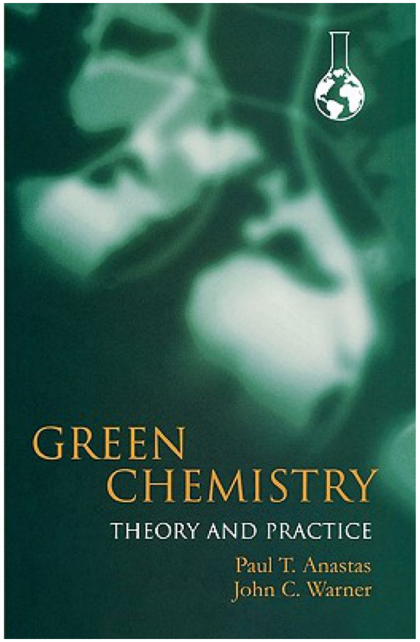
Fundamentals of Green Chemistry

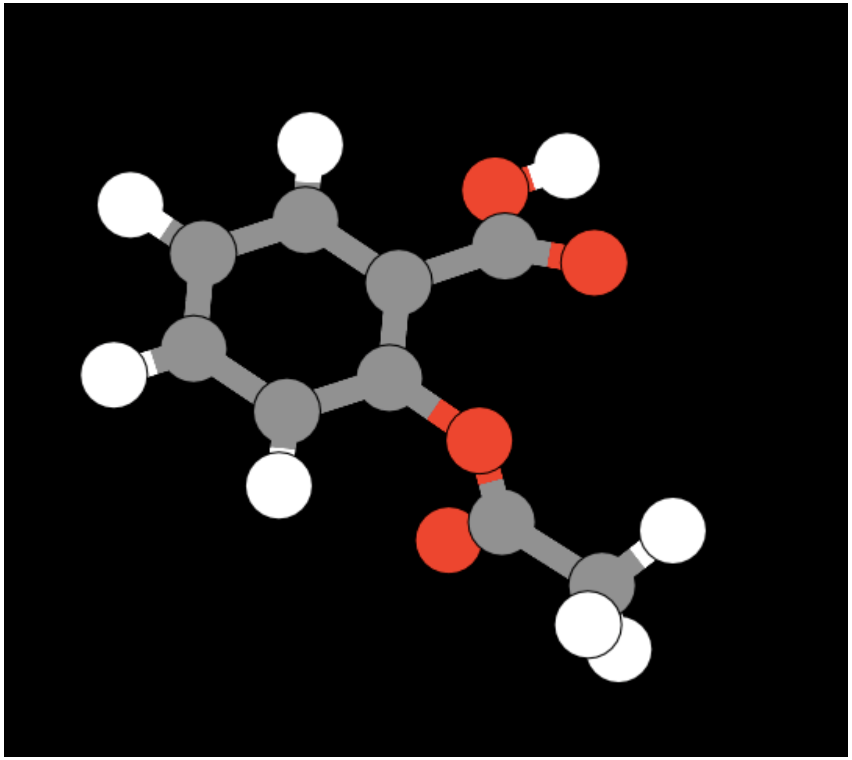
What is Green Chemistry?

Green chemistry is the **design** of chemical products and processes to reduce or eliminate the generation and use of hazardous substances.



Anastas, P. T., Warner, J. C. (2000). Green chemistry: Theory and Practice. New York; Oxford University Press.

Focus on Chemical Design



The moment chemists initiate designing, they are making choices about the human health and environmental impacts of their product:

- Design is intended
- All characteristics, including performance and toxicity, can be designed

Image source: ChemDoodle Web Components

The chemical designing process

DECISION MAKING

<u>Type of resources</u>

- What materials (feedstocks, additives) are needed?
- Are the materials readily available?
- How much material is needed?

<u>Manufacturing process</u>

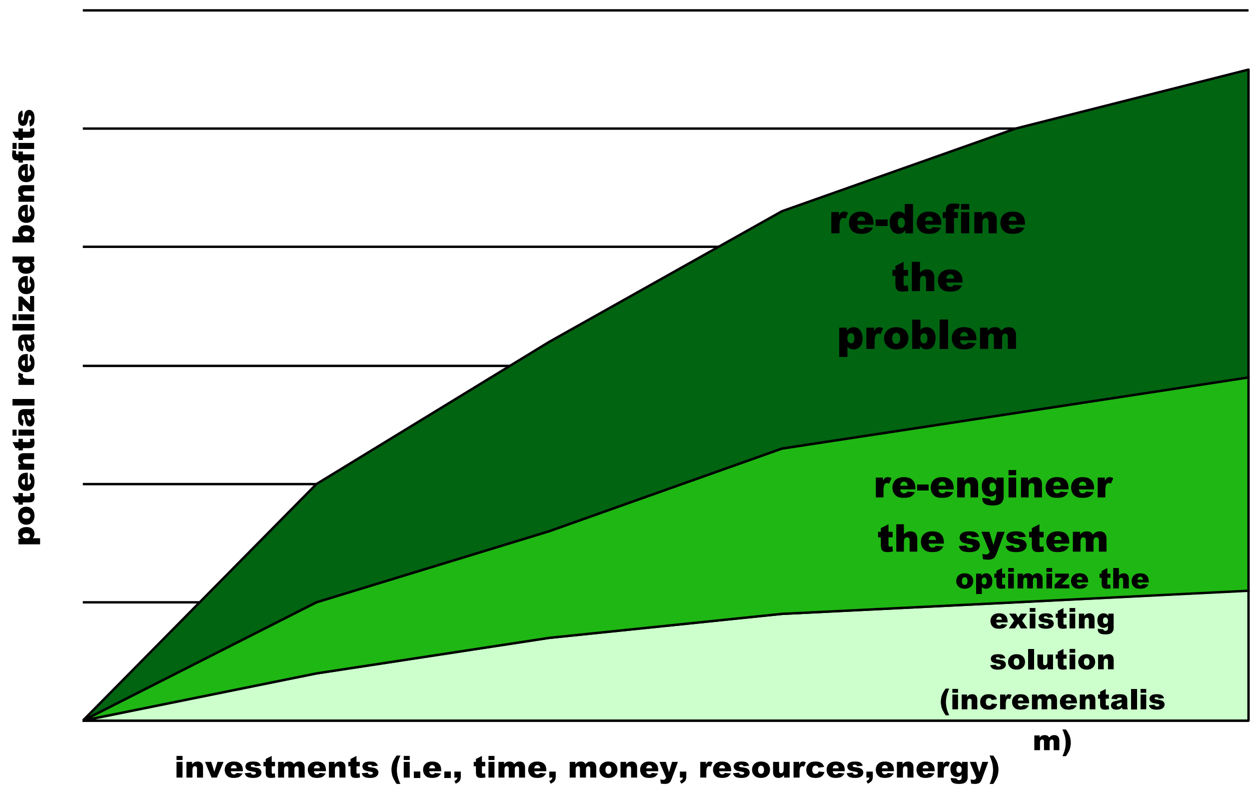
- What technology is needed?
- What is the scale of the experiment?

↓

Ultimately determining the characteristics of the waste stream, energy requirement and the toxicity of the entire process.

Potential benefits vs. investments

It’s not just how you design but what you design…

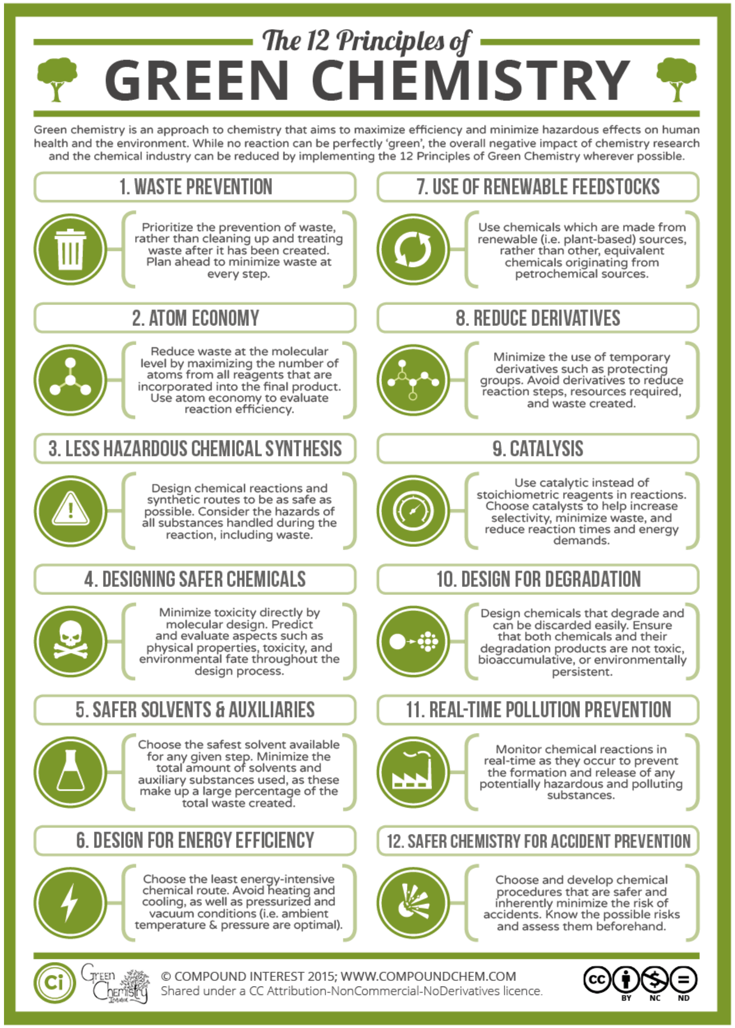


As the investments increase, so do the benefits. The largest benefit is when the company re-defines the problem and finds a novel solution.

The 12 Principles of Green Chemistry

The principles address:

- Toxicity
  - Reducing the hazard
- Feedstocks
  - Use of renewable resources
- Designing safer products
  - Non toxic products by design
- Biodegradability
  - Enhancing breaking down at the end of life
- Energy
  - Reducing the energy needs
- Accidents
  - Eliminating accidents
- Efficiency
  - Shorter processes and synthesis



Source: https://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry/principles/12-principles-of-green-chemistry.html

Isn’t that how it is done now?

- Entire industries are geared toward cleaning up after wasteful chemical syntheses
- Today’s scientific literature is filled with synthetic pathways that are inefficient in terms of design
- Reagents are seldom selected with regard to hazard
- Industrial chemicals do not have minimal hazard as a performance criterion
- Persistence of chemicals in the biosphere and in our bodies is a major global health issue (CDC 250 chemicals since 1945)
- The vast majority of organic chemicals are made by depleting (non-renewable) feedstocks
- Our chemical industry deals with safety through engineering and security through barricades.

Benefits of Green Chemistry

- For the environment: Products which will biodegrade and won't persist in the environment
- For human health: Products with won't cause toxicity to humans
- For the economy: Novel products which boost competitiveness
- For sustainability: Products made from renewable resources
- For science: Fundamental new insights

Green Chemistry across industrial sectors

Defense and aerospace
- Adhesives
- Coatings
- Corrosion, inhibitors

Automotive
- Solvents
- Polymers
- Fuels

Household cleaners
- Surfactants
- Fragrances
- Dyes

Electronics
- Solder
- Housings
- Displays

Agriculture
- Pesticides
- Fungicides
- Fertilizers

Cosmetics
- Builders
- Chelating agents
- Dyes

Pharmaceuticals

A fundamental change in thinking

- Green Chemistry moves our consideration of how to deal with environmental problems from the ***circumstantial*** to the ***intrinsic.***

Circumstantial

- Use
- Exposure
- Handling
- Treatment
- Protection
- Recycling
- Costly

Intrinsic

- Molecular design for reduced toxicity
- Reduced ability to manifest hazard
- Inherent safety from accidents or terrorism
- Increased potential profitability

- Hazard must be recognized as a ***flaw in the designing process***

Approaching risks: exposure vs. design

The traditional approach to hazards focuses on reducing risk by minimizing exposure.

