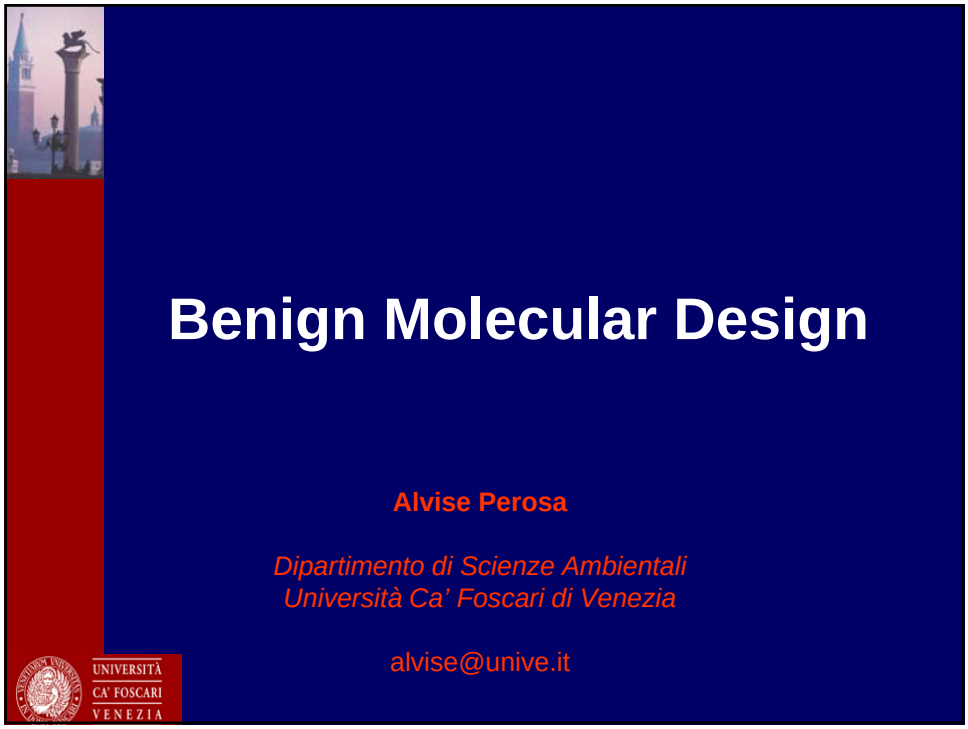
Benign Molecular Design
Alvise Perosa
Dipartimento di Scienze Ambientali
Università Ca' Foscari di Venezia
alvise@unive.it
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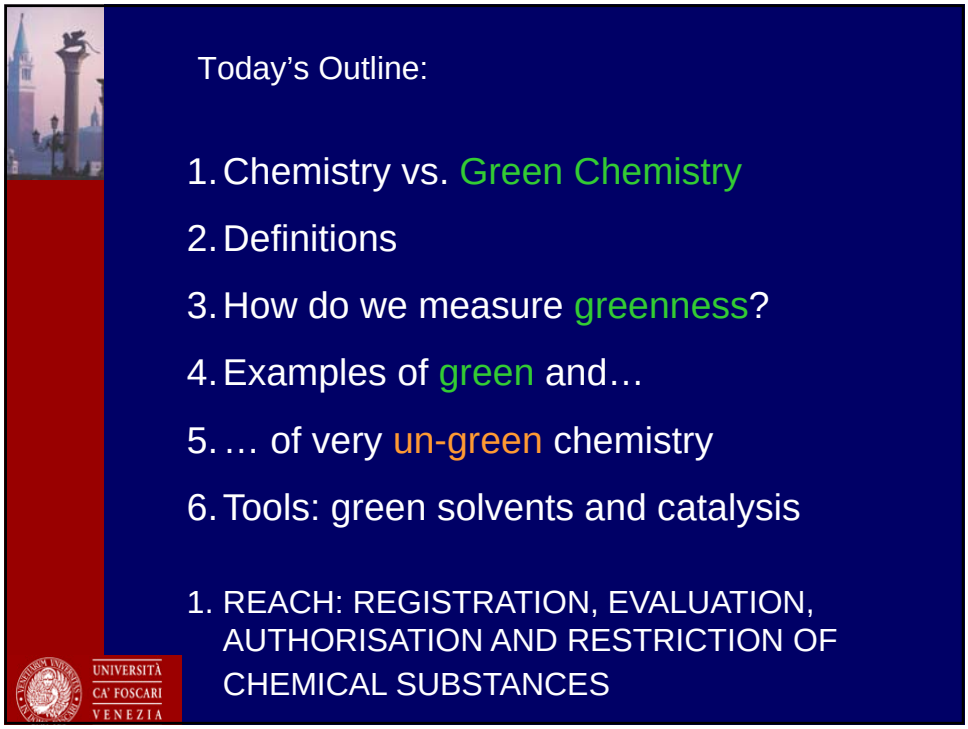
Today's Outline:
1. Chemistry vs. Green Chemistry
2. Definitions
3. How do we measure greenness?
4. Examples of green and…
5. … of very un-green chemistry
6. Tools: green solvents and catalysis
1. REACH: REGISTRATION, EVALUATION, AUTHORISATION AND RESTRICTION OF CHEMICAL SUBSTANCES
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Chemistry?

