American Chemical Society

ACS Green Chemistry Institute®

ACS Chemistry for Life™

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Using Metrics to Drive Innovations in Green Chemistry and Engineering

2014 U.S. EPA TRI Conference

May 8, 2014

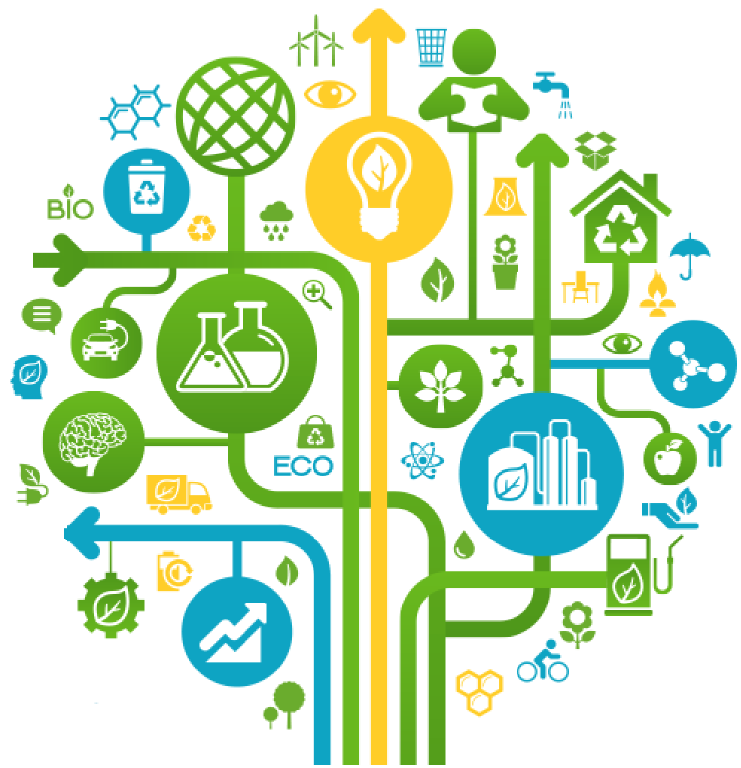
David J. C. Constable, Ph.D.
Director, ACS Green Chemistry Institute®

ACS Green Chemistry Institute®

Engaging *you* to reimagine chemistry and engineering for a sustainable future.

We believe sustainable and green chemistry innovation holds the key to solving most environmental and human health issues facing our world today.

- Advancing Science
- Advocating for Education
- Accelerating Industry

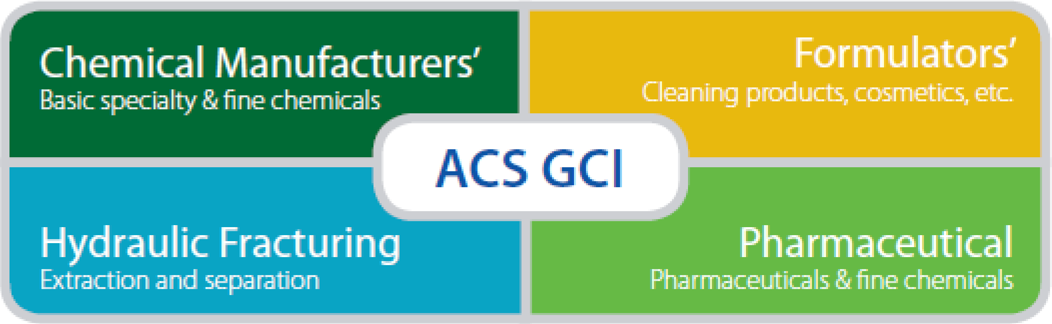


ACS GCI Industrial Roundtables

Catalyzing the integration of sustainable and green chemistry and engineering in the global chemical enterprise.

We convene companies from across the world to focus on the science of sustainable and green chemistry and its implementation.

- Pharmaceutical
- Formulators
- Chemical Manufacturers
- Hydraulic Fracturing



ACS GCI Industrial Roundtables

Catalyzing and enabling the implementation of green chemistry and engineering in the global chemical enterprise

- Collaborate non-competitively
- Address technical challenges
- Develop decision-making tools
- Inform the research agenda
- Drive the use of good science in policy setting
- Influence through the supply chain

Outline

- **Selected Green Chemistry Challenges**
  It isn't going to be easy
- **Green Chemistry Metrics**
  Driving innovation with measurement & tools
- **Success Stories in Sustainable Innovation**
  Reducing toxic releases

Asking the Right Questions is Imperative

Avoid "the perfect uselessness of knowing the answer to the wrong question"

The Left Hand of Darkness
Ursula K. LeGuin
1969

A Few Chemistry Challenges

Reasons Chemist's Use the Chemical Building Blocks they Use

Because they:

- Ensure thermodynamically and kinetically favorable reactions
- Result in the highest yields
- React in predictable ways
- Are "easily" obtained (lowest cost)
- Generally don't require sophisticated reactors or technology in the laboratory

But….

