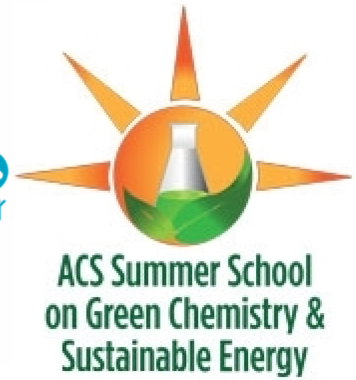
Incorporating chemical safety into green chemistry graduate research and undergraduate curriculum

Kendra Denlinger*, Heather Hopgood, Rebecca Alice Haley, Jessica Ringo, and Anushree Das

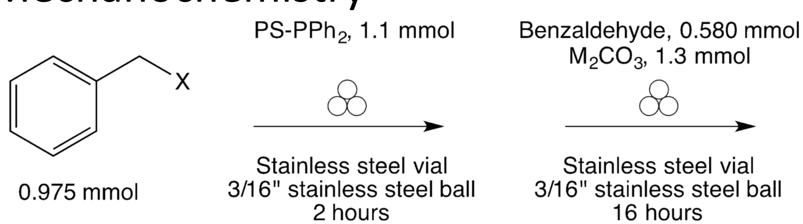
23rd Annual Green Chemistry & Engineering Conference/9th International Conference on Green & Sustainable Chemistry

June 13, 2019

Green chemistry + chemical safety



Mechanochemistry



GCI, OPA, Education internship

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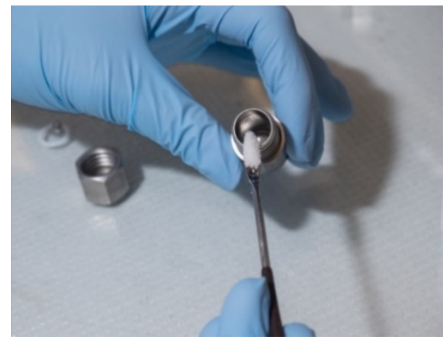
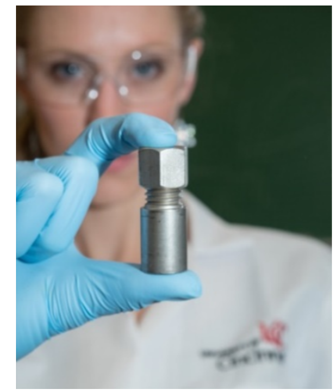
Graduate research in mechanochemistry





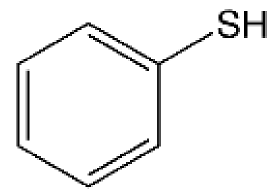
Lessons learned

Mack Lab Safety Form for Ordering Toxic Chemicals

It is mandatory to fill out this form if the chemical you are ordering is labeled with any of the following HCS Pictograms:

GHS Label elements, including precautionary statements

Pictogram



Chemical name:

Signal word Danger

Chemical structure:

Hazard statement(s)

Using the MSDS or SD
hazards, including rou

H226	Flammable liquid and vapour.
H300 + H310 + H330	Fatal if swallowed, in contact with skin or if inhaled
H315	Causes skin irritation.

$LC_{50} \leq 2.0$ mg/L

Provide a detailed exp

h - T32808

For each of the human
here using the table b
obtained from the MS
sources.

Hazard Statement	LD_{50}

H319	Causes serious eye irritation.
H335	May cause respiratory irritation.
H361	Suspected of damaging fertility or the unborn child.
H371	May cause damage to organs (Nervous system) if swallowed.
H372	Causes damage to organs (Kidney) through prolonged or repeated exposure if swallowed.
H410	Very toxic to aquatic life with long lasting effects.

What alternatives to t
for this chemical?

Now that the possible consequences of using this chemical have been described, please explain how the benefits to your research outweigh the potential costs to our health.

https://ehs.unl.edu/sop/s-health_hazards_haz_assessment_risk_min.pdf

Using a green chemistry metric

Prevent waste

- Yield
- Atom economy (Trost, Barry. *Science*, **1991**, *254*, 1471-1477.)
- E-factor (Sheldon, Roger A. *Green Chem.*, **2017**, *19*, 18-43.)
- Reaction mass efficiency (*Green Chemistry Metrics*)
- EcoScale (Van Aken et.al. *Beilstein J. of Org. Chem.* **2006**, *3*.)