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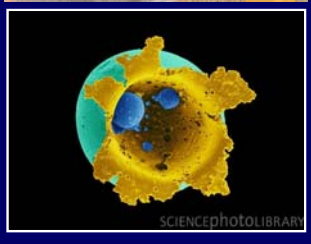
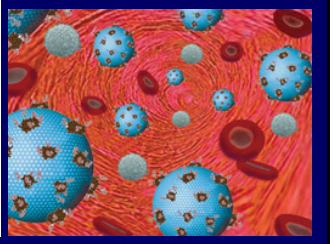
Chemistry makes life better!





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Green Chemistry:

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Green Chemistry: definition 1

Sustainable development

Sustainability: "Given reasonable assumption concerning progress in the technology and the activities of a civilization, a sustainable civilization is one in which the net sum of the daily activities of the people who comprise it, individually and collectively, can be carried on into the indefinite future, without undermining the ability of future generations to live with at least a comparably advantageous welfare".

Terrence Collins, *Science*, **2001**, *291*, 48.

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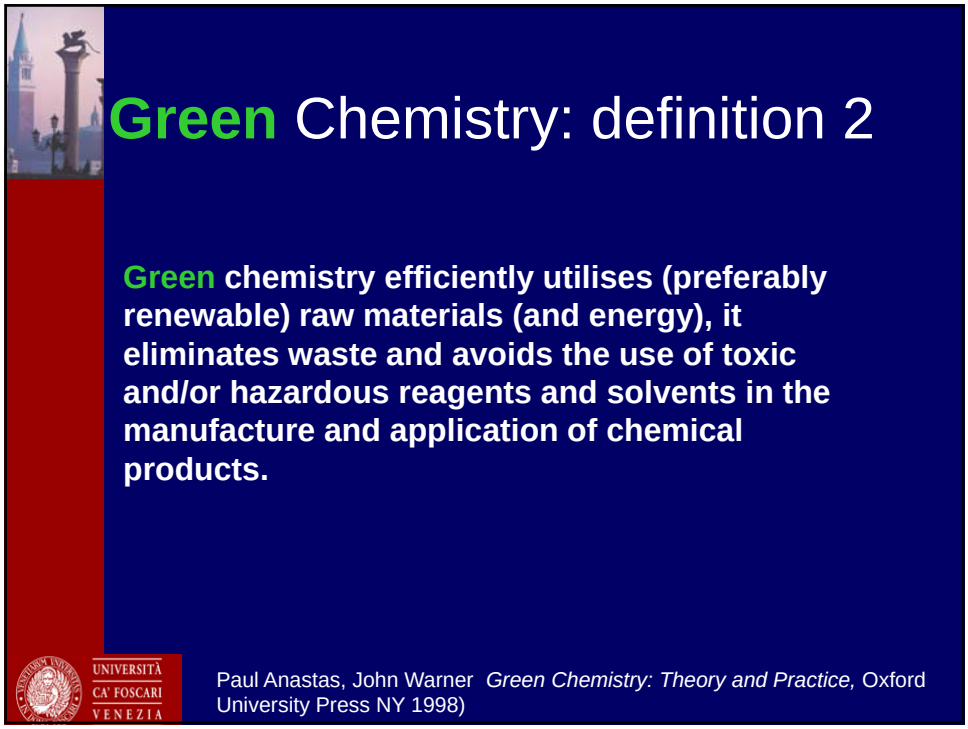
Green Chemistry: definition 2
Green chemistry efficiently utilises (preferably renewable) raw materials (and energy), it eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.
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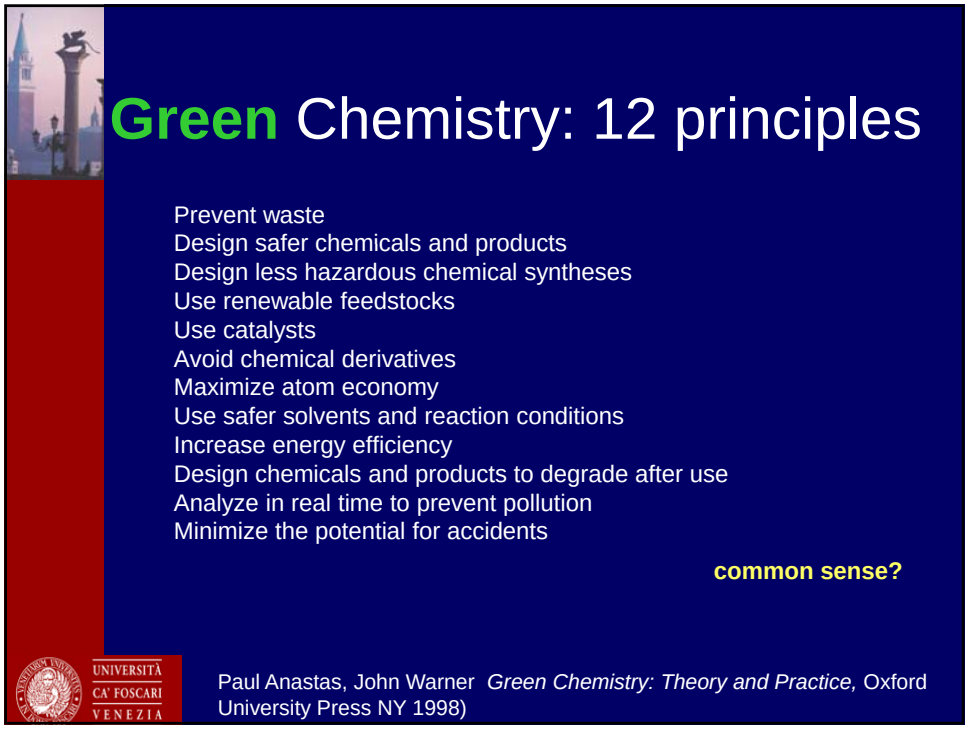
Paul Anastas, John Warner Green Chemistry: Theory and Practice, Oxford University Press NY 1998)