- For example, wearing personal protective equipment or space ventilation if the chemical is volatile.

Green chemistry focuses on reducing risk by reducing hazard

- If there is no hazard, exposure becomes irrelevant

The Twelve Principles of Green Chemistry

PRINCIPLE 1

It is better to prevent waste than to treat or clean up waste after it is formed.

What is waste?

Anything that is is a leftover from the product/process and cannot be re-used.

Waste can be produced in any stage of a process life-cycle:

- Origins of feedstock
- Manufacturing
- Distribution
- Use
- End of life

When is waste *not* waste?

1. When it can be reused, becoming a feedstock.

2. When it can be reduced or completely eliminated.

Principle 1: Waste prevention

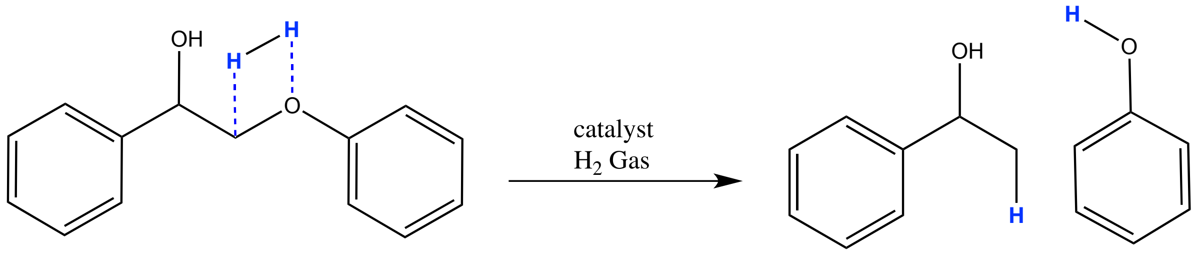
Case study: Phenols

Traditional method of obtaining phenols (drop-in platform chemicals) from petroleum.

Petroleum → **Phenols (benzene, toluene, xylenes)**

Disadvantage: Not sustainable – dependent on depleting resources

Production of phenols from biomass waste using depolymerization



Advantage: Uses abundant product (waste) as a starting material

Principle 1: Waste prevention

Case study: dNTPs

Conventional production of deoxyribonucleotide triphosphates (dNTPs):

- requires multiple steps and purifications
- produces large amounts of hazardous solvent and reagent waste

Alternative synthesis:

- a one-pot, three step sequence
- eliminates the need for several hazardous reagents such as $ZnCl_2$, triphenylphosphine, and solvents such as dimethylformamide and dichloromethane
- E-factor improved by an order of magnitude
- Solvent consumption reduced by 95%, hazardous waste by 65%, preventing 1.5 million tons of hazardous waste per year

PRINCIPLE 2

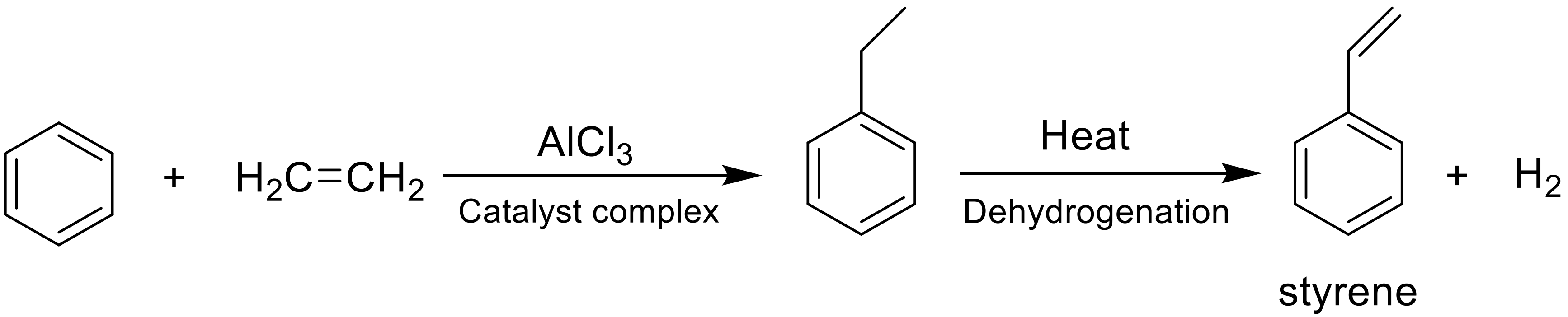
Synthetic methods should be designed to maximize the incorporation of all materials used into the final product.

- Ideally all atoms from the reagents are incorporated into a final product
  - High atom economy ↔ less waste production
- There are no co-products or by products in the reaction
- The molecular waste is therefore reduced

Principle 2: Atom economy

Case study: Styrenes

Traditional method of styrene production:



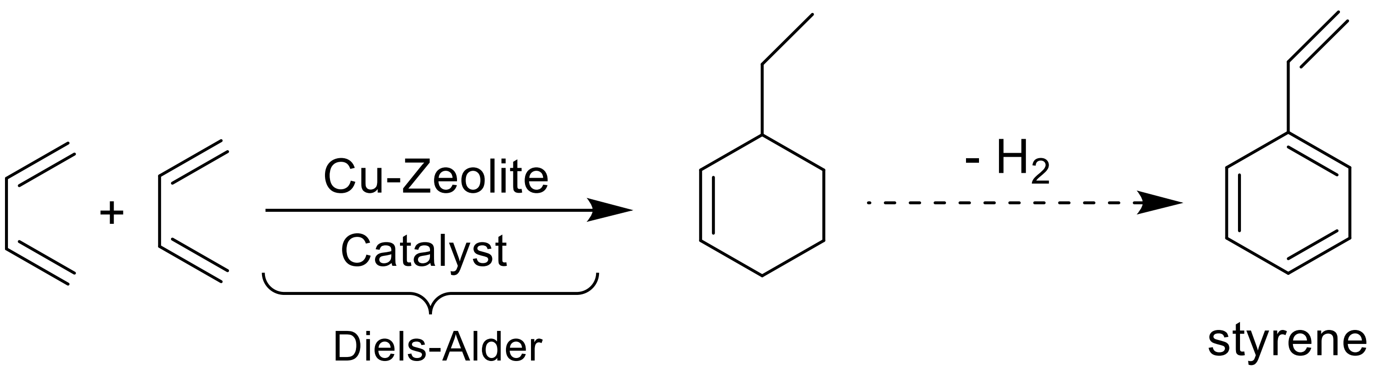
Disadvantages:

- Use of benzene, a known carcinogen, as a starting material
- High temperature (800-950 ^{0}C)

Principle 2: Atom economy

Case study: Styrenes

Styrene production from butadiene using Diels-Alder reaction



Advantages:

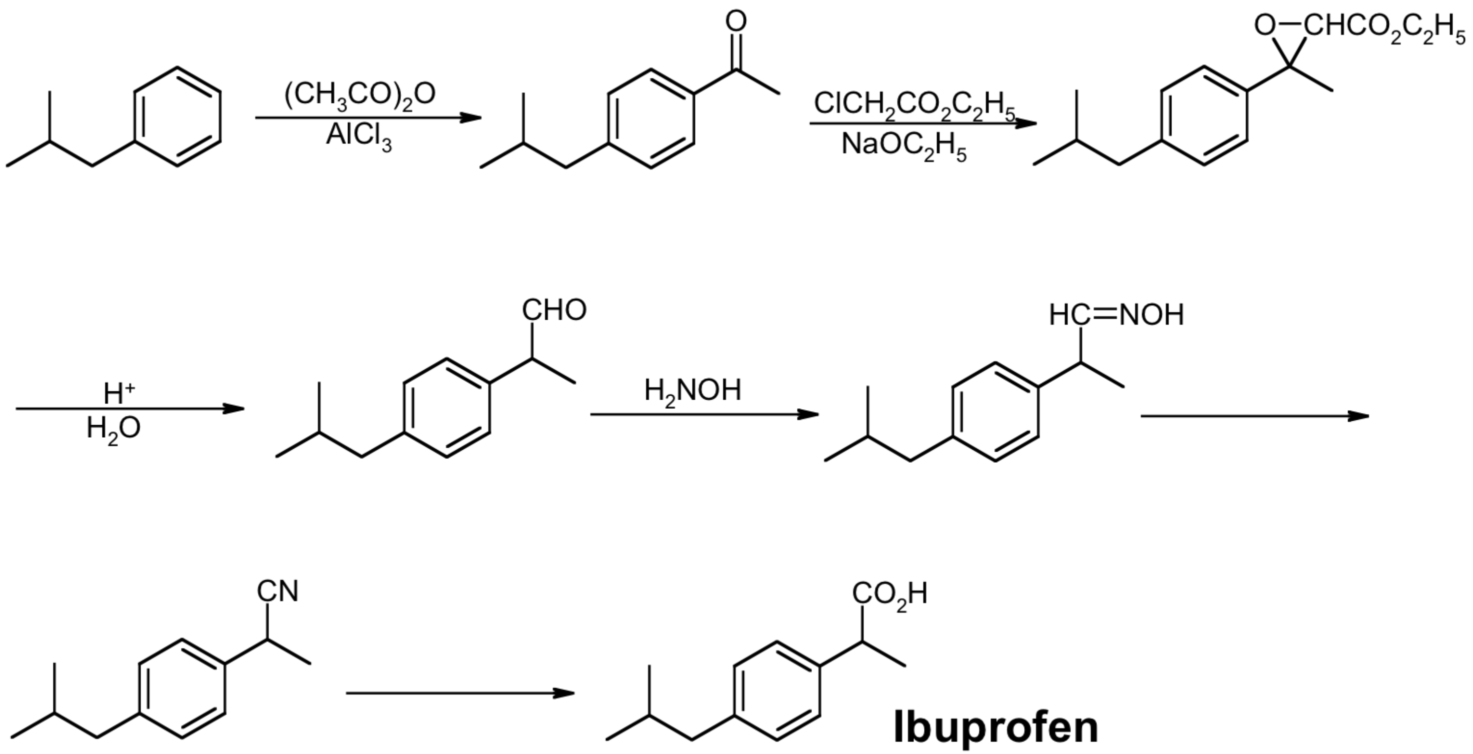
- Diels-Alder reaction =100% atom economy
- Use of non-toxic starting material

Principle 2: Atom economy

Case study: Ibuprofen

Traditional synthesis of ibuprofen was inefficient

- 6 stoichiometric steps
- <40% atom utilization

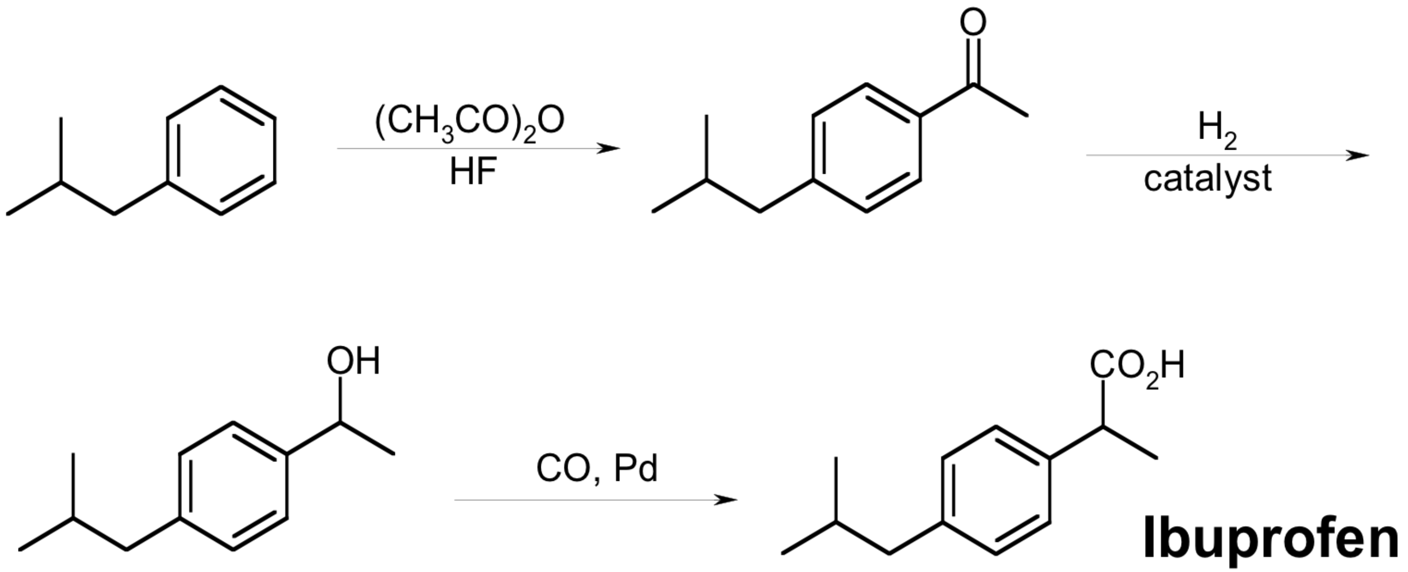


Principle 2: Atom economy

Case study: Ibuprofen

Catalytic synthesis of ibuprofen using Green Chemistry

- 3 catalytic steps
- 80% atom utilization (99% with recovered acetic acid)



BHC

PRINCIPLE 3

Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health or to the environment.