Explicitly addresses safety

The Wittig reaction as an example

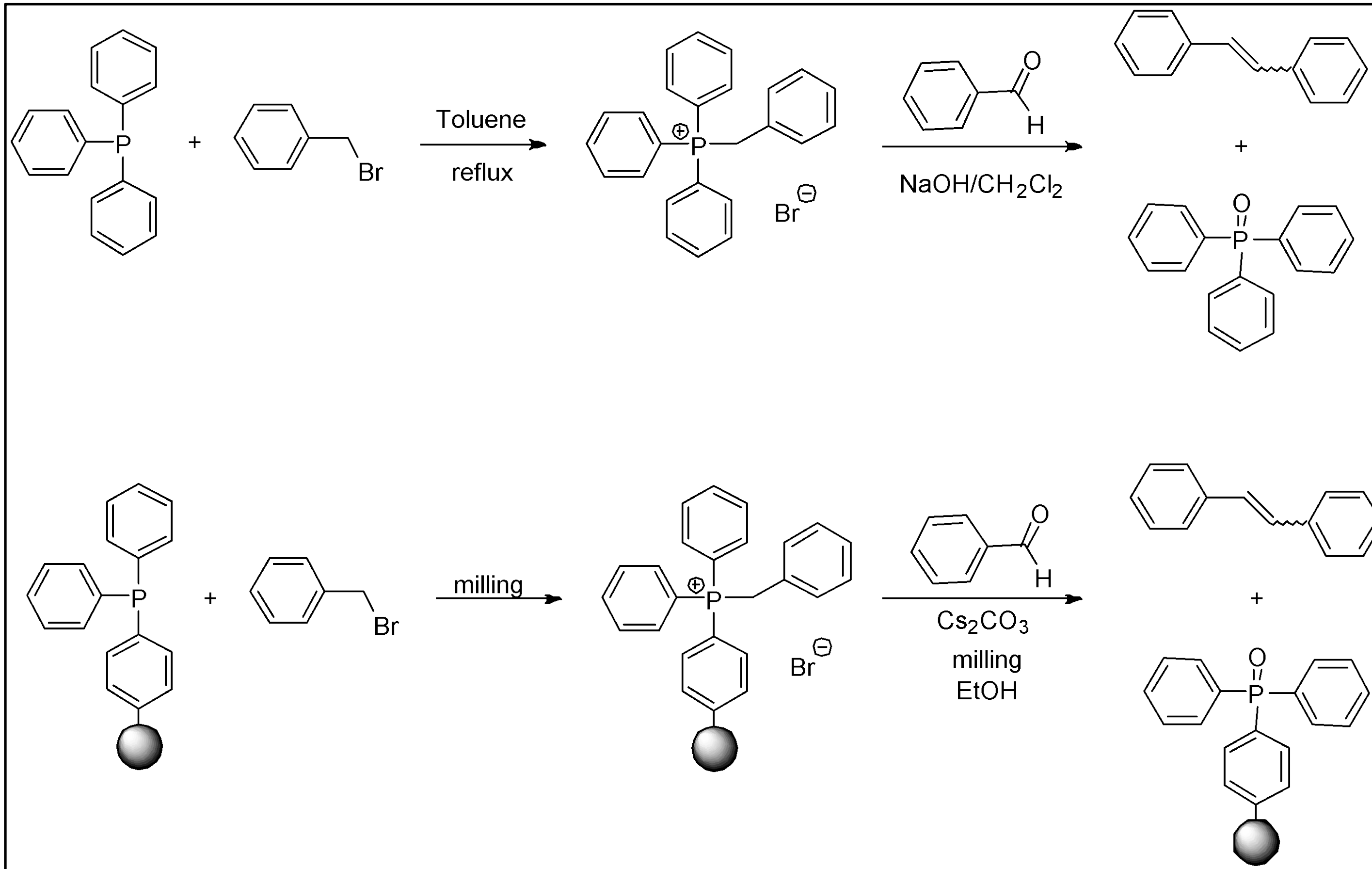


Figure 1. Comparasion of soluion based Wittig (top) against mechanochemical Wittig (botom)

Leahy, Kendra; Mack, Anthony; Mack, James. "An EcoScale Comparison of Mechanochemistry and Solution Based Reactions." *Green Technologies for the Environment*. Obare et. al. ACS Symposium Series; American Chemical Society: Washington, DC, **2014**. 129-137. Print.