Green Chemistry: 12 principles
Prevent waste
Design safer chemicals and products
Design less hazardous chemical syntheses
Use renewable feedstocks
Use catalysts
Avoid chemical derivatives
Maximize atom economy
Use safer solvents and reaction conditions
Increase energy efficiency
Design chemicals and products to degrade after use
Analyze in real time to prevent pollution
Minimize the potential for accidents
common sense?
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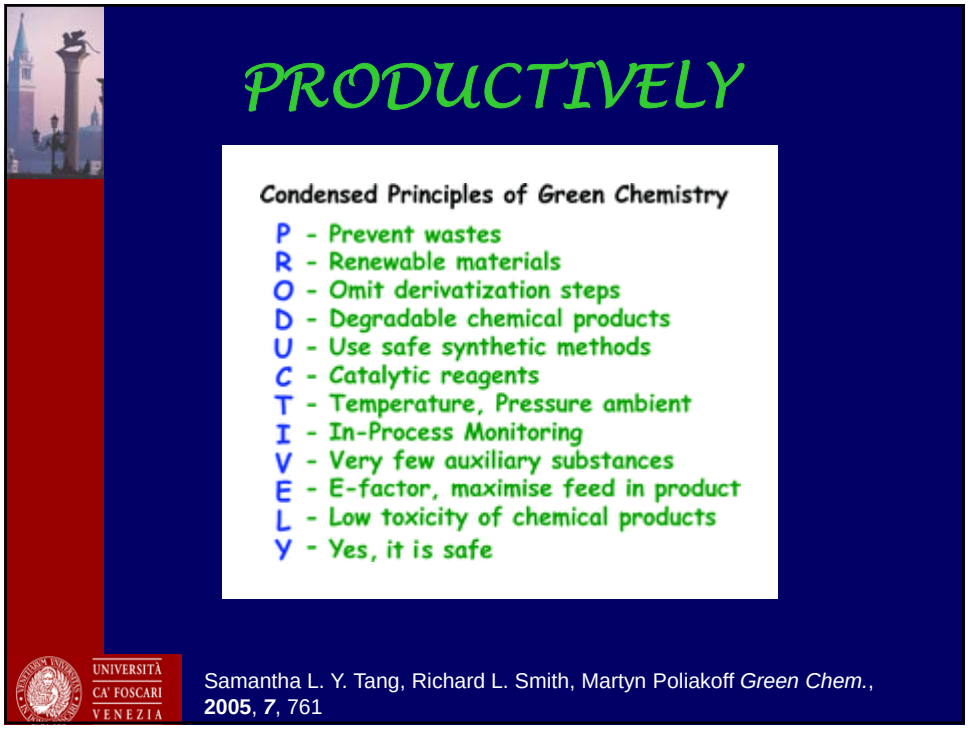
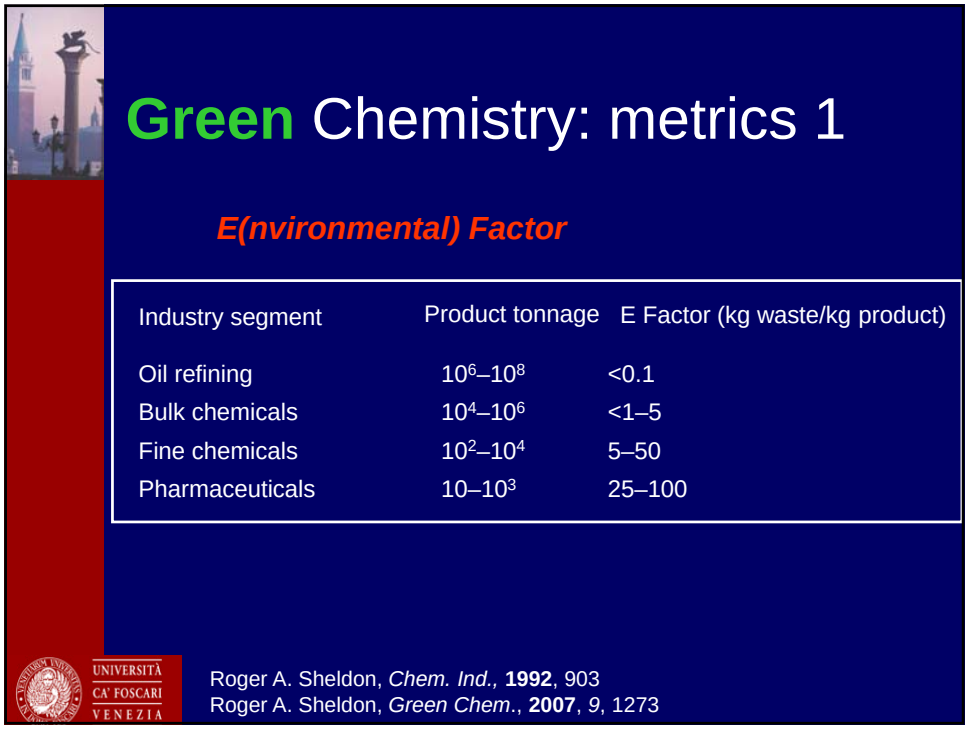
Paul Anastas, John Warner Green Chemistry: Theory and Practice, Oxford University Press NY 1998)