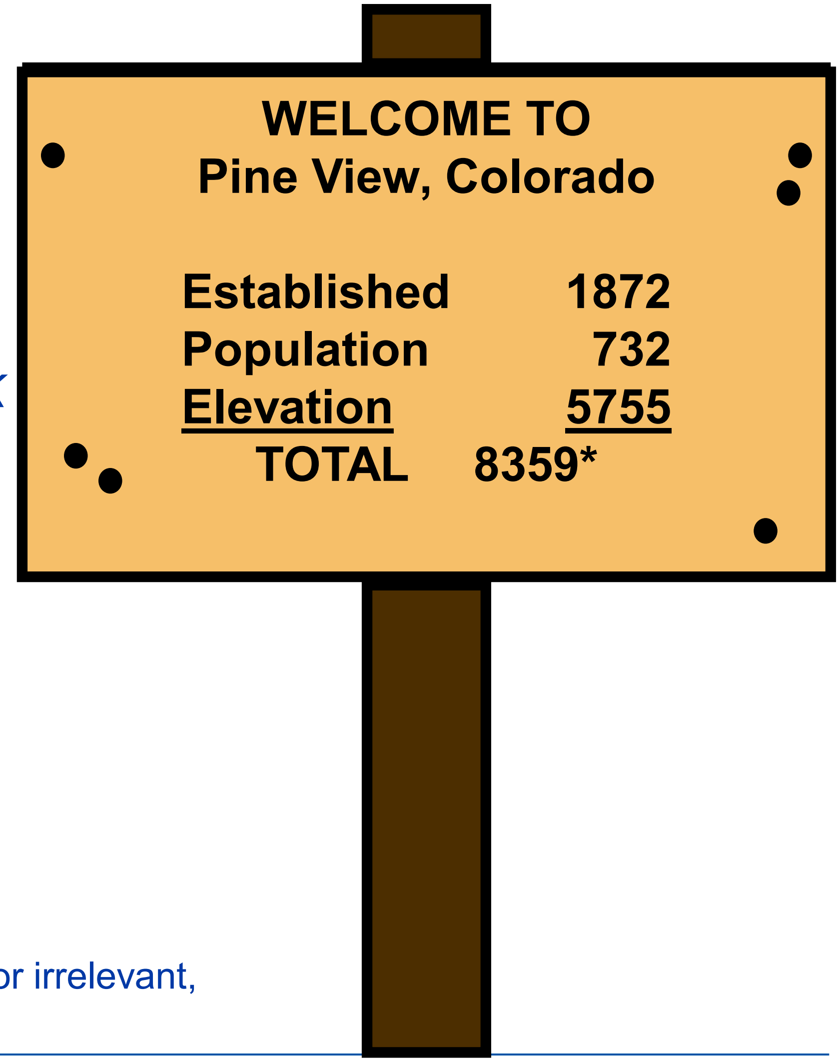
These Chemical Building Blocks have a few Sustainability Risks

- Feedstocks
- Process efficiencies
- Missing Data
- High-hazard materials
- High risk process chemistries
- Inappropriate engineering or process controls
- Human and Environmental Exposures
- Legislation/regulations

Green Chemistry and Metrics

"All he's done is call it *Green*"

The person who sat behind me, GRC Green Chemistry Meeting, Oxford, 1999, *as related by John Hayler, GSK*



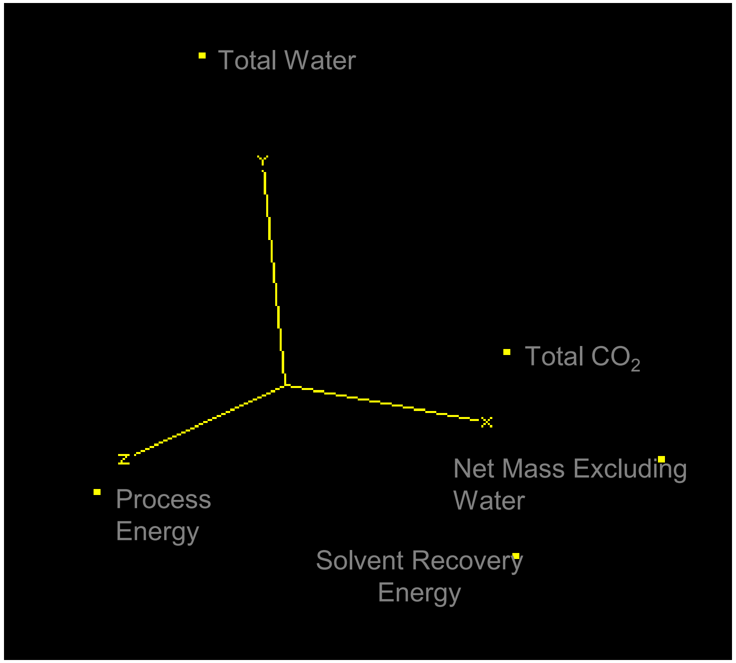
"If you don't keep score, you're only practicing"