The EcoScale

Parameter	Penalty points
1. Yield	(100 – %yield)/2
2. Price of reaction components (to obtain 10 mmol of end product)	
Inexpensive (< $10)	0
Expensive (> $10 and < $50)	3
Very expensive (> $50)	5
3. Safety[a]	
N (dangerous for environment)	5
T (toxic)	5
F (highly flammable)	5
E (explosive)	10
F+ (extremely flammable)	10
T+ (extremely toxic)	10
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals[b]	1
Unconventional activation technique[c]	2
Pressure equipment, > 1 atm[d]	3
Any additional special glassware	1
(Inert) gas atmosphere	1
Glove box	3
5. Temperature/time	
Room temperature, < 1 h	0
Room temperature, < 24 h	1
Heating, < 1 h	2
Heating, > 1 h	3
Cooling to 0°C	4
Cooling, < 0°C	5
6. Workup and purification	
None	0
Cooling to room temperature	0
Adding solvent	0
Simple filtration	0
Removal of solvent with bp < 150°C	0
Crystallization and filtration	1
Removal of solvent with bp > 150°C	2
Solid phase extraction	2
Distillation	3
Sublimation	3
Liquid-liquid extraction[e]	3
Classical chromatography	10

Van Aken, Koen; Strekowski, Lucjan; Patiny, Luc. "EcoScale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters." *Beilstein J. of Org. Chem.* **2006**, *3.*

The EcoScale

3. Safety

Safety is of paramount importance when carrying out organic chemistry experiments. Working with chemicals is never without a risk, and it is necessary to fully understand any potential hazard. Organic compounds can be carcinogenic, mutagenic, teratogenic, corrosive, lachrymatic, highly flammable or explosive, among other things. In addition, the hazard can increase over time, and photooxidation of ether to generate explosive peroxides is a good example. It must also be emphasised that it takes a long time before the safety profiles of new products are fully characterized. Finally, one should never forget that the combination of certain individual compounds can create a hazardous situation (e.g. exothermic reaction between acids and bases).

For assessing these hazards, a wide variety of information is readily available, such as the health and safety information in Risk/Safety phrases, the Material Safety Data Sheets, and the hazard warning symbols on the containers. In order to avoid a complex calculation, the hazard warning symbols are taken as a reference. In particular, each reaction component labelled with T+ (extremely toxic), F+ (extremely flammable) or E (explosive) is penalized with 10 points while reaction components labelled with T (toxic), F (highly flammable) or N (dangerous to the environment) are given 5 penalty points. [22] As can be seen from Table 1, the use of unsafe compounds can downgrade the overall quality of synthesis to the greatest extent in comparison to other entries.

Van Aken, Koen; Strekowski, Lucjan; Patiny, Luc. "EcoScale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters." *Beilstein J. of Org. Chem.* **2006**, *3.*

Wittig reaction comparison

Parameter	Penalty points
1. Yield	(100 – %yield)/2
2. Price of reaction components (to obtain 10 mmol of end product)	
Inexpensive (< $10)	0
Expensive (>	
Very expens	
3. Safety[a]	
N (dangerou	
T (toxic)	
F (highly flan	
E (explosive)	
F+ (extreme	
T+ (extreme	
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals[b]	1
Unconventional activation technique[c]	2
Pressure equipment, > 1 atm[d]	3
Any additional special glassware	1
(Inert) gas atmosphere	1
Glove box	3

5. Temperature/time	
Room temperature, < 1 h	0
Room temperature, < 24 h	1
Heating, < 1 h	2
Heating, > 1 h	3
	4
	5
	0
	0
	0
	0
	0
	1
Removal of solvent with bp > 150°C	2
Solid phase extraction	2
Distillation	3
Sublimation	3
Liquid-liquid extraction[e]	3
Classical chromatography	10