Principle 3: Non-toxic substances

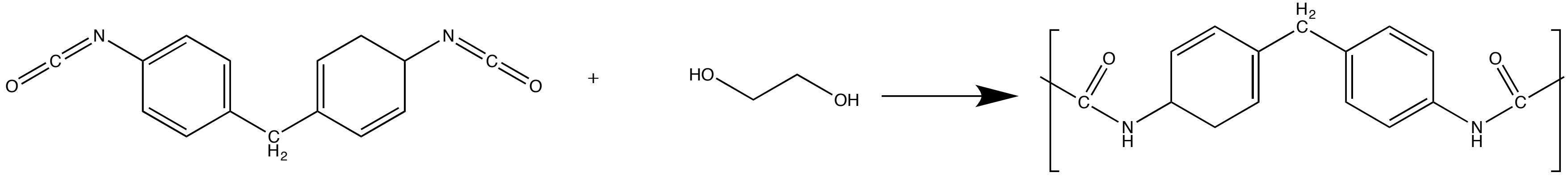
Ideally, non-toxic substances are used to synthesize a chemical product.

Polycarbonate (thermoplastic polymer) has been made using phosgene, a chemical warfare agent.

◆Principle 3: Non-toxic substances

Case study: Polyurethane

Traditional synthesis of polyurethane using isocyanides



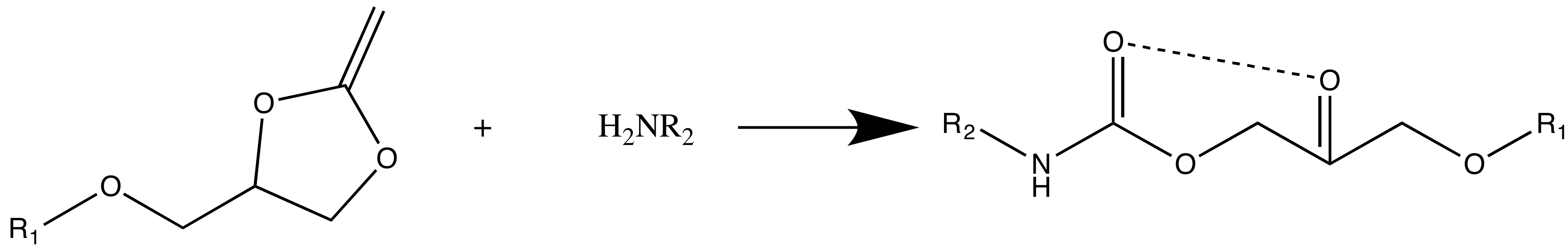
Disadvantages

- Using isocyanides which cause skin and respiratory problems
- When burned, they form toxic and corrosive fumes
- Highly regulated by the US government

Principle 3: Non-toxic substances

Case study: Polyurethane

Non-isocyanide synthesis of polyurethane using green chemistry



Advantages

- No isocyanide is used in the synthesis.
- Product is stable, and has increased resistance properties due to intramolecular hydrogen bonds.

Hybrid Coating Technologies
Nanotech Industries

◆Principle 3: Non-toxic substances

Case study: Paper Bleaching

Conventional paper bleaching: Chlorine dioxide (ClO_2)

Disadvantages:

- Produces unacceptable quantities of chlorinated pollutants, and many are exceptionally toxic.

Novel technology for paper bleaching with TAML/H_2O_2 using green chemistry.

Advantages:

- Alternative catalytic breakdown of H_2O_2 to provide the oxidative equivalent
- Lower temperature and time requirement

PRINCIPLE 4

Chemical products should be designed to preserve efficacy of function while reducing toxicity.

The modern motto of toxicology

"Everything is toxic. It is simply depends on the dose"

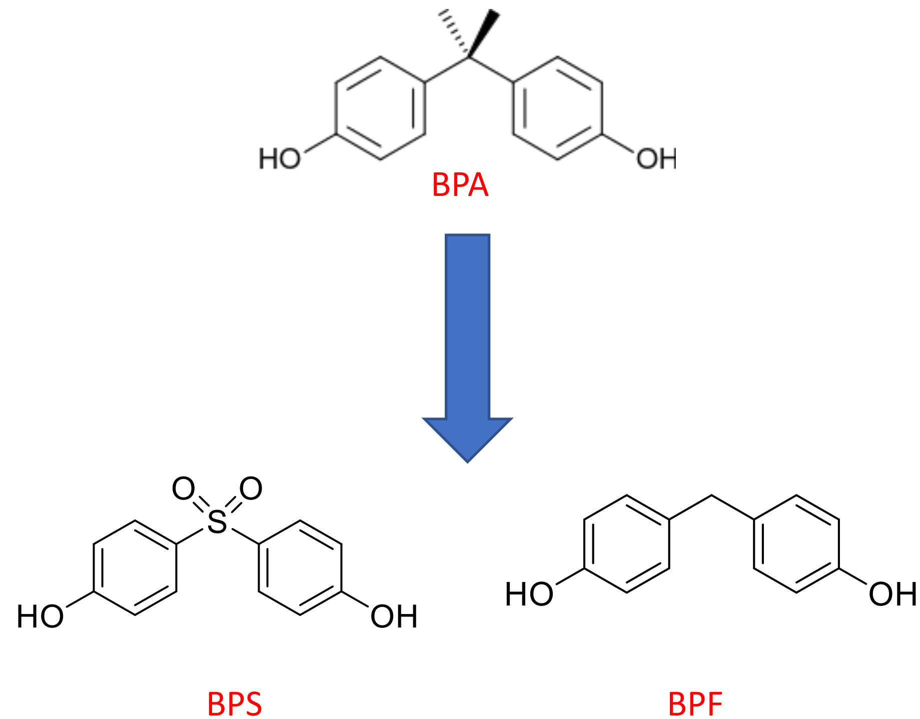
Often otherwise phrased as

"The dose makes the poison."

Risk = Hazard x Exposure

Green chemistry and engineering focus on reducing risk by reducing hazard.

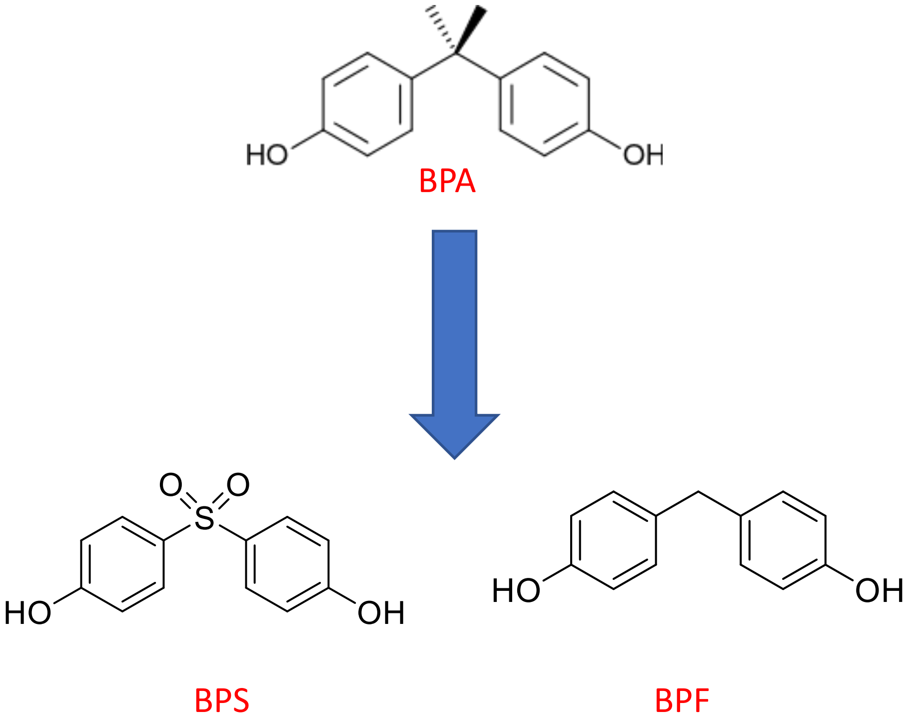
Out of the frying pan and out of the fire: replacement flame retardants now found in breast milk



Rochester JR, Bolden AL. 2015. Environ Health Perspect 123:643–650.

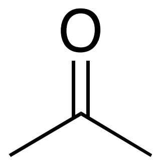
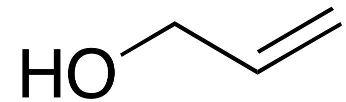
Preventing Regrettable Substitution

Out of the frying pan and out of the fire: replacement flame retardants now found in breast milk



Rochester JR, Bolden AL. 2015. Environ Health Perspect 123:643–650.

The structure makes the poison

Molecular formula (C_3H_6O)			
Name	Acetone 	Methyl vinyl ether 	Allyl alcohol 
Toxicity LD_{50} (mg/kg, oral rat)	9.0	4.9	0.06

◆Principle 4: Designing safer chemicals

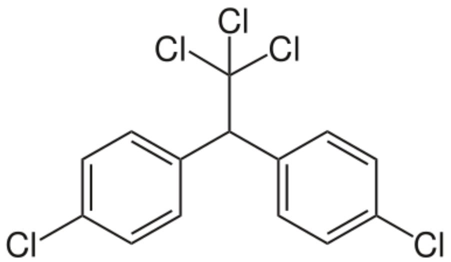
Chemists can design chemicals which have reduced toxicity by:

- Manipulation of chemical bonds, chemical functional groups
  - Reactive functional groups have a greater potential to be toxic -> removing these groups is likely to reduce toxicity
- Modification or termination of the biological pathway
  - While difficult to achieve, if the chemical is modified not to interact with the biological pathway, no biological effect is triggered and the toxicity can be avoided.
- Reducing or eliminating bioavailability.
  - If a chemical does not absorb into a body, it cannot cause harm.