PRODUCTIVELY
Condensed Principles of Green Chemistry
P - Prevent wastes
R - Renewable materials
O - Omit derivatization steps
D - Degradable chemical products
U - Use safe synthetic methods
C - Catalytic reagents
T - Temperature, Pressure ambient
I - In-Process Monitoring
V - Very few auxiliary substances
E - E-factor, maximise feed in product
L - Low toxicity of chemical products
Y - Yes, it is safe
UNIVERSITÀ CA' FOSCARI VENEZIA
Samantha L. Y. Tang, Richard L. Smith, Martyn Poliakoff Green Chem., 2005, 7, 761


Green Chemistry: metrics 1
E(nvironmental) Factor
Industry segment | Product tonnage | E Factor (kg waste/kg product)
Oil refining | 10^6–10^8 | <0.1
Bulk chemicals | 10^4–10^6 | <1–5
Fine chemicals | 10^2–10^4 | 5–50
Pharmaceuticals | 10–10^3 | 25–100
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Roger A. Sheldon, Chem. Ind., 1992, 903
Roger A. Sheldon, Green Chem., 2007, 9, 1273

Green Chemistry: metrics 2

Atom economy

$$\% \text{ AE} = \frac{\text{molecular weight (gmol}^{-1}\text{) product}}{\Sigma \text{ molecular weights of all reagents}}$$

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

Atom economy: an example

1. Chorohydrin process

$H_2C{=}CH_2 + Cl_2 + H_2O \longrightarrow ClCH_2CH_2OH + HCl$

$\xrightarrow{Ca(OH)_2}$  $+ CaCl_2 + 2\,H_2O$

Overall:

$H_2C{=}CH_2 + Cl_2 + Ca(OH)_2 \longrightarrow C_2H_4O + CaCl_2 + H_2O$ 25 % atom utilisation

2. Direct oxidation

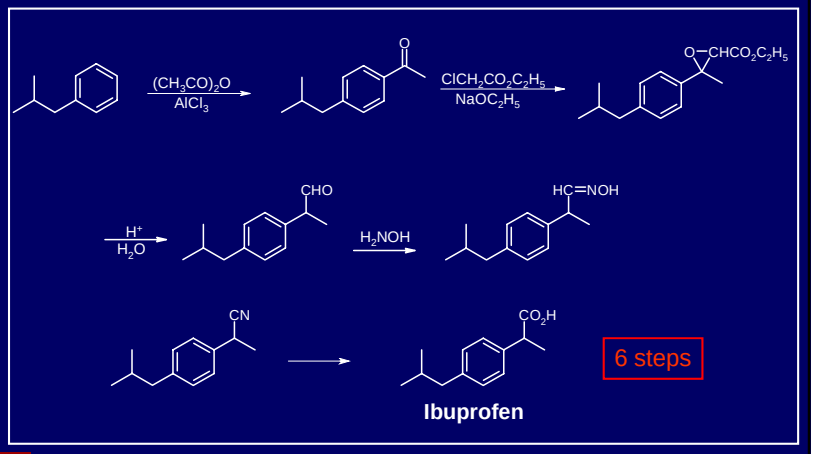
$H_2C{=}CH_2 + 0.5\,O_2 \longrightarrow$  100% atom utilisation

$E_{th} = 75/25 = 3$

$E_{th} = 0/100 = 0$

Theoretical E factor (E_{th}) is the MW of wasted atoms divided by the MW of product (always much lower than the true E).