	Solution		Mechanochemistry	
Total Penalty Points		65		23
EcoScale rating	100-65	35	100-23	77
Overall Assessment		Inadequate		Excellent

Van Aken, Koen; Strekowski, Lucjan; Patiny, Luc. "EcoScale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters." *Beilstein J. of Org. Chem.* **2006**, *3.*

Leahy, Kendra; Mack, Anthony; Mack, James. "An EcoScale Comparison of Mechanochemistry and Solution Based Reactions." *Green Technologies for the Environment*. Obare et. al. ACS Symposium Series; American Chemical Society: Washington, DC, **2014**. 129-137. Print.

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Green Chemistry class

- Designed at UC by 5 graduate students with help from some faculty members
- Taught as an online course in the spring starting in 2017
- Taught at Xavier as a face-to-face class (Fall 2017)

Haley, Rebecca; Ringo, Jessica; Hopgood, Heather; Denlinger, Kendra Leahy; Das, Anushree; Waddell, Daniel. "Graduate student designed and delivered: An upper-level online course for undergraduates in green chemistry and sustainability." *Journal of Chemical Education*, **2018**, *95*, 560–569.

Green chemistry class overview

Tentative Schedule:

Week	Topic	Assigned Reading
1	Introduction/History	*Deceit and Denial* Chapter 5
2	Introduction/History	
3	12 Principles of Green Chemistry	*Green Chemistry Theory & Practice Chapter 4*
4	Hazard Identification	TBA: [current literature]
5	Metrics: Atom economy, E Factor	
6	Metrics: Reaction mass efficiency, EcoScale	
7	Metrics: Life cycle assessment	Excerpt from *Cradle to Cradle*
8	Issues of Sustainability I	*Deceit and Denial* Chapter 8
9	Issues of Sustainability II	
10	Sustainability: Methodologies	TBA: [current literature]
11	Sustainability: Alternatives	
12	Sustainability: The Elements	
13	Communication I	*Deceit and Denial* Introduction
14	Communication II	

Haley, Rebecca; Ringo, Jessica; Hopgood, Heather; Denlinger, Kendra Leahy; Das, Anushree; Waddell, Daniel. “Graduate student designed and delivered: An upper-level online course for undergraduates in green chemistry and sustainability.” *Journal of Chemical Education*, **2018**, *95*, 560–569.

12 Principles

Greener chemistry is very often safer chemistry, and safer chemistry is very often greener chemistry!

Hazard Identification

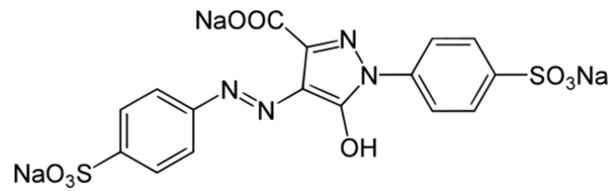
Name of Product: Pumpkin Spice Hershey's Kisses

Ingredient List:

Chemical 2: Yellow 5 Lake*

*A "lake" is a type of dye that has been combined with a salt in order to be more soluble in fats and oils than the dye itself. The following information is about Yellow 5 (the dye itself), whose chemical name is tartrazine.

Chemical structure:



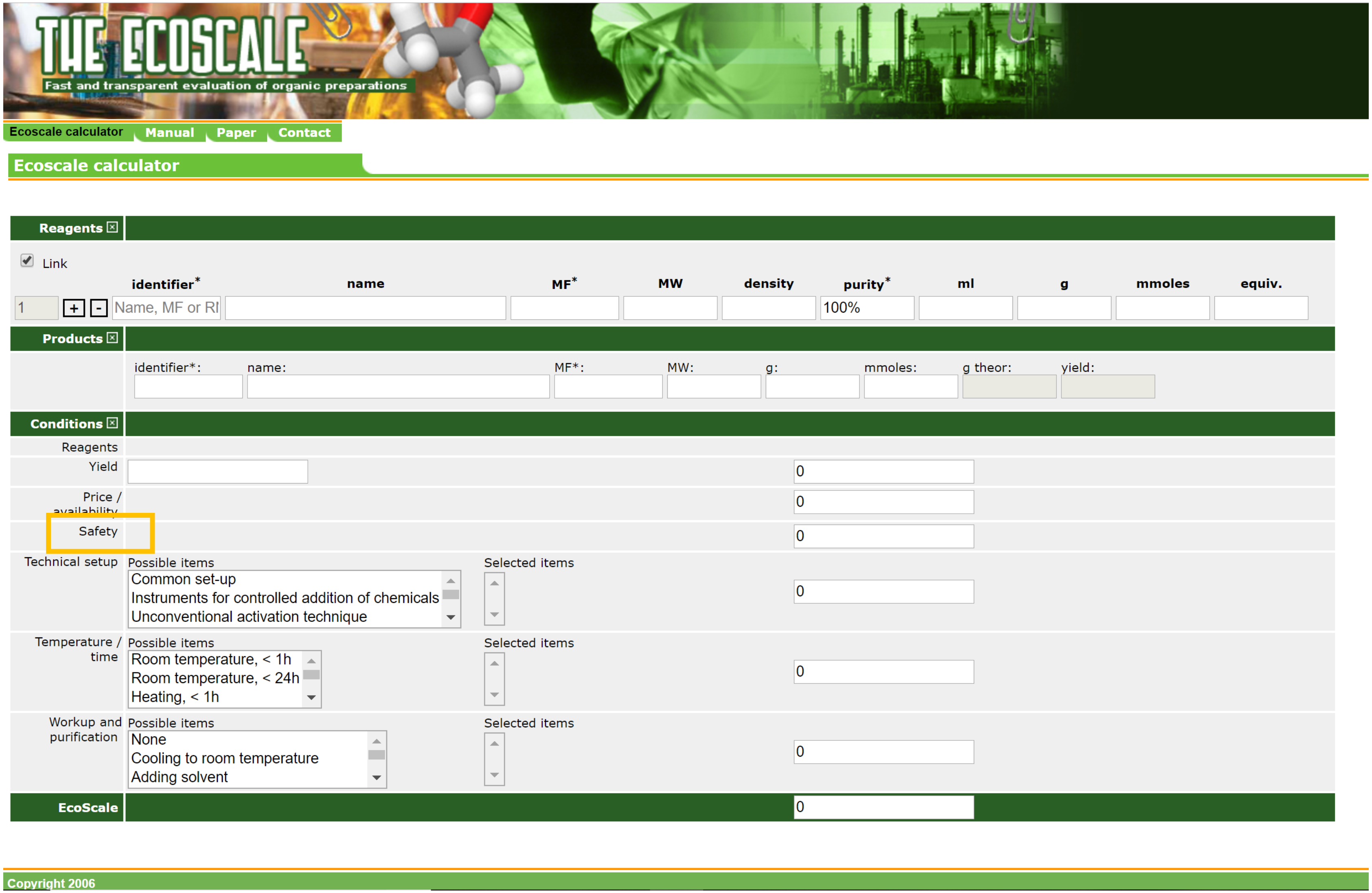
Summary of SDS:
There is one pictogram present, for a health hazard. The signal word is "Danger." Hazard statements include: "May cause an allergic skin reaction" and "May cause allergy or asthma symptoms or breathing difficulties if inhaled." There are many precautionary statements:

Avoid breathing dust/fume/gas/mist/vapours/spray.
Contaminated work clothing should not be allowed out of the workplace.
Wear protective gloves.
In case of inadequate ventilation wear respiratory protection.
IF ON SKIN: Wash with plenty of soap and water.
IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing.
If skin irritation or rash occurs: Get medical advice/attention.
If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician.
Wash contaminated clothing before reuse.
Dispose of contents/container to an approved waste disposal plant.

The only data available about its form is that it's a powder. The oral LD50 (mouse) is 12,750 mg/kg.

Summary of Wikipedia page:
Tartrazine is a synthetic dye used primarily as food coloring (yellow). It can be found in many colored foods, like desserts, candy, beverages, snacks (Doritos, etc.), and other processed foods. According to this page, tartrazine is the most common food coloring to cause allergic and intolerance reactions. These reactions are more common in people with asthma or aspirin intolerance.