◆Principle 4: Designing safer chemicals

Case study: Pesticides

Dichlorodiphenyltrichloroethane (DDT) - agricultural pesticide and a malarial control agent



DDT

Disadvantages

- Carcinogenic
- Threat to wildlife, especially birds- almost led to the extinction of a bald eagle population

◆Principle 4: Designing safer chemicals

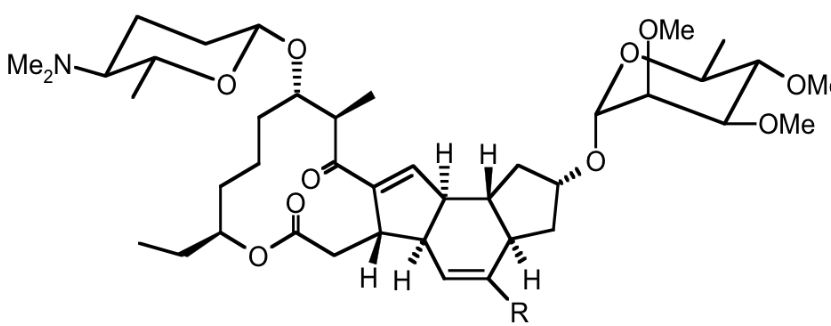
Case study: Pesticides

Spinosad: a natural product for insect control

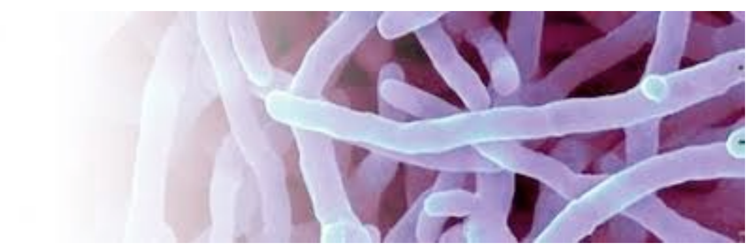
- Produced by bacteria *Saccharopolyspora spinosa*
- Isolated from Caribbean soil sample (sugar mill)
- It selectively targets nervous system of insects
- Demonstrates high selectivity, low mammalian toxicity, and a good environmental profile

Toxicity scorecard

Rat: LD_{50}>5000 mg/kg
Duck: LD_{50}>5000 mg/kg
Fish: $LC_{50\text{-}96h}$=30.0 mg/L
Bee: LD_{50}=0.0025 mg/bee



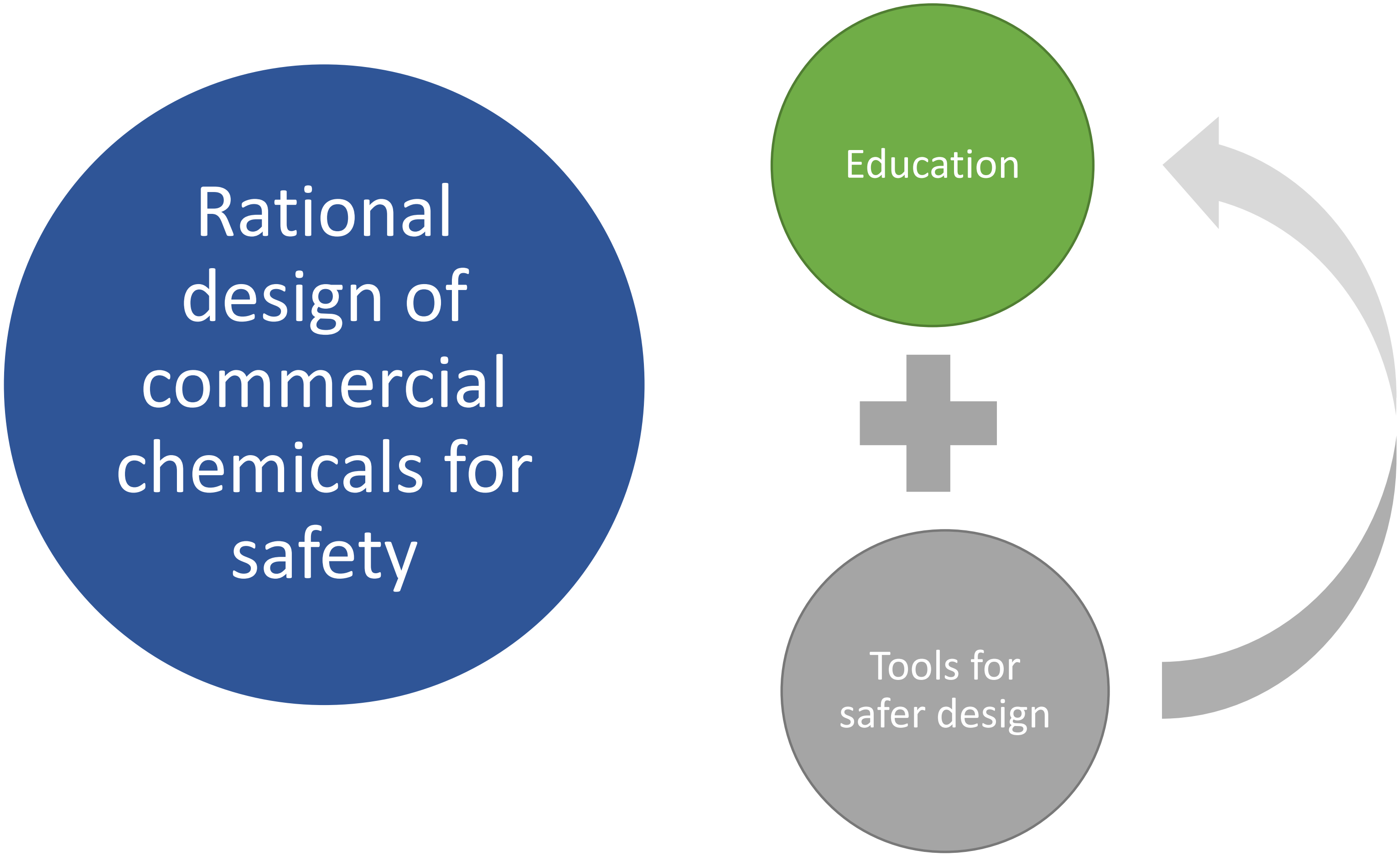
Spinosyn A: R = H
Spinosyn D: R = CH_3



Saccharopolyspora spinosa

Dow AgroSciences

Role of Chemists in Minimizing Health Risk from Commercial Chemicals



Safer Chemical Design Game

Main objectives

- Develop an educational game which can be used by non-major undergraduate students to make connection between physiochemical properties and health.

http://gwiz.yale.edu

LEVEL 1

GOAL	HUMAN TOXICITY	AQUATIC TOXICITY	PERFORMANCE
	Skin absorption	Avoiding toxicity	
	Lung absorption		
	Intestine absorption		

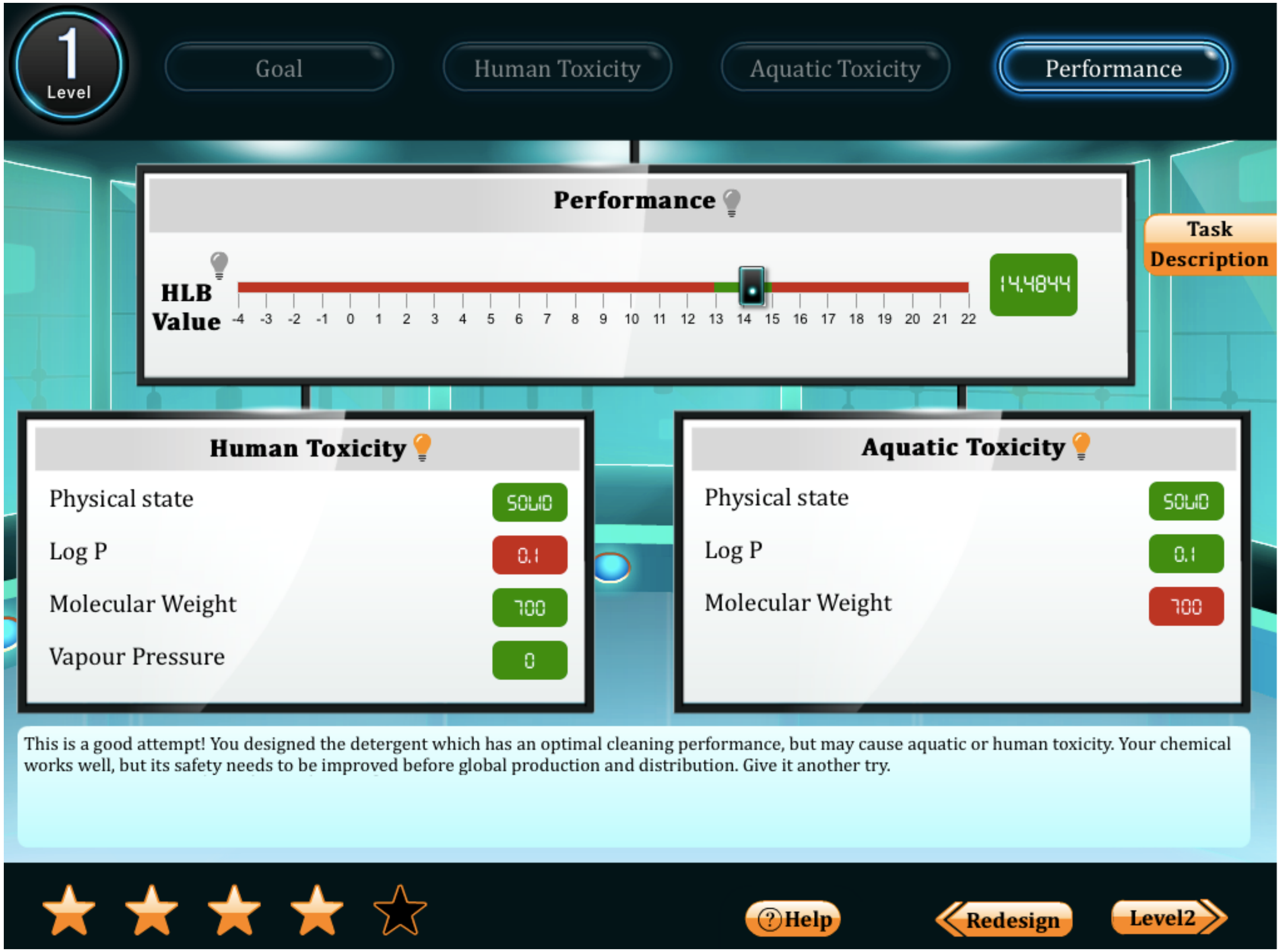
LEVEL 2

GOAL	HUMAN TOXICITY	AQUATIC TOXICITY	PERFORMANCE
	Distribution	Biodegradation	
	Metabolism		
	Elimination		