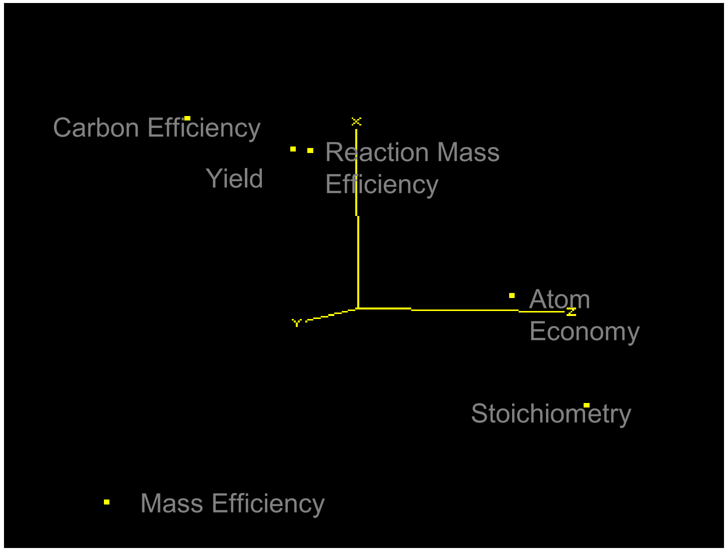
Jan Leshley, former CEO SB & GSK

*Audited by 3iDataCen (Formerly, the Center for irrelevant, immaterial and inconvenient Data)

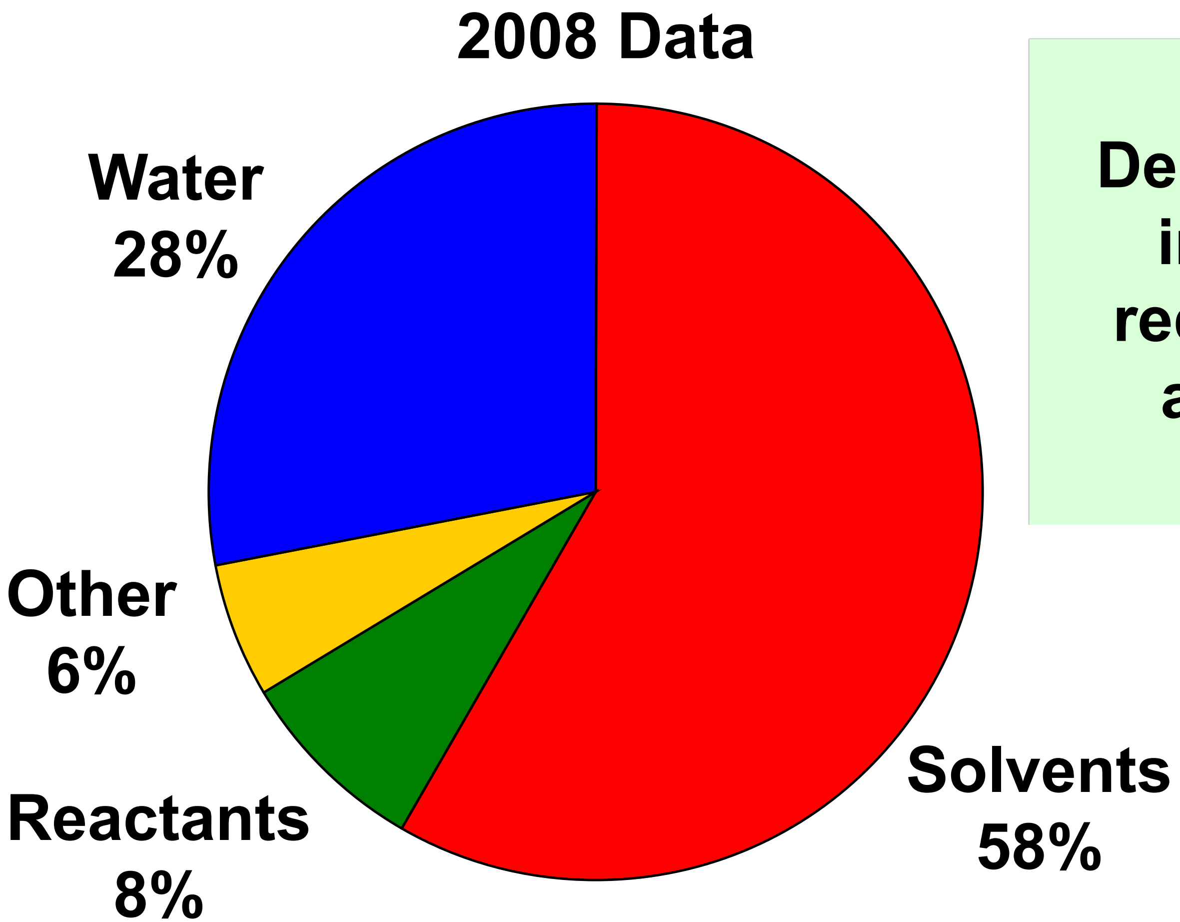
Find the Right Metrics

- Make objective comparisons
- Benchmark progress
- Drive change
- Demonstrate improvement
- Increase transparency





Composition of PMI: Pharma Benchmarking



INSIGHTS: Demonstrated the importance of reducing the use and hazard of solvents

A Few Key Metrics are Essential

- Reaction Mass Efficiency (RME)
- No. of stages and no. of chemistry steps
- Total no. of solvents and solvents per stage
- Mass Intensity (PMI) and Mass Productivity (Efficiency)
- Materials of Concern
- Process life cycle environmental impact

Can we change the chemistry?

Telescope, maximize convergency, pay attention to order of side chain coupling

Recycle/reuse 80 – 90 % of the mass!

Focus on optimizing use of a few key materials

Starting materials matter!