Green Chemistry Metrics



http://ecoscale.cheminfo.org/calculator

Alternatives: Solvents

GSK Solvent Selection Guide

	Few issues (bp°C)	Some issues (bp°C)	*Major* issues
Chlorinated	....before using chlorinated solvents, have you considered TBME, isopropyl acetate, ethyl acetate, 2-Methyl THF or Dimethyl Carbonate?		Dichloromethane ** Carbon tetrachloride ** Chloroform ** 1,2-Dichloroethane **
Greenest Option	Water (100°C)		
Alcohols	1-Butanol (118°C) 2-Butanol (100°C)	Ethanol/IMS (78°C) 1-Propanol (97°C) t-Butanol (82°C) 2-Propanol (82°C) Methanol (65°C)	2-Methoxyethanol **
Esters	t-Butyl acetate (95°C) Isopropyl acetate (89°C) Propyl acetate (102°C) Dimethyl Carbonate (91°C)	Ethyl acetate (77°C) Methyl acetate (57°C)	
Ketones		Methyl isobutyl ketone (117°C) Acetone (56°C)	Methyl ethyl ketone
Aromatics		p-Xylene (138°C) Toluene ** (111°C)	Benzene **
Hydrocarbons		Isooctane (99°C) Cyclohexane (81°C) Heptane (98°C)	Petroleum spirit ** 2-Methylpentane Hexane
Ethers		t-Butyl methyl ether (55°C) 2-Methyl THF (78°C) Cyclopentyl methyl ether (106°C)	1,4-Dioxane ** 1,2-Dimethoxyethane ** Tetrahydrofuran Diethyl ether Diisopropyl ether **
Dipolar aprotics		Dimethyl sulfoxide (189°C)	Dimethyl formamide ** N-Methyl pyrrolidone ** N-Methyl formamide ** Dimethyl acetamide ** Acetonitrile

** = EHS Regulatory Alerts: please consult the detailed solvent guide and the GSK Chemicals Legislation Guide for more information

GSK SSG-MC-02 September 2010

http://www.rsc.org/suppdata/gc/c0/c0gc00918k/c0gc00918k.pdf

Alternatives: Solvents

GSK Solvent Selection Guide 2009

Classification	Solvent	CAS number	Melting point °C	Boiling point °C	Waste recycling, incineration, VOC, and biotreatment issues	Environmental Impact fate and effects on the environment	Health acute and chronic effects on human health and exposure potential	Flammability & Explosion storage and handling	Reactivity/ Stability factors affecting the stability of the solvent	Life Cycle Score Environmental Impacts to produce the solvent	Legislation Flag alerts regulatory restrictions
Greenest	Water	7732-18-5	0	100	4	10	10	10	10	10	
Alcohols	1-Butanol	71-36-3	-89	118	5	7	5	8	[illegible]	5	
	2-Butanol	78-92-2	-115	100	4	6	8	7	9	6	
	Ethanol/IMS	64-17-5	-114	78	3	8	8	6	9	9	
	t-Butanol	75-65-0	25	82	3	9	6	6	10	8	
	Methanol	67-56-1	-98	65	4	9	5	5	10	9	
	2-Propanol	67-63-0	-88	82	3	9	8	6	8	4	
	1-Propanol	71-23-8	-127	97	4	7	5	7	10	7	
	2-Methoxyethanol	109-86-4	-85	124	3	8	2	7	6	7	
	t-Butyl acetate	540-88-5	-78	95	6	9	8	6	10	8	

http://www.rsc.org/suppdata/gc/c0/c0gc00918k/c0gc00918k.pdf

Where else could safety be incorporated?