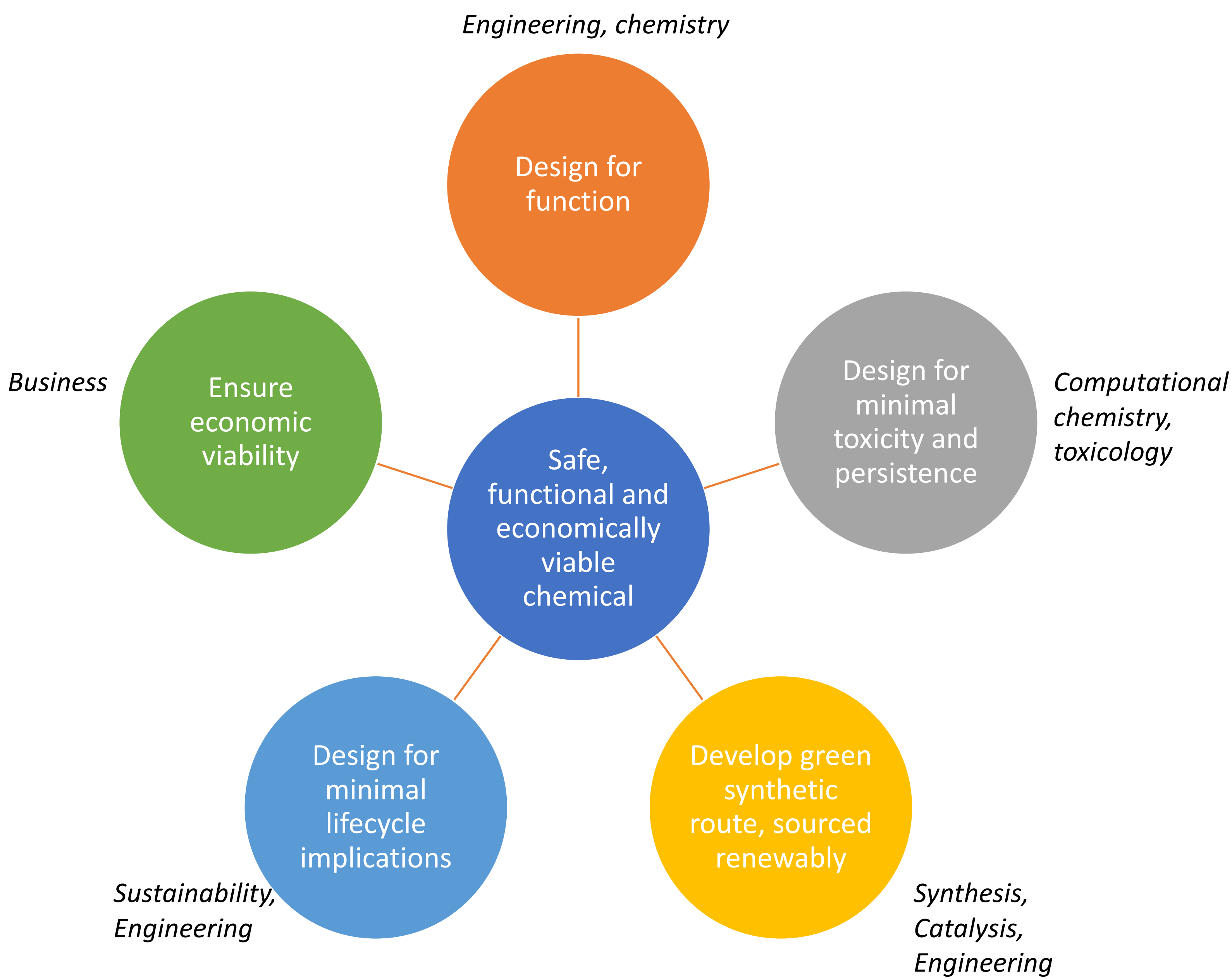
http://gwiz.yale.edu

Safer Chemical Design Game

Feedback



http://gwiz.yale.edu


Engineering, chemistry
Design for function
Business
Ensure economic viability
Safe, functional and economically viable chemical
Design for minimal toxicity and persistence
Computational chemistry, toxicology
Design for minimal lifecycle implications
Sustainability, Engineering
Develop green synthetic route, sourced renewably
Synthesis, Catalysis, Engineering

PRINCIPLE 5

The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible, and innocuous when used.

Principle 5: Reduce auxiliaries

Case study: Organic compounds in the atmosphere

- Volatile Organic Compounds:
  - Chloroform, carbon tetrachloride, methylene chloride, perchloroethylene (PERC)
  - Benzene, Toluene, Xylene (BTX)
  - Acetone, Ethylene Glycol, methylethyl ketone (MEK)

Image source: Adobe Stock

Principle 5: Reduce auxiliaries

Case study: CFCs

- Inherent toxicity
  - Many of them are known carcinogens
- Flammability
  - Relatively low flash point and ignition point lead to high flammability profile
- Explosivity
  - They can easily explode causing harm
- Stratospheric Ozone Depletion
  - Decreasing ozone layer causes more radiation to reach the earth and causing skin cancers, cataracts, damage to immune systems, injury to plants, injury to marine organisms
- Atmospheric Ozone Production
  - Increasing Global Warming Potential

◆Principle 5: Reduce auxiliaries

Alternatives

- Aqueous Solvents
  - Solvents based on water and not organic solvents
- Solventless Conditions
  - Reactions done without solvents, for example, the ones used in mechanochemistry
- Supercritical Fluids
  - $scCO_2$ which can evaporate after changing reaction conditions
- Ionic Liquids

PRICINPLE 6

Energy requirements should be recognized for their environmental and economic impacts and thus should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

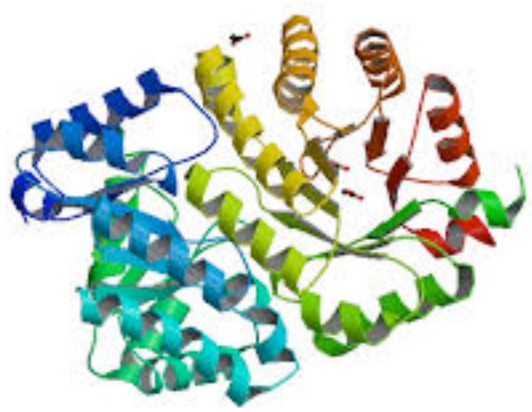
◆Principle 6: Minimize energy use

Most energy is used for heating, cooling, separations and pumping.

Ideally, all reactions are performed at ‘ambient’ conditions – room temperature and atmospheric pressure – in order to minimize energy usage.

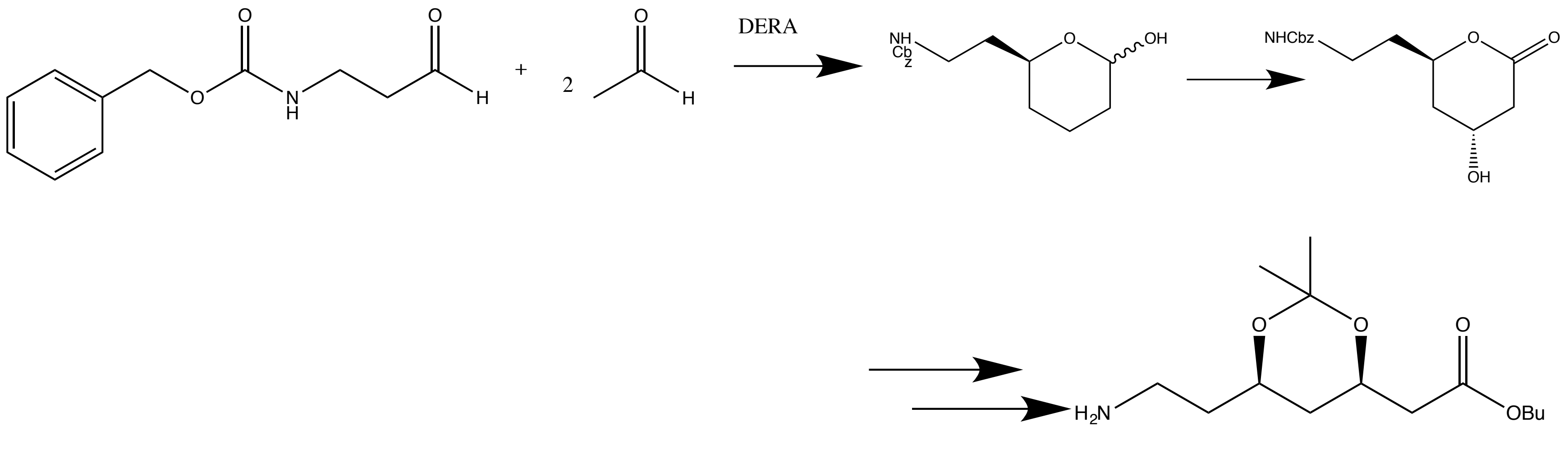
Principle 6: Minimize energy use

Case Study: Atorvastatin



Atorvastatin, a cholesterol-lowering drug, suffers from an energy-demanding synthesis as a result of two cryogenic reactions at - 70 ^{o}C

New ***biocatalytic*** synthesis uses enzyme DERA and shortens the process by removing two energy intensive chemical steps.



PRINCIPLE 7

A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.

Principle 7: Use Renewable feedstocks

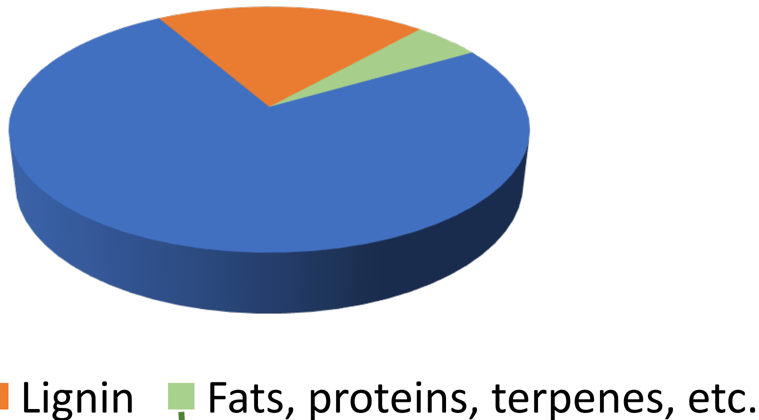
- CO_2
- Biomass (algae, corn, switchgrass, poplar, willow, sorghum, and bamboo)
- Agricultural waste (ex. Manure)

Images from Adobe Stock

Biomass Platforms

Biomass production in nature:
180 billion metric tons/yr

Only about 4% utilized by humans
(food, ethanol, sweeteners)



Building blocks for a diverse chemical platform.

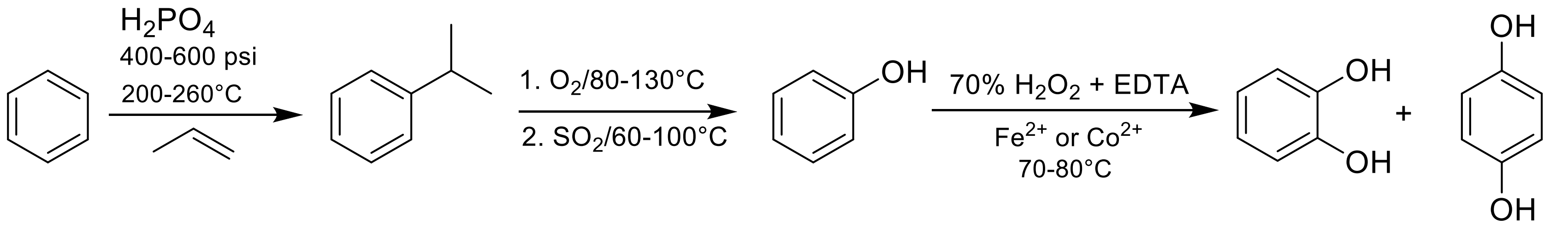
Nature's richest source of aromatic carbon. Used in polymers, adhesives, production of phenolic chemicals.

Converted into polymers, lubricants, and detergents.

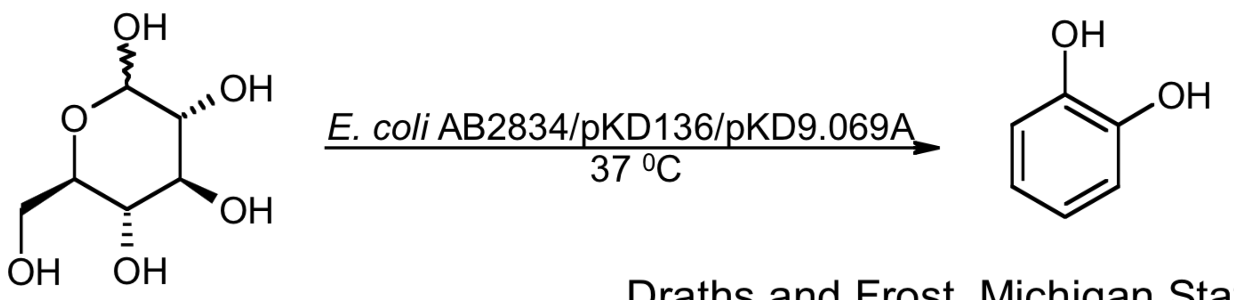
Principle 7: Use Renewable feedstocks

Case Study: Catechol Synthesis

Traditional synthesis of Catechol using benzene



Synthesis of Catechol from D-Glucose using Green Chemistry



Draths and Frost, Michigan State University

Principle 7: Use Renewable feedstocks

- Design and manufacture of new, high-performance bio-based materials
- Many applications—resins, polymers, composites, and foams, and even circuit boards and a leather substitute
- Derived from renewable, biological feedstocks such as chicken feathers, flax, vegetable oils, lignin, and cellulose
- Manufacture process consumes less water and energy than conventional petroleum-based processes, produces less waste, and is industrially viable