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Process Mass Intensity (PMI)

Step 1: A + B + C + D + E → F (Intermediate)

Step 2: F + G + H + I + J → K (API)

PMI = (A + B + C + D + E + G + H + I + J) / K

- Includes all materials used in synthesis (i.e., Reagents, solvents water, etc.)

From: NSF

PMI Calculator Tool

Step Name/Number	1	
	Value	Units
Physical Batch Size		
Assay Purity		
Assay Batch Size		
Yield		
Assay Kg product		
Product Purity		

Raw Materials	Physical Charge (kg)
Substrates	
Reagents	
Solvents	
Aqueous	

PROCESS STEP METRICS	
Mass Substrate (kg)	0
Mass Reagents (kg)	0
Mass Solvents (kg)	0
Mass Aqueous (kg)	
Step PMI	#DIV/0!
Step PMI Excluding H2O	#DIV/0!
Cumulative PMI	#DIV/0!
Cumulative PMI Excluding H2O	#DIV/0!

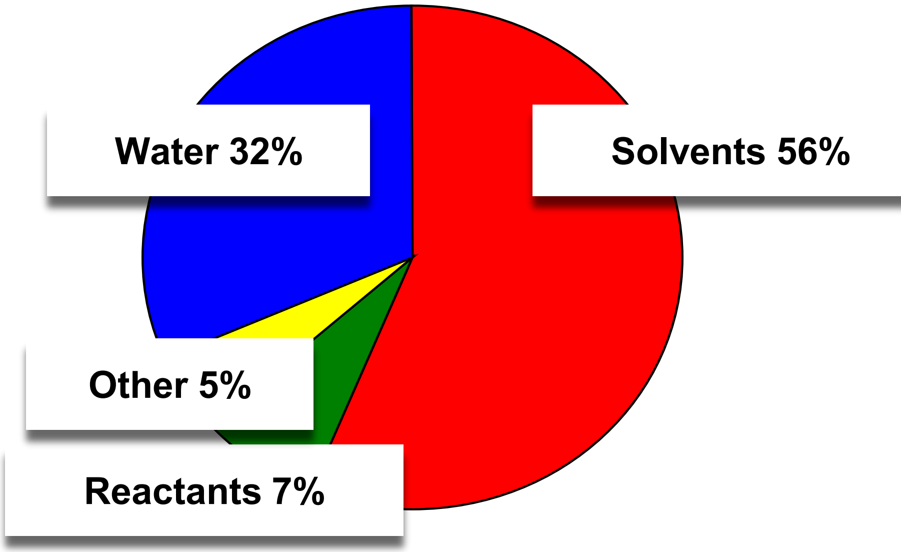
– Embedded calculations
– Only need to fill in amounts of reagents, solvents, and water
– Spreadsheet calculates step and overall PMI for linear sequences
– Calculates separate PMI for solvents, water, and reagents

Publicly available spreadsheet:

http://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html

Solvent Use in Batch Chemical Processing is Significant

- In 2008, 10 solvents represented approximately 80% of all solvents used in GSK
- Solvent use is the largest contributor to:
  - Primary manufacturing ***process mass intensity***
  - Primary manufacturing ***life cycle environmental impacts*** (e.g., ~80% mass, ~75% energy)



Composition by mass of types of material used to manufacture an API
American Chemical Society Green Chemistry Institute
Pharmaceutical Roundtable Benchmarking 2006 & 2008

What would it take for alternative solvents to be routinely used?

- Stop focusing solely on the chemistry of reactants
- Focus on problems (chemistries, synthetic schemes, separations, flowsheet schemes, etc.) that need a solution
- Start with a superior replacement(s) for DCM, ethers, some dipolar aprotic solvents and perhaps alkanes
- Demonstrated comparability with conventional solvents from a life cycle and economic basis

Ideally, replacements should show significant benefits across the entire process leading to an active pharmaceutical substance!

- Limited number of solvents with broad applicability to a significant number of different processes with EHS and operational data established