RAMP Principles

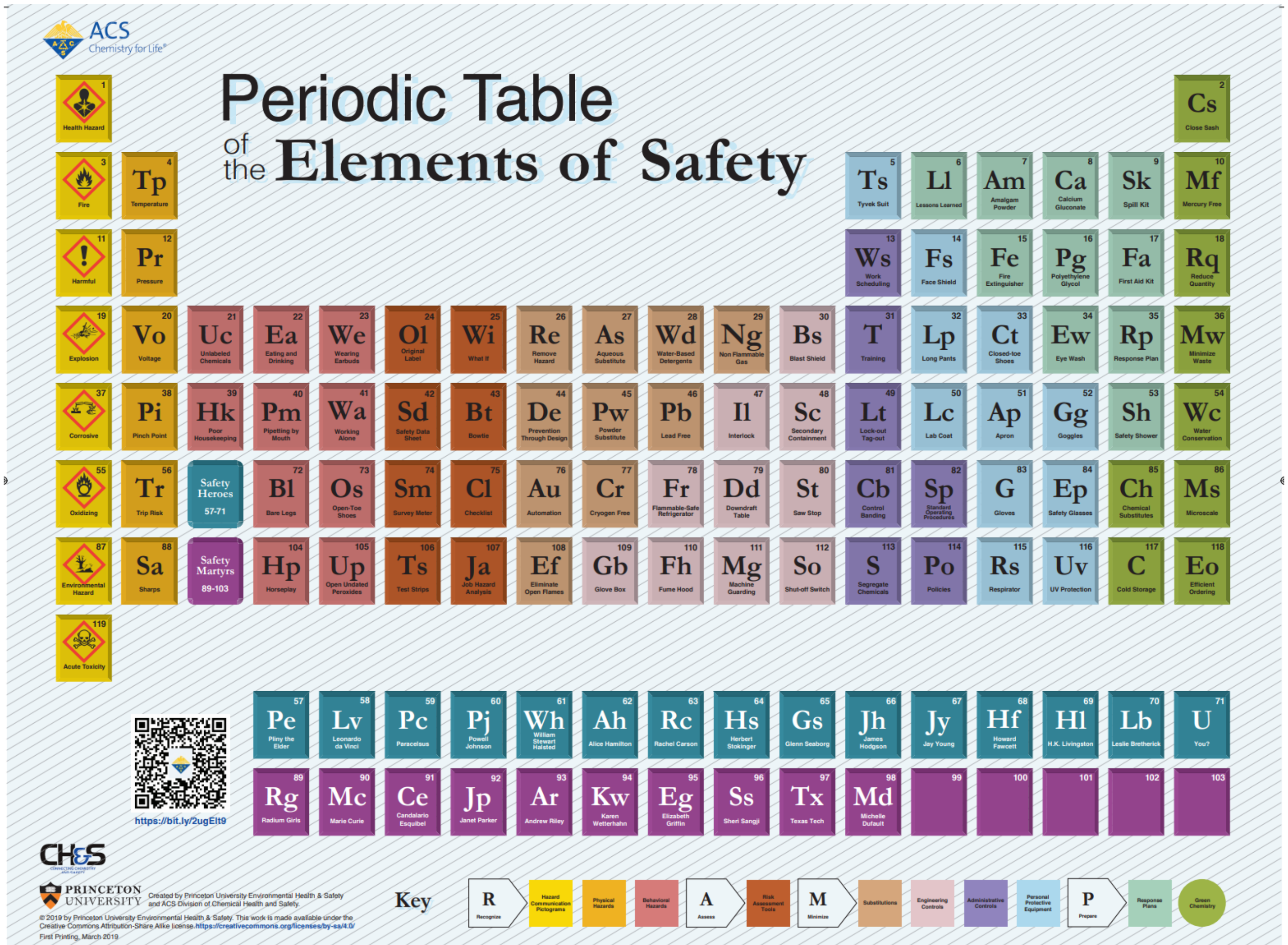
R	A	M	P
Recognize Hazards	Assess the Risks of Hazards	Minimize the Risks of Hazards	Prepare for Emergencies

Learn more about the origins of RAMP: "RAMPing up safety education: The time is now" - *C&EN*

http://www.acs.org/safety

Hill and Finster *Laboratory Safety for Chemistry Students*

Where else could safety be incorporated?



Recognize the hazards and assess the risks.

What if the risk is too high?

Green chemistry.

https://ehs.princeton.edu/news/elements-of-safety-poster-acs

Where else could safety be incorporated?