Traditional Boot's synthesis of ibuprofen



6 steps

Ibuprofen

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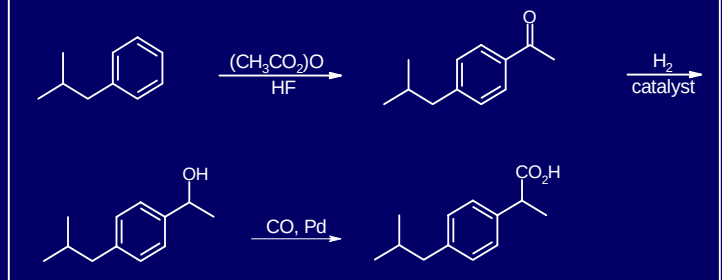
BHC green synthesis of ibuprofen:



Ibuprofen

3 steps

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Reagent		Used in ibuprofen		Unused in ibuprofen	
Formula	M_r	Formula	M_r	Formula	M_r
$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
$C_4H_6O_3$	102	C_2H_3	27	$C_2H_3O_3$	75
$C_4H_7ClO_2$	122.5	CH	13	$C_3H_6ClO_2$	109.5
C_2H_5ONa	68		0	C_2H_5ONa	68
H_3O	19		0	H_3O	19
NH_3O	33		0	NH_3O	33
H_4O_2	36	HO_2	33	H_3	3
Total		Ibuprofen		Waste products	
$C_{20}H_{42}NO_{10}ClNa$	514.5	$C_{13}H_{18}O_2$	206	$C_7H_{24}NO_8ClNa$	308.5

40% Atom economy in the Boots' synthesis of ibuprofen

Reagent		Used in ibuprofen		Unused in ibuprofen	
Formula	M_r	Formula	M_r	Formula	M_r
$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
$C_4H_6O_3$	102	C_2H_3O	43	$C_2H_3O_2$	59
H_2	2	H_2	2		0
CO	28	CO	0		0
Total		Ibuprofen		Waste products	
$C_{15}H_{22}O_4$	266	$C_{13}H_{18}O_2$	206	$C_2H_4O_2$	60

77% Atom economy in the green synthesis of ibuprofen

http://www.rsc.org/education/teachers/learnnet/green/ibuprofen/home.htm

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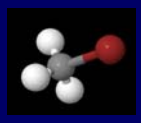
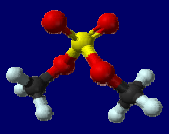
Dimethylcarbonate: an alternative green methylating reagent



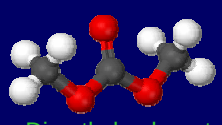


CH_3Br

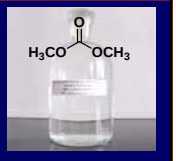
$H_3CO-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-OCH_3$

Toxic!

100% NON-TOXIC



Dimethylcarbonate



Ibuprofen

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Redesign of the Sertraline Process

- Sertraline: active ingredient in Zoloft (Pfizer).
- In 2007, it was the most prescribed antidepressant on the U.S. retail market, with 29,652,000 prescriptions
- Combined process
  - Doubled yield
  - Ethanol replaced CH_2Cl_2, THF, toluene, hexane
  - Eliminated use of 140 metric tons/year $TiCl_4$
  - Eliminated 150 metric tons/year 35% HCl