Some Important Work to do…

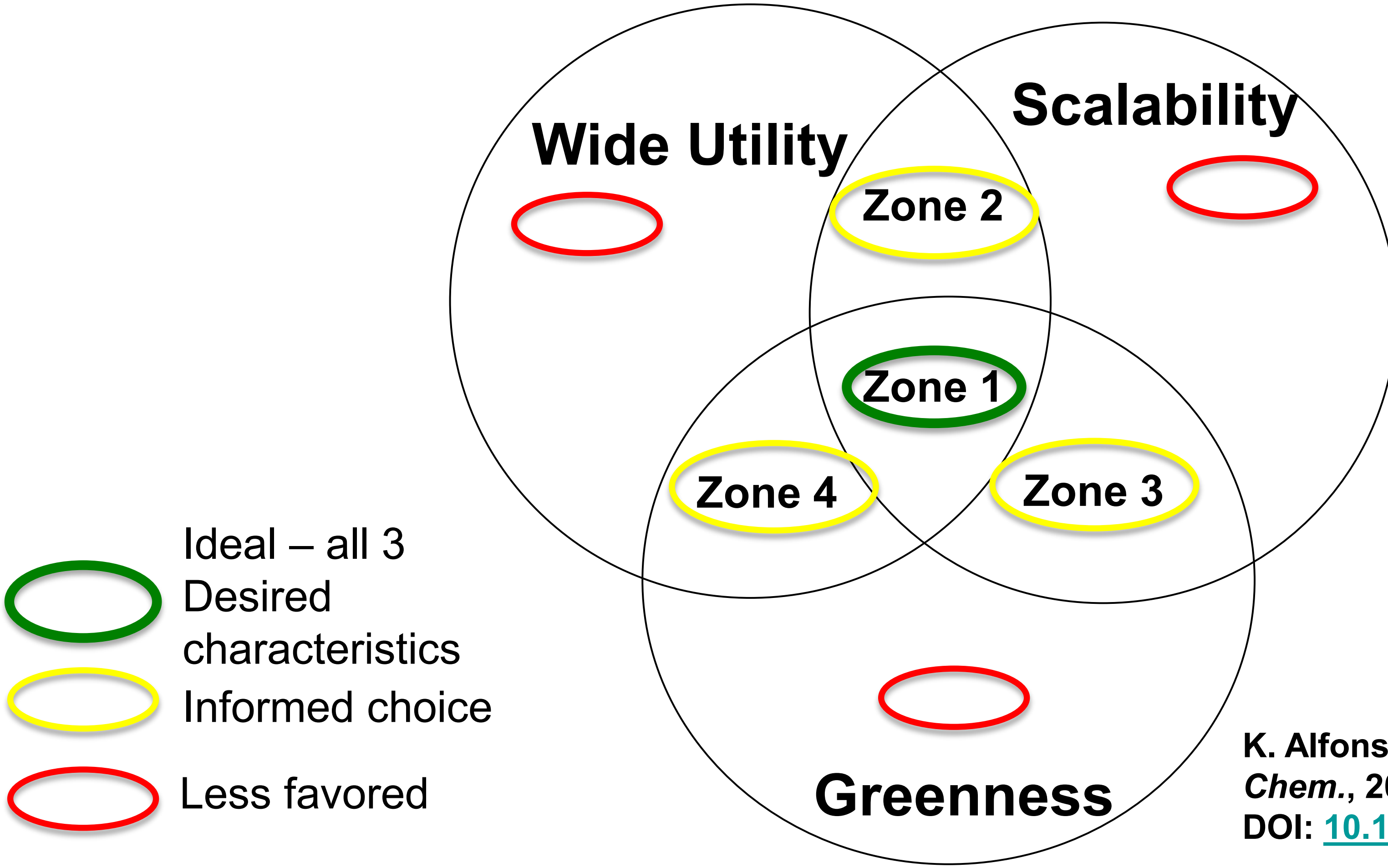
- Inclusion of *solvent selection* as an important design consideration in route selection.
- Greater collaboration between synthetic *chemists and chemical engineers*
- *Literature and databases* on solvent selection with respect to specific chemistries
- Synthesis strategies that *optimize solvent use, reuse, and end-of-life considerations (life cycle approach)*
- Development of *solvent options* that provide the desired function without the undesirable EHS issues
- Technology options that facilitate *process intensification*
- Development of *solvent-less and biotechnology options*

Assessing 100+ pharma processes

- No correlation between non-solvent mass and several different measures of greenness.
- Mass based metrics do not appear to account for the complexity of the chemistry.
- Mass based metrics do not account for the nature and impact of chemicals.

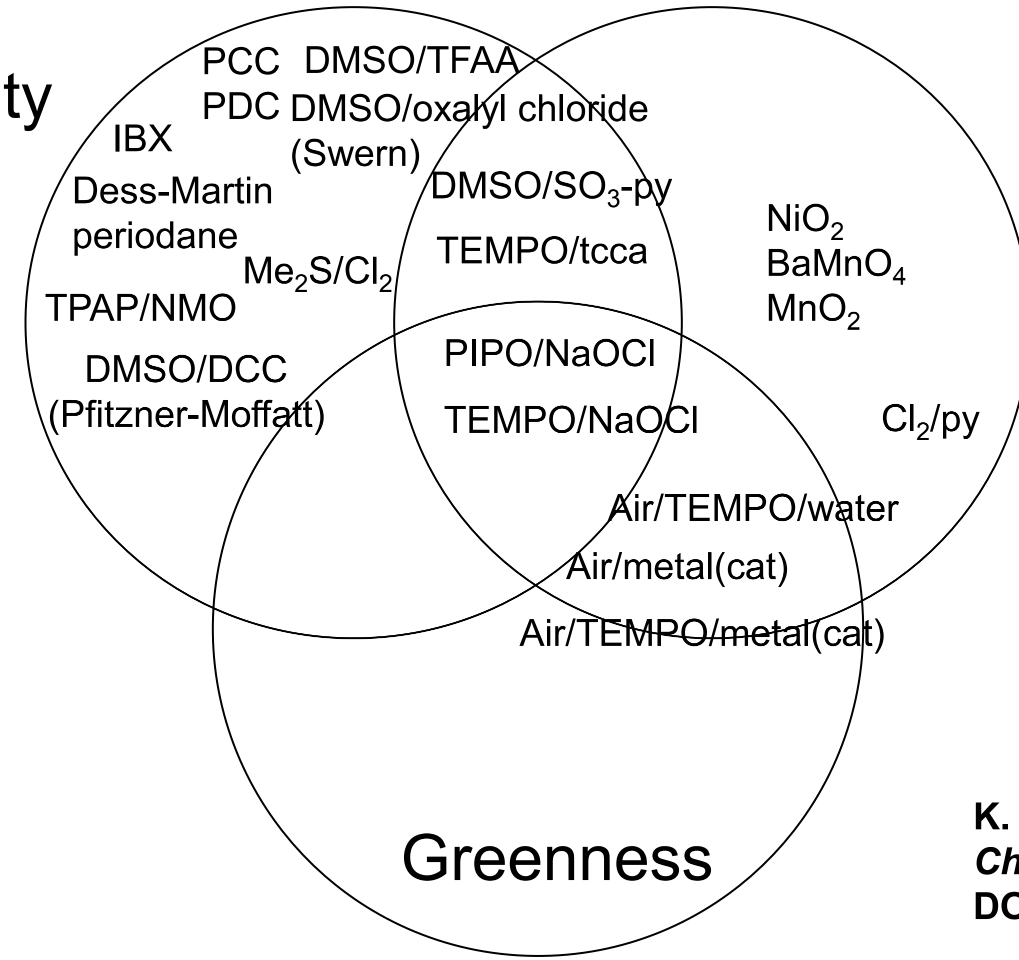
Is there more we should be doing to influence the selection of reagents to reduce the impact of solvents?

