Selected Green Chemistry Metrics & Tools at the Process Level

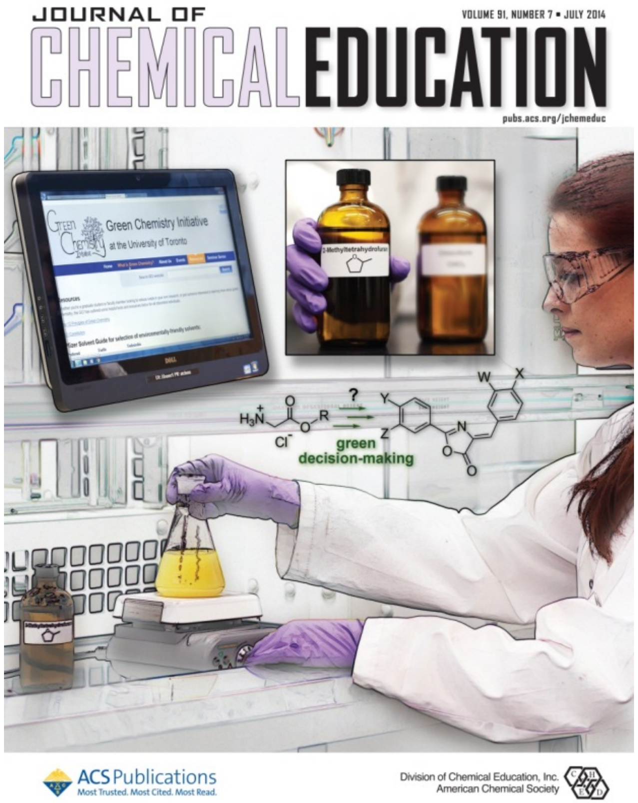
Dr. Andrew P. Dicks

adicks@chem.utoronto.ca

Department of Chemistry
University of Toronto

10th Annual GC3 Innovators Roundtable
Beaverton, OR

29th April 2015



***JCE* cover, July 2014**

"Green chemistry decision-making in an upper-level undergraduate organic laboratory"

Edgar, L. J. E. et al. *J. Chem. Educ.* **2014**, *91*, 1040

Aim for today

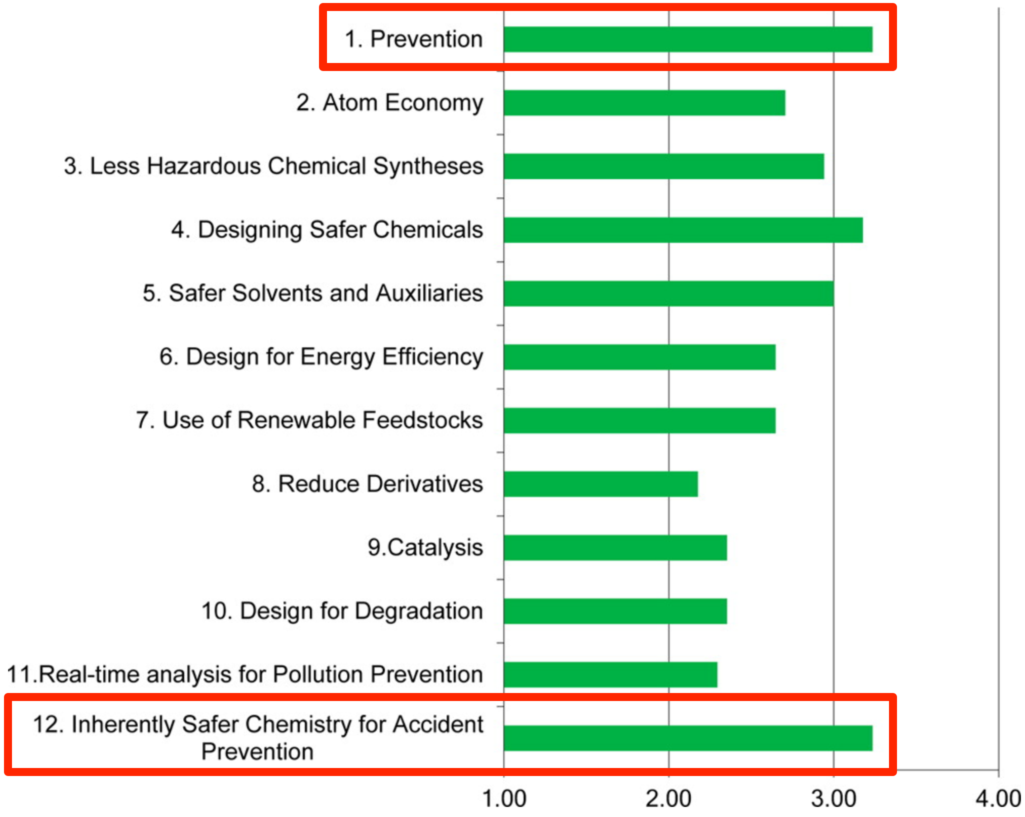
- to highlight **some** important metrics/tools used at the process level in chemical manufacturing:
    - process efficiency (mass metrics)
    - substance nature/suitability
    - life-cycle assessment