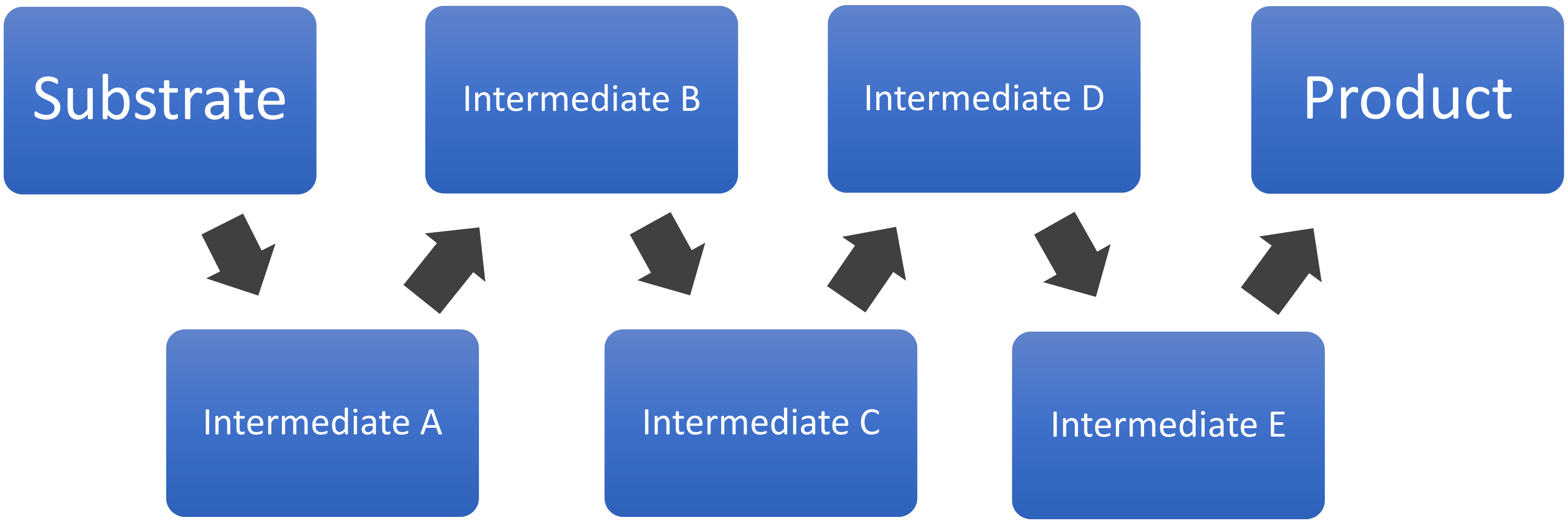
Wool

PRINCIPLE 8

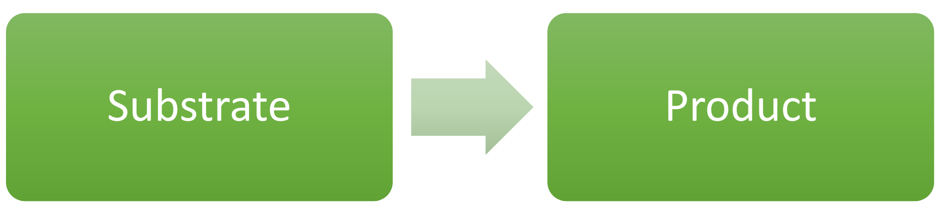
Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.

Principle 8: Derivatization

Traditional approach



Green Chemistry approach

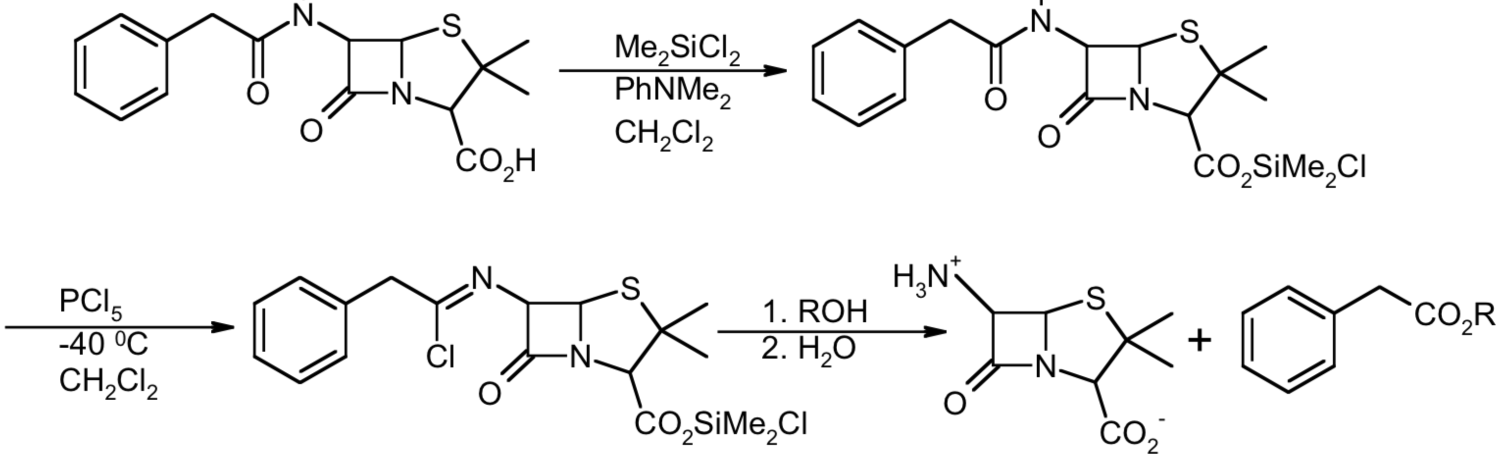


Principle 8: Derivatization

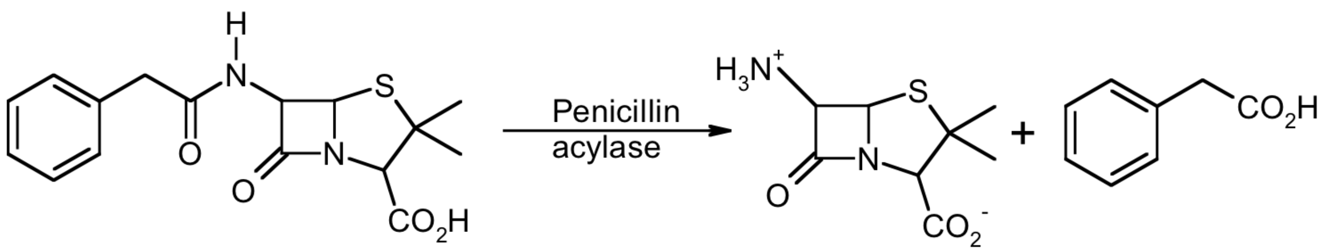
Case Study: 6-aminopenicillanic acid

Synthesis of 6-aminopenicillanic acid – core moiety of penicillin

Traditional synthesis of 6-aminopenicillanic acid using 3 steps and intermediate products:



New synthesis using enzyme and less derivatives



PRINCIPLE 9

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

Catalysts can facilitate complex reactions by:

- Lowering the activation energy of the reaction
- Reducing temperature necessary to achieve a reaction
- Controlling the site of the reaction (selectivity enhancement)

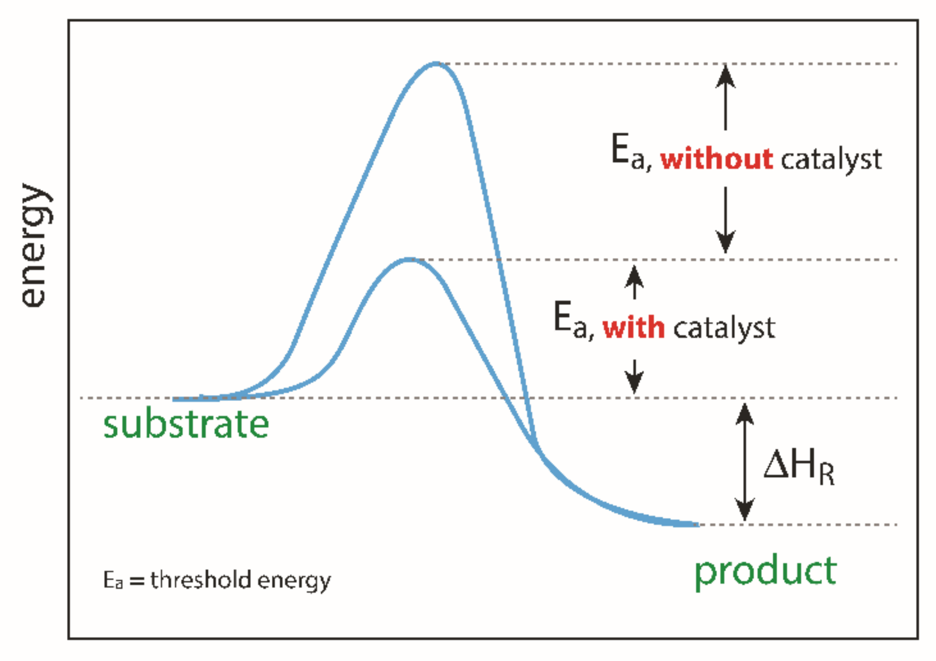
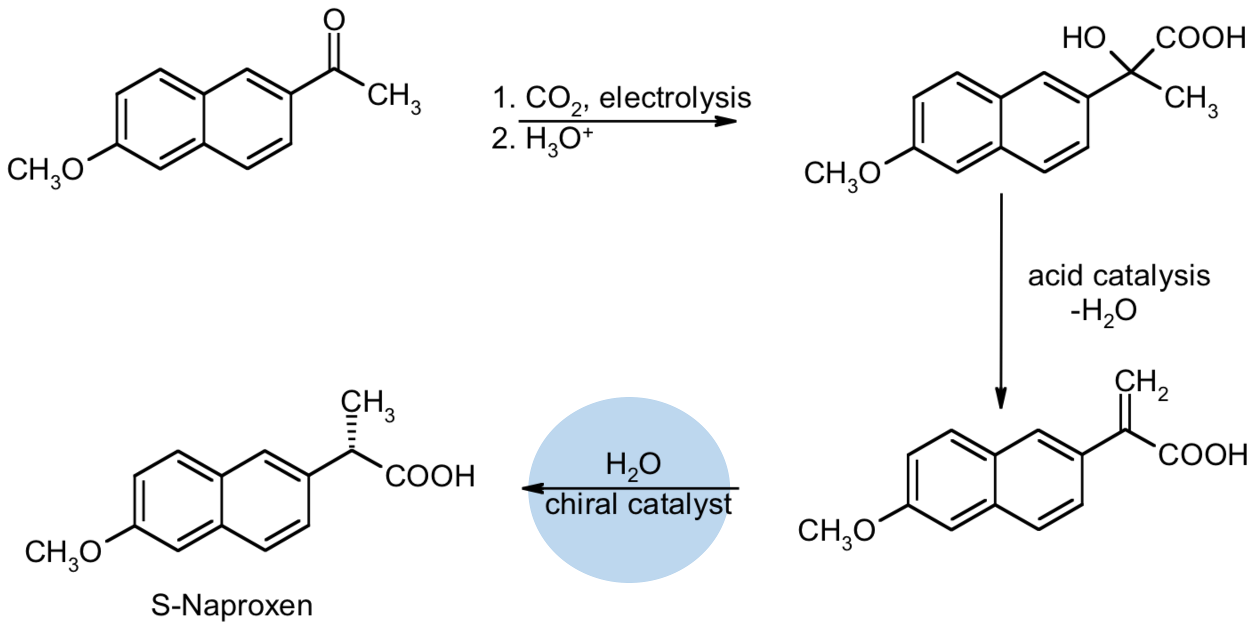


Image source: Adobe stock

Principle 9: Catalysis

Case Study: Green Naproxen synthesis

Nonsteroidal anti-inflammatory drug (NSAID) of the propionic acid class (the same class as ibuprofen) that relieves pain, fever, swelling, and stiffness; COX inhibitor