Venn Diagram for Reagent Selection



K. Alfonsi et al., *Green Chem.*, 2008, 10, 31 - 36, DOI: 10.1039/b711717e

Oxidation of Primary Alcohol to Aldehyde



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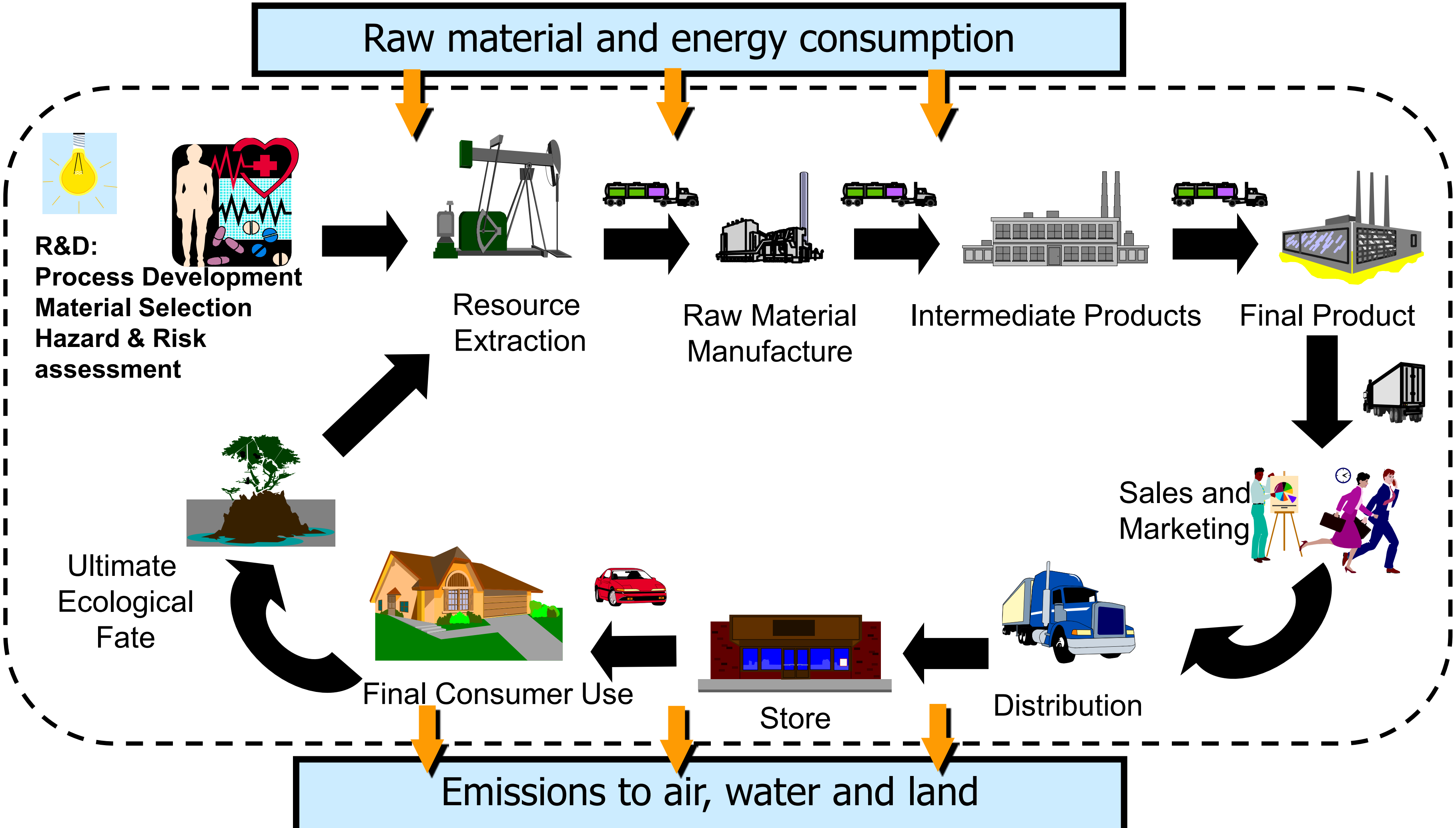
Life Cycle Assessment – The very big picture