The twelve principles…

- **Prevent waste rather than clean it up**
- **Incorporate (all) starting materials into desired product**
- **Use and generate substances possessing little/no toxicity**
- Design of efficacious products while reducing toxicity
- **Avoid use of auxiliary substances**
- Minimize energy requirements
- **Use renewable raw materials/feedstocks**
- **Avoid unnecessary derivatization**
- **Use catalysts**
- Design products that degrade into innocuous substances
- Develop analytical methodologies that allow in-process monitoring
- **Use substances that minimize potential for accidents**

www.epa.gov/research/sciencematters/june2011/principles.htm

Frequency of their application



Average chemical manufacturer responses (*n* = 17) to the survey question:

"In your opinion, how frequently does your company implement the following principles of green chemistry?" on a scale of 1 to 4: (1 = never; 4 = fully implemented)

Giraud, R. J. et al. *ACS Sustainable Chem. Eng.* **2014,** *2*, 2237

Well-known mass metric: atom economy (#2)

$$\text{\% Atom Economy} = \frac{\text{mol. weight of desired product}}{\text{mol. weight of all reactants}} \times 100$$

- ❑ useful as can **quickly** judge which reactions are "atom-economical" (or not…)

$$\underset{\text{mol. wt.: 100}}{\mathbf{A}} + \underset{\text{mol. wt.: 200}}{\mathbf{B}} \longrightarrow \underset{\text{mol. wt.: 300}}{\mathbf{C}}$$

100% atom economy

- ❑ reaction mass efficiency?
- ❑ issue: just consider the reaction, **not everything around it**

Trost, B. M. *Science* **1991**, *254*, 1471

Better: process mass intensity (PMI)

$$\text{PMI} = \frac{\text{total input mass (kg)}}{\text{mass product (kg)}}$$

- "input mass": reactants, reagents, catalysts, reaction **solvents**, drying agents, workup **solvents**, product purification substances (e.g. column chromatography adsorbents/**solvents**)

- ideal PMI value = 1 (all input mass ends up in product): median industry PMI values of 433 (pre-clinical) and 68 (commercial): GlaxoSmithKline target of 20 in 2015

- **moving away from an emphasis on waste (E factor)**

Jimenez-Gonzalez, C. et al. *Org. Process Res. Dev.* **2011**, *15*, 912
Leahy, D. K. et al. *Org. Process Res. Dev.* **2013**, *17*, 1099