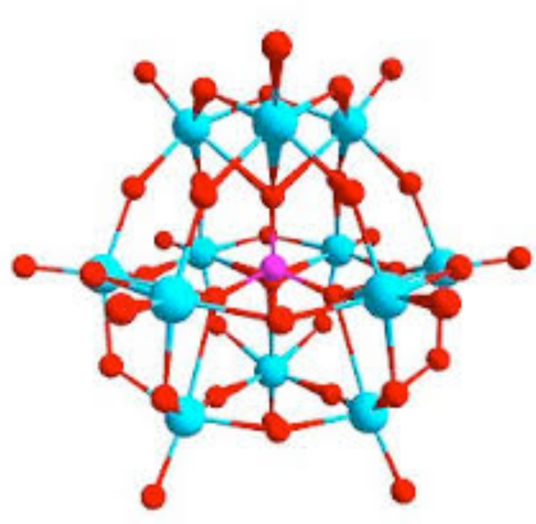
97% yield in three steps

Dartt and Davis

Principle 9: Catalysis

Case Study: Paper production

- Polyoxometalate (POM) catalysts
  - non-toxic, inorganic cluster compounds
  - selectively delignify wood
  - utilize only air and water



- Allows use of oxygen instead of chlorine as the whitener of paper pulp and water as the solvent
- Generates only CO_2 and H_2O, instead of chlorinated organics

Hill, Emory University;
Hill et al, *Nature* **2001**, *414*, 191–195

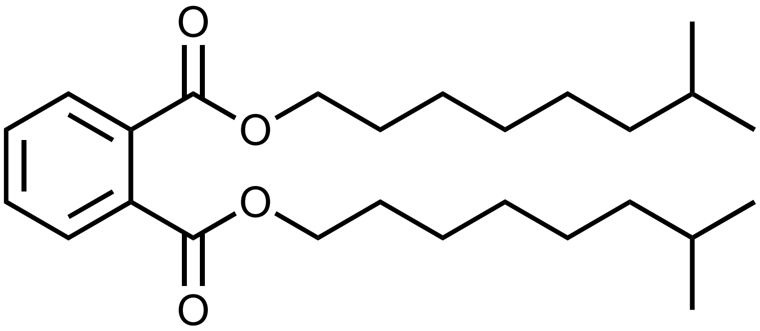
PRINCIPLE 10

Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

Principle 10: Biodegradability

Case Study: Plasticizers

Conventional plasticizers such as DiNP are a needed additive to soften plastics



Diisononyl phthalate, DiNP

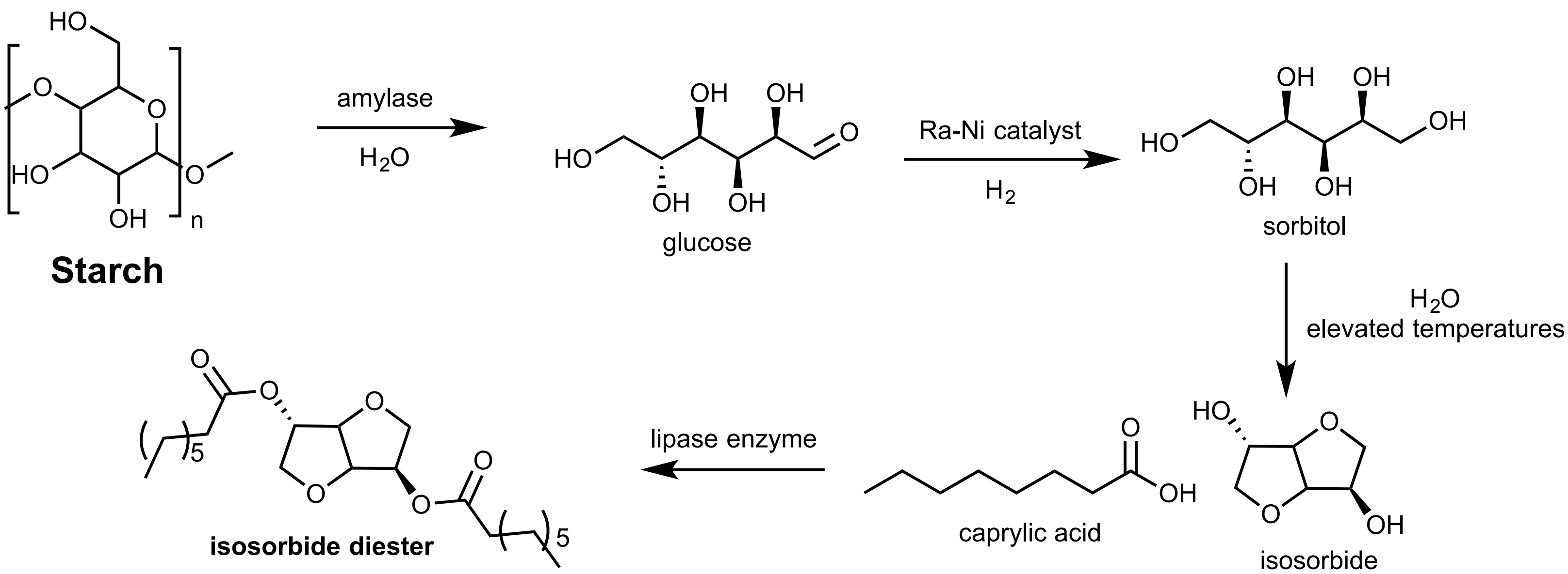
Disadvantages:

- DiNP exposure has been linked to liver toxicity, endocrine disruption and carcinogenicity
- They are persisting in the environment

Principle 10: Biodegradability

Case Study: Paper production

Alternative plasticizers, such as isosorbide diester, are derived from starch:



Advantages:

- Offers 1 to 1 substitution of DiNP in plastics
- Thermally stable and biodegradable

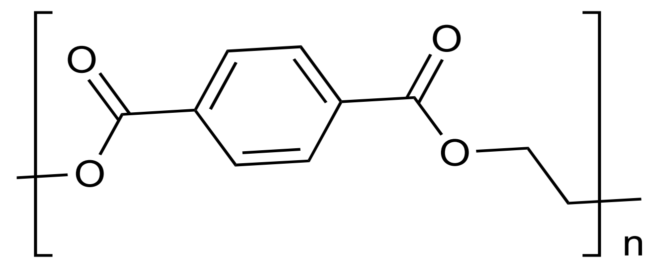
Principle 10: Biodegradability

Case Study: Plastics

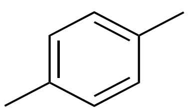
Conventional plastics (PET) are made from petroleum

Disadvantages

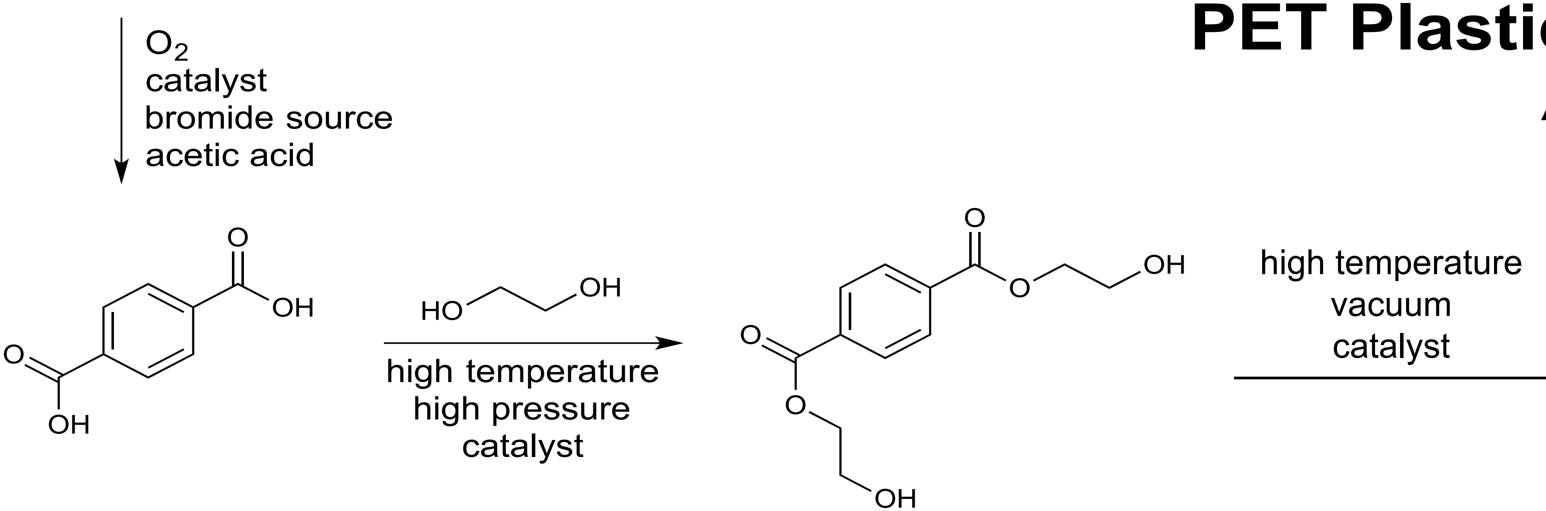
- Will persist in the environment
- Is made from depleting resources



PET Plastic



Petroleum

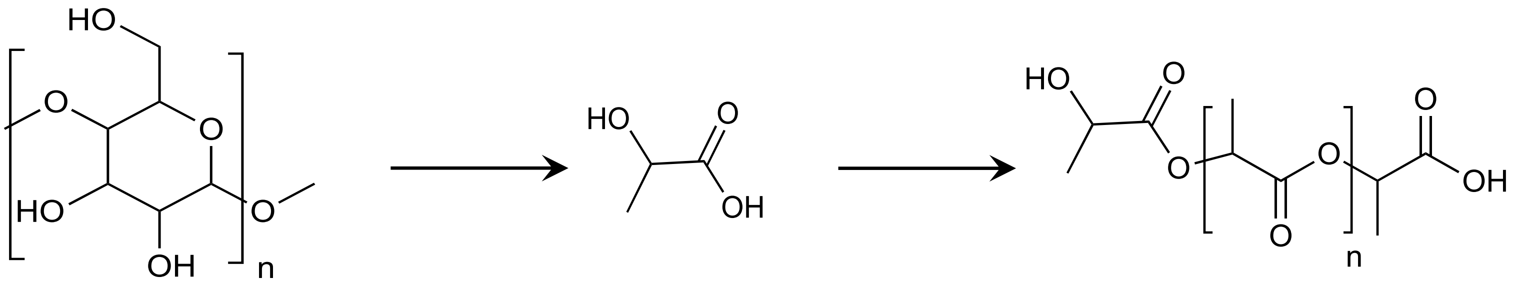


Principle 10: Biodegradability

Case Study: Plastics

Synthesis of PolyLactic Acid (PLA) from starch:

Advantages
- Has PET performance
- Made from renewable materials
- Biodegradable in the environment