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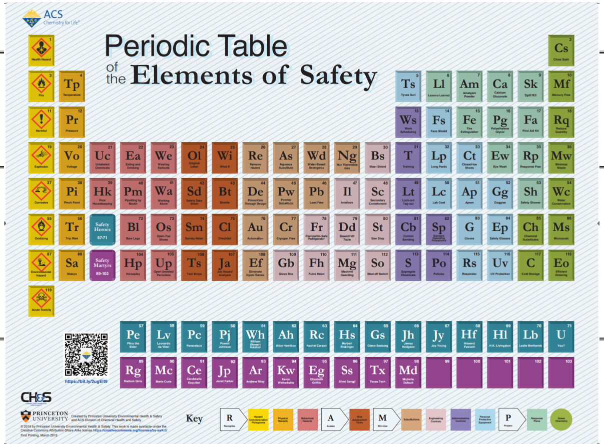

Hill and Finster *Laboratory Safety for Chemistry Students*

In what other courses could you teach safety?

- All of them…duh!
- Undergraduate organic chemistry laboratory
  - Division of Chemical Health and Safety Innovative Project Grant to design an electronic tool to guide students through the process of risk assessment

eRAMP

Job Hazard Analysis te

RAMP Principles

R	A	M	P
Recognize Hazards	Assess the Risks of Hazards	Minimize the Risks of Hazards	Prepare for Emergencies

Table 9–1

Job Location:	**Labor**
Activity or Job	
Completed By	
Equipment and Chemicals Required	

Work Steps and Tasks *Describe the tasks or steps involved in the work in the order performed*	**Hazards Identified for each Task/Step**	**Risk Level** *Risk Nomogram can be used (see APPENDIX B)*	**Control/Safe Work Procedures for each Task/Step** *Controls to be implemented*
Add rows, as needed			

Hazards Checklist [Note: This section can be modified, as needed. See Table D-1: Common Hazards and Descriptions in APPENDIX D.]	
Can someone be exposed to chemicals?	If so, what is the nature of the chemical hazard?
Can someone slip, trip, or fall?	Can someone injure someone else?
Can someone be caught in anything?	Can someone strike against or make contact with any physical hazards?
Laboratory supervisor or PI comments	
Laboratory supervisor or PI signature	Date
Lab worker signature	Date

This file is excerpted from "Identifying and Evaluating Hazards in Research Laboratories: Guidelines developed by the Hazard Identification and Evaluation Task Force of the American Chemical Society's Committee on Chemical Safety".

https://www.acs.org/content/acs/en/chemical-safety/hazard-assessment/ways-to-conduct/job-hazard-analysis.html

eRAMP

A	B	C	D	E	F	G	H	I	J	K	L
	RAMP		**RECOGNIZE**			**ASSESS**			**MANAGE**		**PREPARE**
	Work steps and tasks		Chemical	Physical		Chemical	Physical		Control/safe work procedures		What-if analysis
1	Obtain chromatography liquids		•Ethyl acetate has narcotic effects • Acetic acid is corrosive to eyes and skin; flammable; avoid inhalation	Spilled solvents		Chemical Risk Matrix exposure score less than 25: Hazards are low and minimized in mixture and fume hood			•Wear nitrile gloves and safety goggles for entire procedure; keep arms covered •Use situational awareness and make sure aisles are clear •Pour in fume hood • Work on spill tray •Remove ignition sources		Nitrile gloves offer only minimal splash protection. Replace with splash or double glove.
2	Prepare chromatography chamber by adding four (4) mL of the mobile phase, 95% ethyl acetate and 5%		Ethyl acetate is a highly flammable liquid and vapor, causes serious eye irritation, and may cause drowsiness or dizziness; acetic acid is a flammable liquid and	Flammable solvents		Chemical Risk Matrix exposure score less than 25: Hazards are low and minimized			•Wear gloves and safety goggles; keep arms covered •Work in fume hood •Keep solvent from ignition		Notify instructor immediately if a mistake is made

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Summary

- There is room in green chemistry research groups for chemical safety and risk assessment, especially in choosing comparison techniques
- Green chemistry class already incorporated some key concepts of chemical safety, but there is room to explicitly add risk assessment topics such as RAMP
- DCHAS will be releasing an eRAMP tool for the undergraduate organic chemistry laboratory

Acknowledgments

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- Course design advisor: Prof. Daniel Waddell
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- ACS: Prof. Joel Shulman
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