Pharmaceutical industry perspective

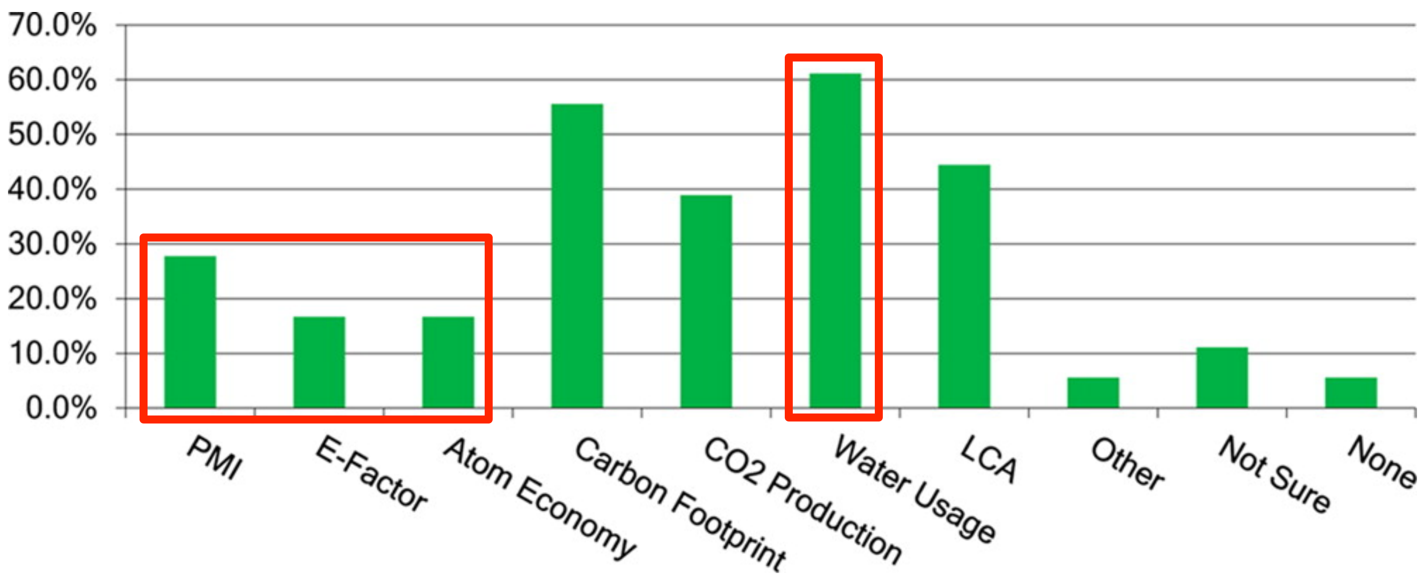
- ACS GCI Pharmaceutical Roundtable has chosen **PMI** as the key metric for evaluating progress towards more sustainable manufacturing

"to truly integrate green chemistry and engineering into chemical processes, one has to look at the inputs instead of the outputs"

"focusing on reducing waste helps companies to reduce costs, but focusing on efficiency also enables innovation to create additional value"

acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html
Jimenez-Gonzalez, C. et al. *Org. Process Res. Dev.* **2011**, *15*, 912

Industry metric use



Chemical manufacturer responses (n = 18) to the survey question:

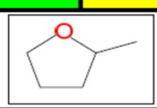
“What green chemistry and engineering related metrics does your company use? Select all that apply”

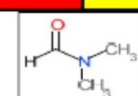
PMI = process mass intensity = (mass of raw materials)/(mass of final product)
E-factor = (mass of waste)/(mass of final product)
LCA = life cycle assessment

Giraud, R. J. et al. *ACS Sustainable Chem. Eng.* **2014,** *2*, 2237

The nature of process substances used (1)

- Industrial solvent and reagent selection guides have been published: aim to "rank greenness"
- Sanofi solvent guide sets up ID cards: overall ranking, H, S & E hazards, ICH limit, physical properties, cost, **substitution advice**

METHYL-THF 2-Methyl tetrahydrofurane					DANGER
CAS : 96-47-9			SDS (SEDDA) : FR10910		
Recom-mended	ICH limit: n. a.	Guide 709-2 : n. a.	OEB V2	SHB 4	EHB 3
		C5H10O	Other constraints : peroxides, cost		
		MW: 86,13	BP: 79°C	MP: -137°C	FP: -11°C
Sol in water : 140 g/L		d : 0,854	Resistivity : dissipative		Cost : 18
Biodeg. : low		Sustain. : Hydrogenation or furfural			AIT = 270°C
Advice : the most advisable ether. Due to its cost, recycling is recommended.					

DIMETHYLFORMAMIDE DMF					
CAS : 68-12-2			SDS (SEDDA) : FR00185		
Substitution requested	ICH limit : 880 ppm	Guide 709-2 : list B	OEB V4G2 Sk CMR	SHB 2	EHB 1
		C3H7NO	Other constraints : CMR (R1B)		
		MW: 73,10	BP: 153°C	MP: - 61°C	FP: 58°C
Miscible with water		d : 0,944	Resistivity : dissipative		Cost : 3
Biodeg. : > 90%		Sustain. : synthesis from dimethylamine			
Advice : CMR solvent, use it only if there is no alternative such as acetontrile, ureas or sulfolane					

Prat, D. et al. *Org. Process Res. Dev.* **2013**, *17*, 1517

Prat, D. et al. *Green Chem.* **2014**, *16*, 4546 **(survey of different guides, 51 solvents)**

The nature of process substances used (2)

- Reagent selection guides: examples from Pfizer, GlaxoSmithKline
- GSK approach: reagents scored for a particular reaction by H, S & E risks, atom economy, stoichiometry, workup, **LCA**