Success Stories in Sustainable Innovation

CASE 1: Chlorine

Process Intensification

The role of chemistry and engineering

Example: Process Intensification

- Understand what controls a chemical reaction (or a process) so that the engineer can design equipment to optimize the reaction
  - Mass / heat transfer
    - Mixing
    - Between phases/across surfaces
  - Chemical equilibrium
  - Molecular processes

Adapted from: Dennis C. Hendershot, Rohm and Haas Company (DOW), Engineering Division, Bristol, PA

Better engineering can make existing chemistry "Greener"

- Chlorination reaction – traditional stirred tank reactor
- Mixing and mass transfer limited
  - Chlorine gas → liquid reaction mixture → solid reactant particle → rapid reaction
- Loop reactor – similar design to polymerization reactor in previous slide
  - Reduce:
    - Chlorine usage from 50% **excess** to stoichiometric
    - Reactor size by 2/3
    - Cycle time by ¾
    - Sodium hydroxide scrubber solution usage by 80%

Adapted from: Dennis C. Hendershot, Rohm and Haas Company (DOW), Engineering Division, Bristol, PA

CASE 2: Arsenic and Hexavalent Chromium

Chemical Specialties, Inc. (now Viance)

PGCCA Winner in the Designing Greener Chemicals Category

Arsenic and Hexavalent Chromium

- Traditional technologies for preserving wood used chromated copper arsenate (CCA).
- This new approach used an alkaline copper quaternary preservative (2:1 bivalent Cu:quaternary ammonium).
- 90% of the 44 million pounds of arsenic used in the US was for CCA production; Ar use was dramatically cut as well as 64 million pounds of chromium(VI).

Source: EPA

CASE 3: Formaldehyde

Columbia Forest Products & Hercules Incorporated (now Ashland Inc.)

PGCCA Winner in the Greener Synthetic Pathways Category

Formaldehyde

- Biomimicry→ soy proteins modified to mimic mussels secretion of binding proteins known as byssal threads

- Columbia Forest Products used the new product to replace 47 million pounds of conventional formaldehyde-based adhesives
  - Also reduced hazardous air pollutants (HAPs) from each plant by 50 to 90 percent

Source: EPA

CASE 4: Halogenated and Toxic Solvents

Argonne National Laboratory

PGCCA Winner in the Greener Reaction Conditions Category

Halogenated and Toxic Solvents

(CFCs), methylene chloride, ethylene glycol ethers, perchloroethylene, and chloroform

- Ethyl lactate—a nontoxic, biodegradable solvent derived from renewable carbohydrates
- ANL's process cuts the selling price of lactate esters in half
- More than 4.5 million metric tons of solvents are used in the US per year; ethyl lactate could replace conventional in more than 80% of applications.

Source: EPA

Conclusions

- Sustainable & Green chemistry is more than just hazard and pollution reduction
- Innovation & metrics are key
- Early design that incorporates sustainable and green chemistry and engineering principles is imperative to achieve the most cost effective gains
- Quantify impact, benchmark progress—you can't improve if you don't measure!
- Tools are available for design guidance but chemists generally don't know how to use them
- There's a lot more going on in this space than many realize
- Never underestimate the challenge of getting people to change

Future Challenges

- Less toxic alternatives for hazardous solvents and reagents
- Integration of chemistry and technology
  - Application of continuous processing, novel reactors, solvent systems
  - Bioprocessing
    - Further development of tools to objectively compare bioprocesses with chemical processes
    - Greater attention to downstream processing issues
    - Integration of life cycle considerations
- Ready access to renewable feedstocks as framework molecules.
- New, greener, reactions and methodology.

