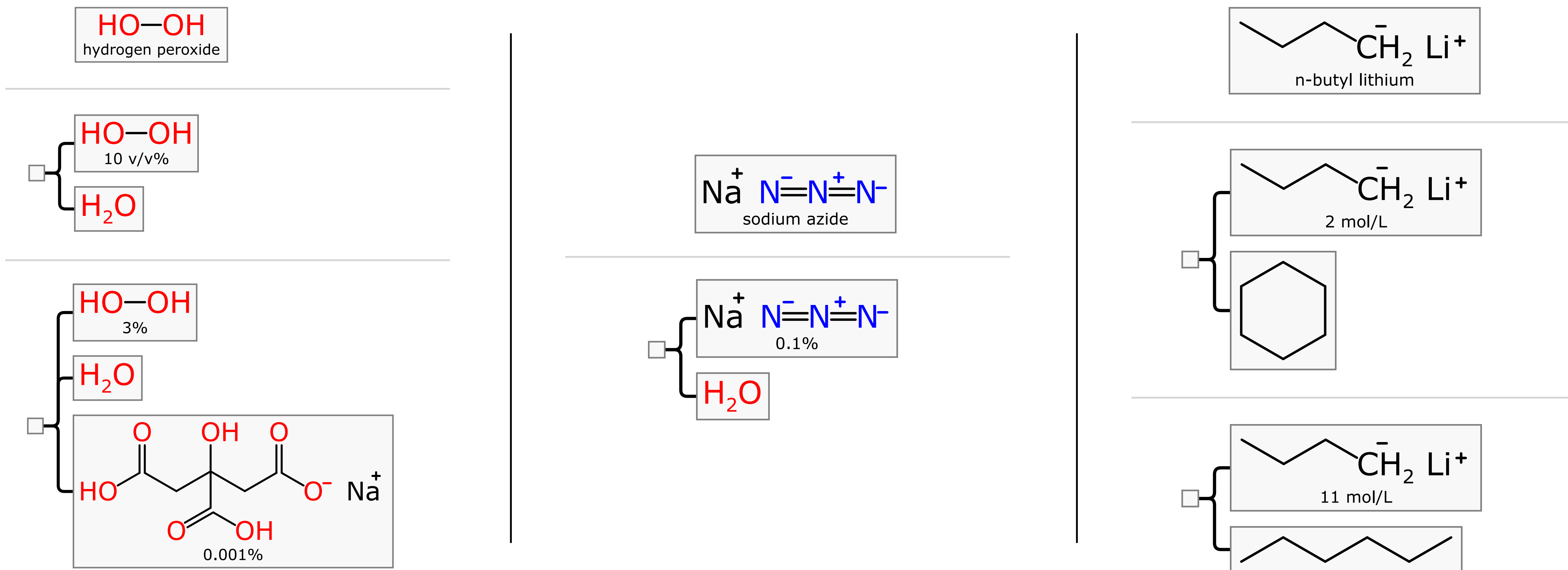
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 <p>LAURYL OLEATE UNII 9XXV8Q13PP CASRN 36078-10-1 PubChemCID 6437535 ECNO 252-862-4</p>	LAURYL OLEATE
 <p>LAURYL BROMIDE UNII 90T93T409D CASRN 143-15-7 PubChemCID 8919 ECNO 205-587-9</p>	LAURYL BROMIDE
 <p>LAURYL CAPRATE UNII Z748G4E40 CASRN 42231-50-5 PubChemCID 162504 ECNO 255-719-4</p>	LAURYL CAPRATE
 <p>LAURYL SULFATE UNII D1Q16UC154 CASRN 151-41-7 PubChemCID 8778 ECNO 205-791-8</p>	LAURYL SULFATE
 <p>LAURYL LACTATE UNII G5SU0BFK7O CASRN 6283-92-7 PubChemCID 22692 ECNO 228-504-8</p>	LAURYL LACTATE
 <p>LAURYL LAURATE UNII GPW77G0937 CASRN 13945-76-1 PubChemCID 84113 ECNO 237-725-9</p>	LAURYL LAURATE
 <p>LAURYL ACETATE UNII 76136K44B</p>	LAURYL ACETATE

❖ Chemical Abstracts in mixture form would be nice

❖ Reagents and materials from vendors: could search, copy, paste from site

Hazards

- ❖ Automated lookup of hazard classifications, toxicity data, etc. needs structures *and* mixture context... each of these is not like the other



- ❖ Machine readability and open access are both major hurdles

Longevity

- ❖ Any ELN, private registration system or public database:
 - capture data in *machine readable form*
 - if a machine can understand it, so can a human
 - if standards are followed, data will always be interpretable
 - data can be shared as much or as little as needed
- ❖ Sophisticated queries and analysis become possible
- ❖ Institutional knowledge does not evaporate
- ❖ An open ecosystem means that tools will evolve
 - tools can be free or proprietary, general purpose or specific

Questions?

Journal of Cheminformatics (2019)
[10.1186/s13321-019-0357-4](https://doi.org/10.1186/s13321-019-0357-4)

❖ Contact:

- ▶ Leah R. McEwen irm1@cornell.edu (Cornell University, IUPAC/InChI Trust)
- ▶ Alex M. Clark alex@collaborativedrug.com (Collaborative Drug Discovery)