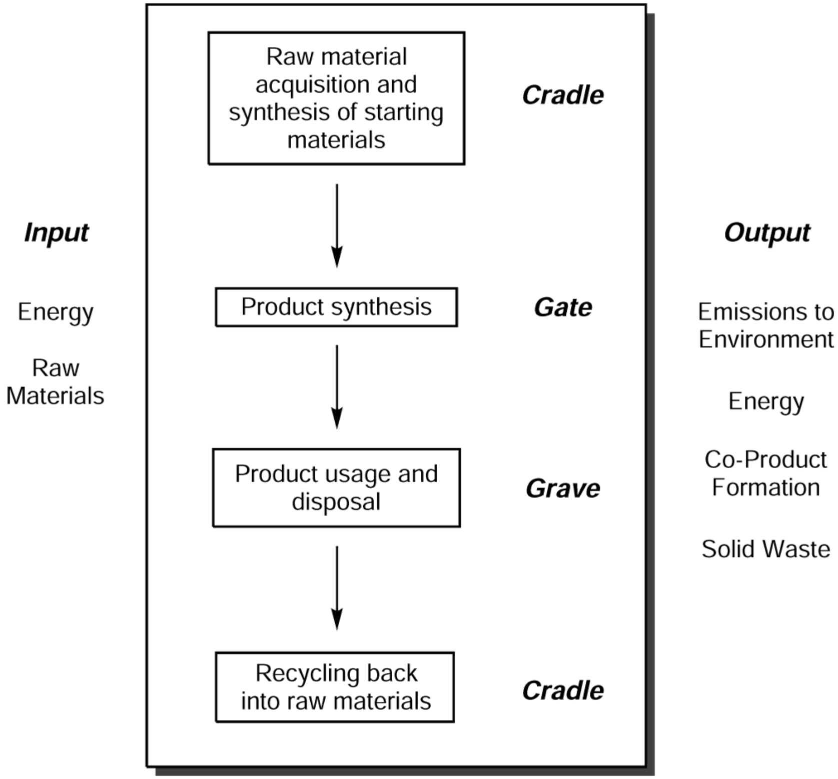
GSK Reagent Selection Guide – Alkene Reduction

Few Issues	Some Issues	Major Issues
H_2, Pd/C	HCO_2Na, Pd/C	Li, 4,4'-Di-*t*-butylbiphenyl
H_2, Ru/C	$NaBH_4$, Pd/C	Li, NH_3
H_2, $Pd(OH)_2$/C	HCO_2NH_4, Pd/C	H_2, Raney Ni
H_2, Pt/C	Li, *n*-Propylamine, Ethylenediamine	Cyclohexene, Pd/C
H_2, Rh/C	H_2, $Rh(PPh_3)_3Cl$	HI, Red phosphorus
H_2, Crabtree's catalyst	Et_3SiH, TFA	Hydrazine, *N*-Ethylriboflavin
H_2, PtO_2	Et_3SiH, Pd/C	
	HCO_2NEt_3H, Pd/C	
	Stabilized sodium	

Adams, J. P. et al. *Green Chem.* **2013**, *15*, 1542
Henderson, R. K. et al. *Green Chem.* **2015**, *17*, 945 **(acid/base selection guide)**

Life cycle assessment

- ❑ Very resource-intensive approach: expensive!
- ❑ Availability of information often an issue



GSK FLASC analysis:

Fast **L**ifeCycle **A**ssessment of **S**ynthetic **C**hemistry:

reduced LCA for materials arriving, undergoing processing and leaving (cradle to gate): eight "impact categories"

Curzons, A. et al. *Int. J. Life Cycle Assessment* **2007**, *12*, 272

The twelve principles…

- Prevent waste rather than clean it up
- Incorporate (all) starting materials into desired product
- Use and generate substances possessing little/no toxicity
- Design of efficacious products while reducing toxicity
- Avoid use of auxiliary substances
- Minimize energy requirements
- Use renewable raw materials/feedstocks
- Avoid unnecessary derivatization
- Use catalysts
- Design products that degrade into innocuous substances
- Develop analytical methodologies that allow in-process monitoring
- Use substances that minimize potential for accidents

www.epa.gov/research/sciencematters/june2011/principles.htm

(Some) other considerations

- Measuring energy usage (e.g. cost of recovering solvent versus incineration – equipment cleaning)
- Measuring process safety (eliminating substances that are inherently unsafe)
- Product degradation potential (resistance to biodegradability, but not too much!)
- Improved toxicity information (wide range of chemicals have little/no data)

Jimenez-Gonzalez, C. et al. *Chem. Soc. Rev.* **2012**, *41*, 1485