Starch **Lactic Acid** **PolyLacticAcid PLA**

PRINCIPLE 11

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

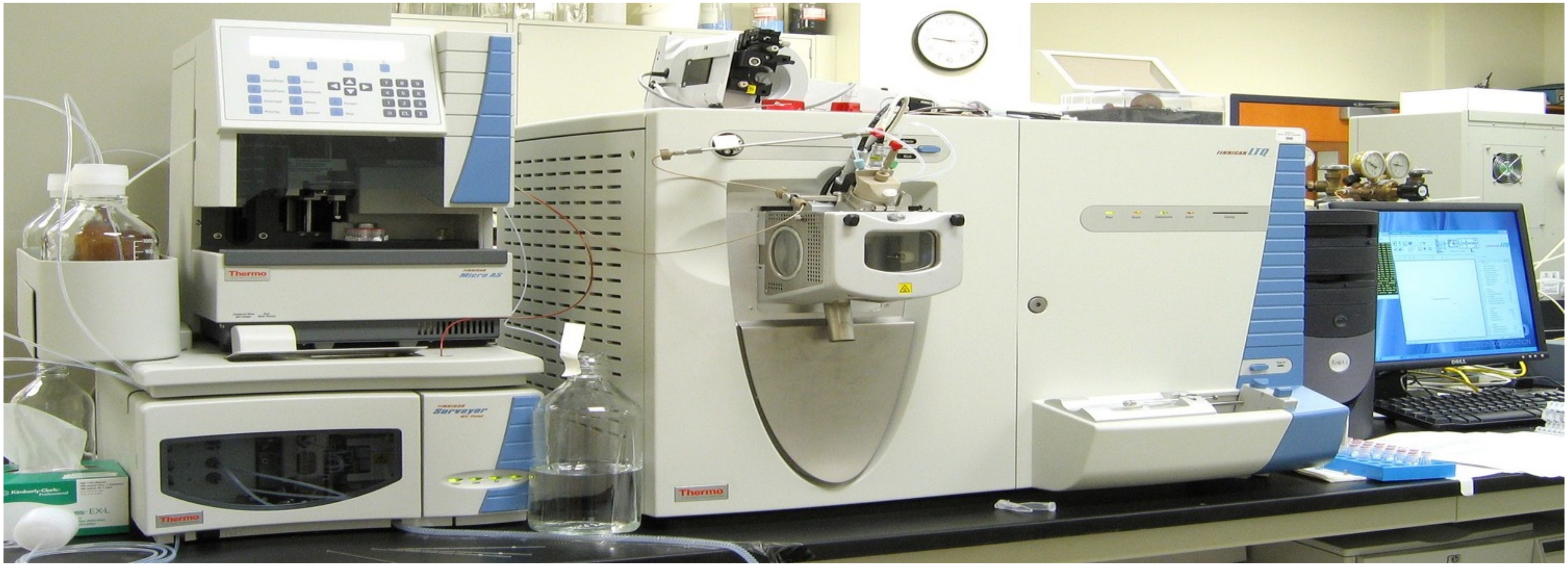
Role of Analytical Chemistry

Analytical chemistry has been at the heart of the environmental movement since its inception. It's been used in:

- Identification
- Monitoring
- Measurement
- Characterization

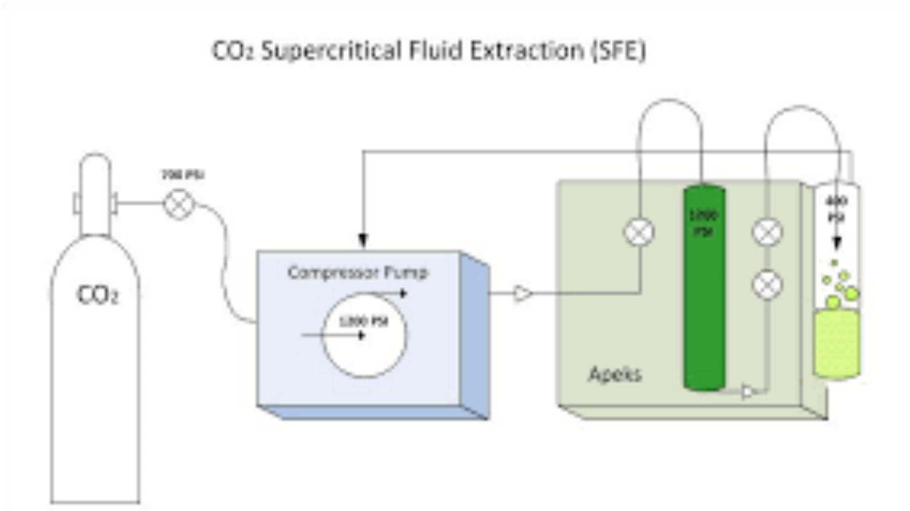
What Does Green Analytical Chemistry Mean?

Green Chemistry is applicable to all chemical processes, including the methods, protocols and processes of environmental analytical chemistry.

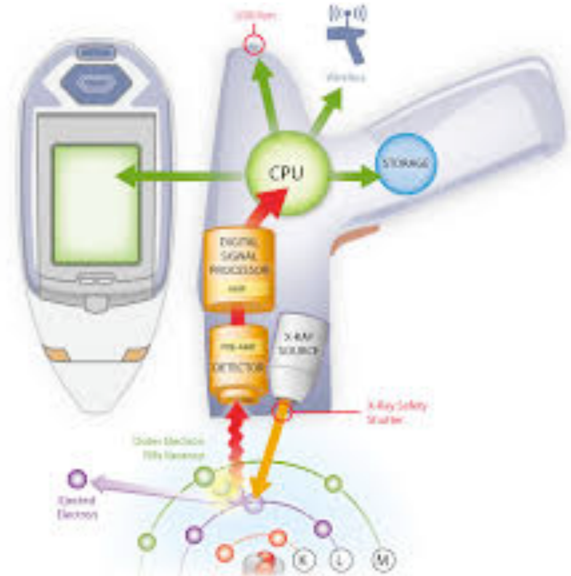


Source: Wikipedia

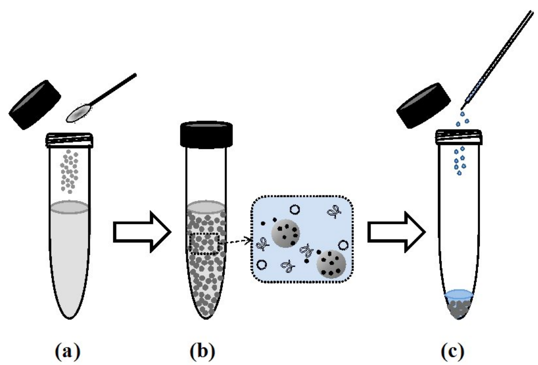
Examples of Green Analytical Chemistry Methodologies



Supercritical Fluid Extraction



X-ray fluorescence detection for multi-metal matrix



Solid-phase extraction and micro-extraction

Process Analytical Chemistry to Minimize Waste Generation

Through the use of real-time, in-process monitors, sensors, etc., pollution and hazardous waste generation can be prevented rather than simply measured after it is produced.

Solid-acid catalyzed 1-butene/isobutane alkylation process:

- replaces HF and H_2SO_4 catalysts
- process utilizes supercritical CO_2 to prevent coke accumulation in pores of solid catalyst
- on-line GC analysis

Subramaniam, University of Kansas
Ind. Eng. Chem. Res., 2001, 40 (18), pp 3879–3882

Continuous Flow Reactors

- Replacing batch reactors on large, medium and even small scale

- Advantages:
  - Precise control of reaction conditions
  - Reproducible reaction outcome (product purity)
  - Minimizes waste, and provides increased safety

PRINCIPLE 12

Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Principle 12: Minimize chemical hazard

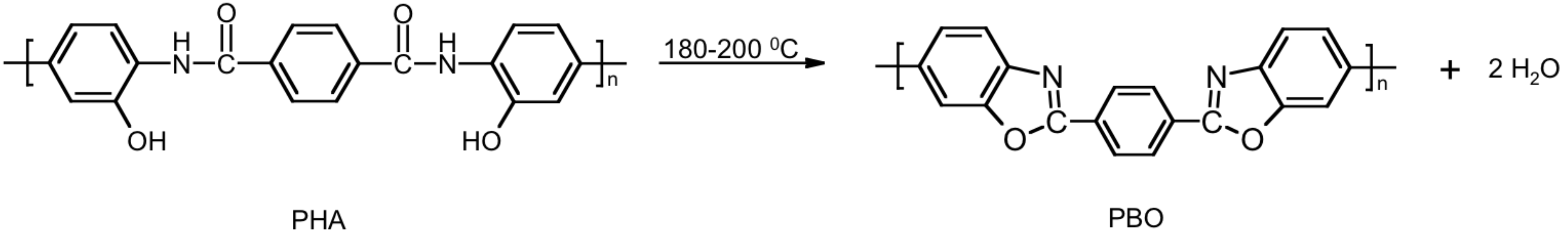
- Accidents can be avoided by minimizing hazard.
- Approaches to design safer chemistry can include the use of solids or low vapor pressure substances in place of volatile liquids.
- Other approaches include avoiding the use of molecular halogens in large quantities.
- Continuous flow processes can minimize chemical hazards

Principle 12: Minimize chemical hazard

Case study: Designing safer polymers for use in airplanes

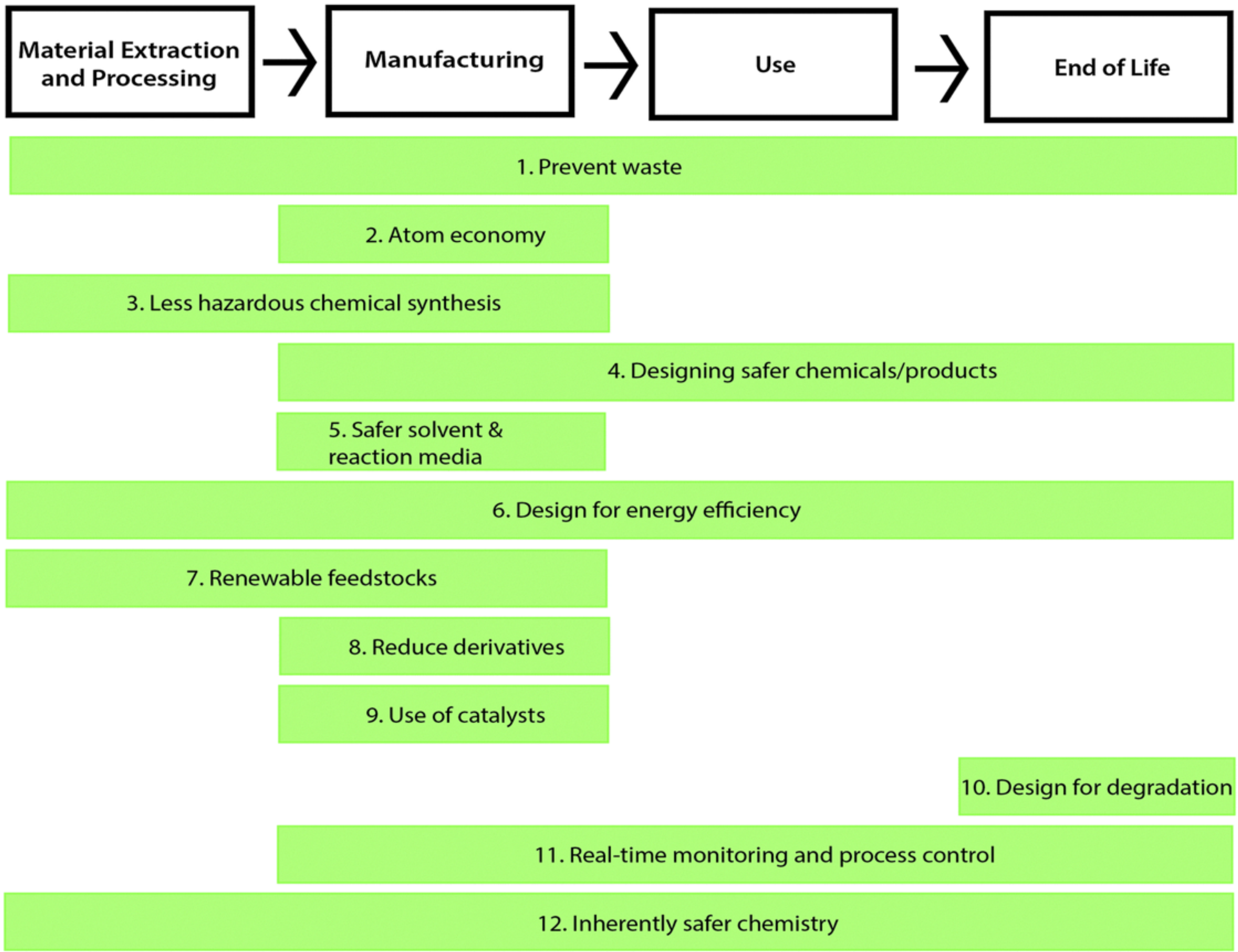
Polyhydroxyamide (PHA):

- moldable into seats, bins and wall panels
- synthesized under mild conditions
- decomposes into fire-resistant polybenzoxazole (PBO) and water upon heating



Westmoreland, UMass Amherst

Life-cycle thinking



Chem. Soc. Rev., 2015, 44, 5758-5777

Thank you!