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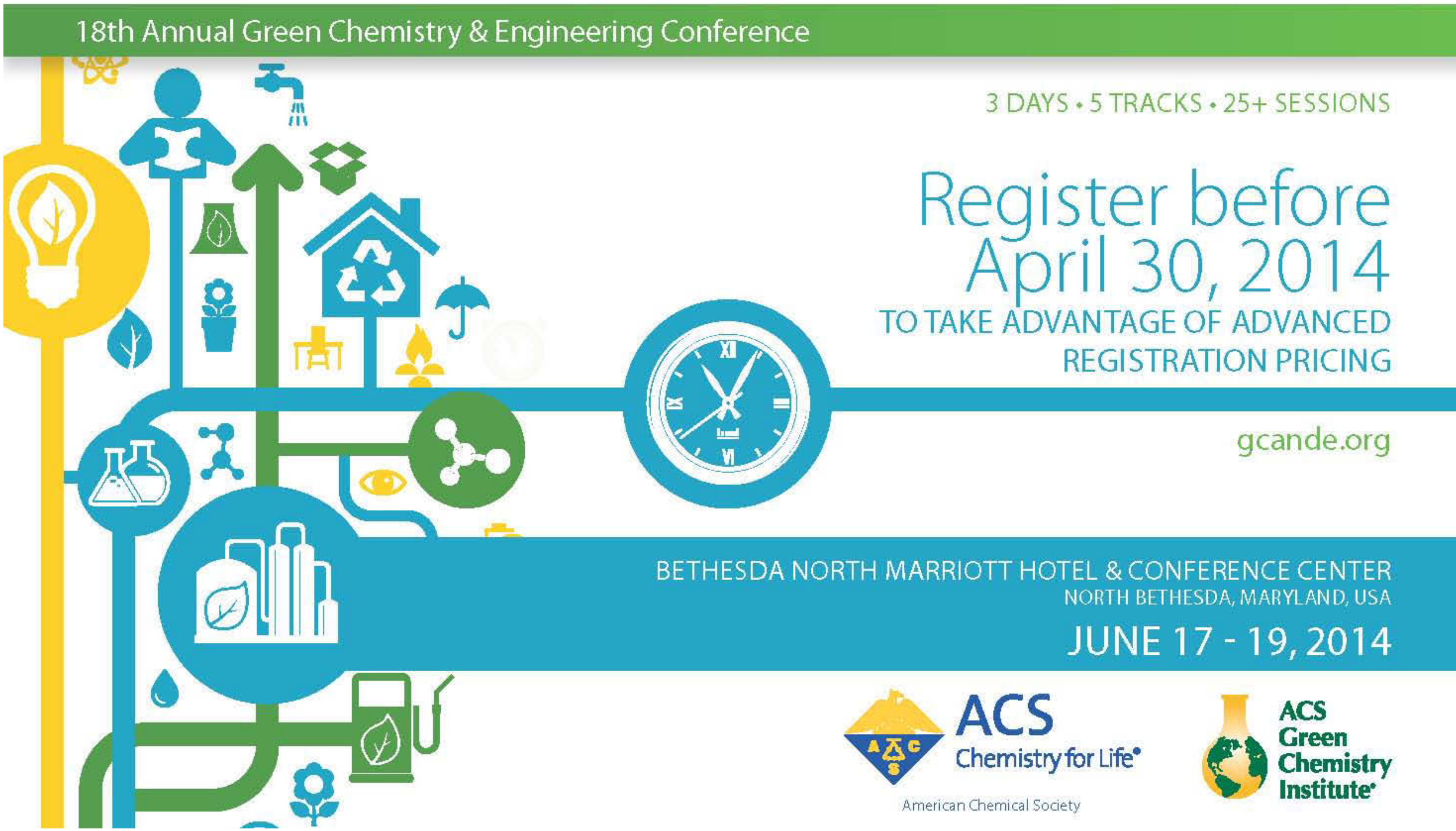
Advancing Chemistry, Innovating for Sustainability



Chemists Use Ancient Chemistries

A random selection of 100 chemistries in a review of named reactions:

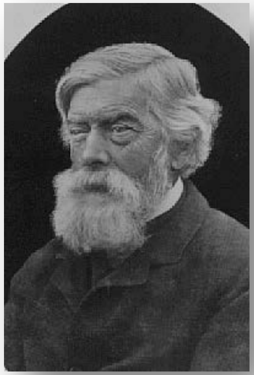
54% *before* World War 1

74% *before* World War 2

91% *before* 1975

9% *during* the 1980's

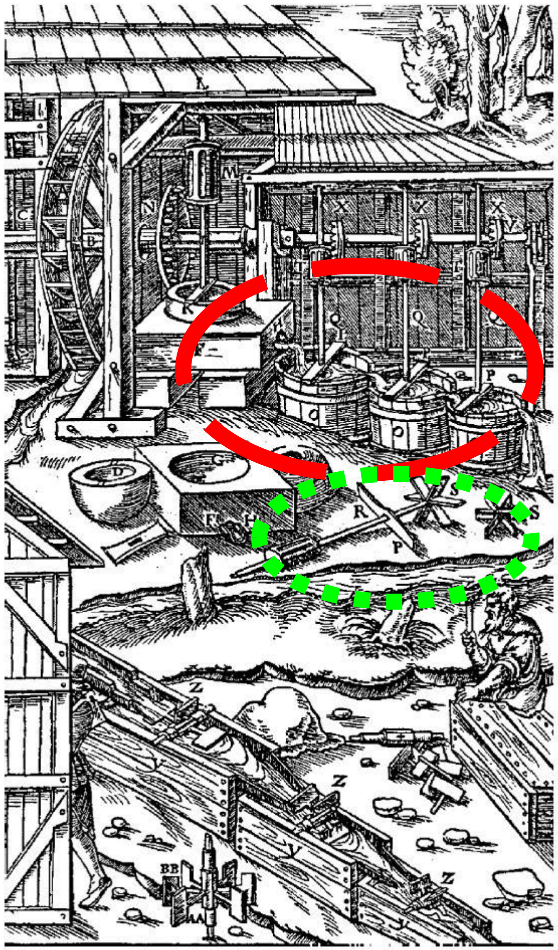
Wurtz, Charles Adolphe
Born: Wolfisheim, 1817
Died: Paris, 1884



Williamson, Alexander William
Born: London, 1824
Died: Hindhead, 1904

Grignard, François Auguste
Born: Cherbourg, 1871
Died: Lyon, 1935

Chemical Technology Hasn't Changed Much



- Batch reactor ----> Bronze age
- Distillations ----> e.g., Dutch gin was imported before the English industry for distilled spirits took over in the 18th century
- Crystallization ----> Salt crystallization during bronze age

"The difficulty lies, not in the new ideas, but in escaping the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds."

- John Maynard Keynes

Thinking About Design

"Design is a signal of intention"

"Cradle to Cradle"

William McDonough

2002