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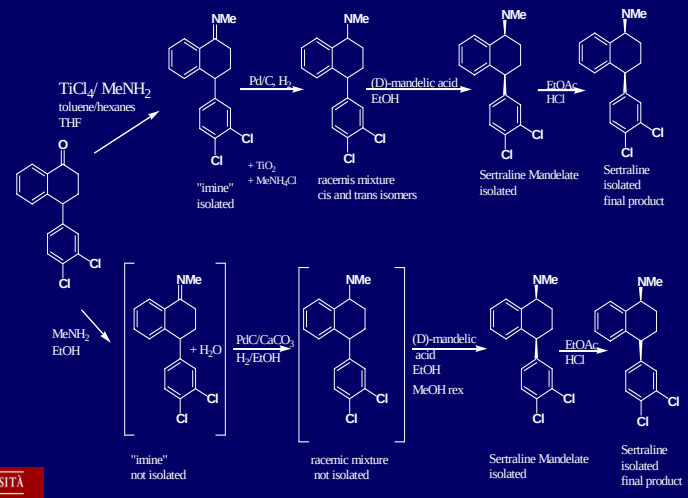
Redesign of the Sertraline Process



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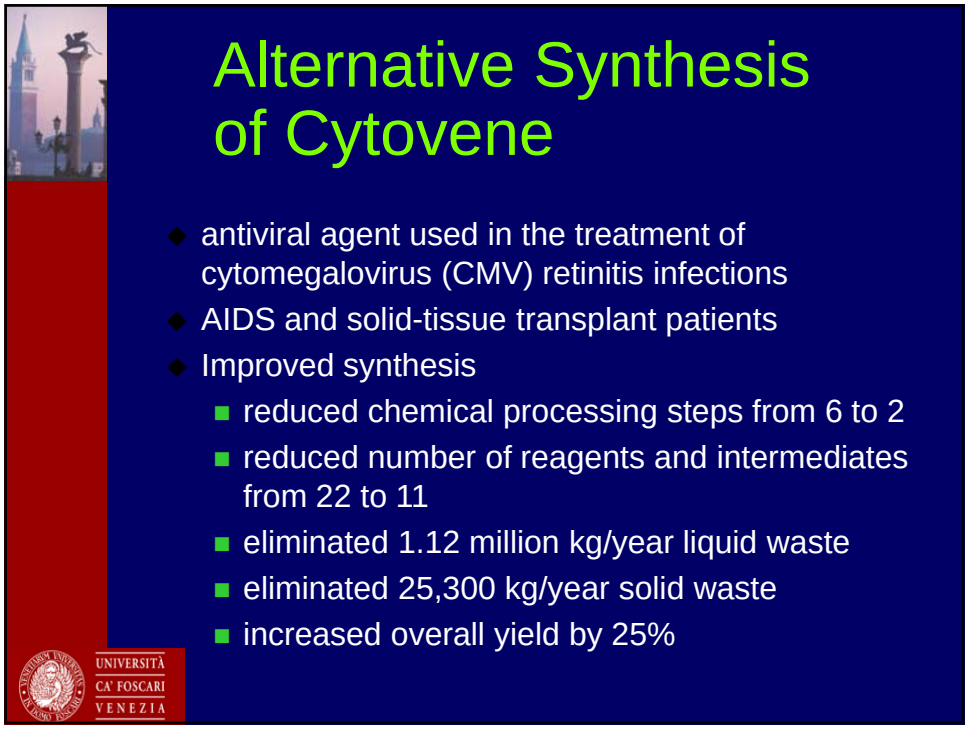
Alternative Synthesis of Cytovene
antiviral agent used in the treatment of cytomegalovirus (CMV) retinitis infections
AIDS and solid-tissue transplant patients
Improved synthesis
reduced chemical processing steps from 6 to 2
reduced number of reagents and intermediates from 22 to 11
eliminated 1.12 million kg/year liquid waste
eliminated 25,300 kg/year solid waste
increased overall yield by 25%
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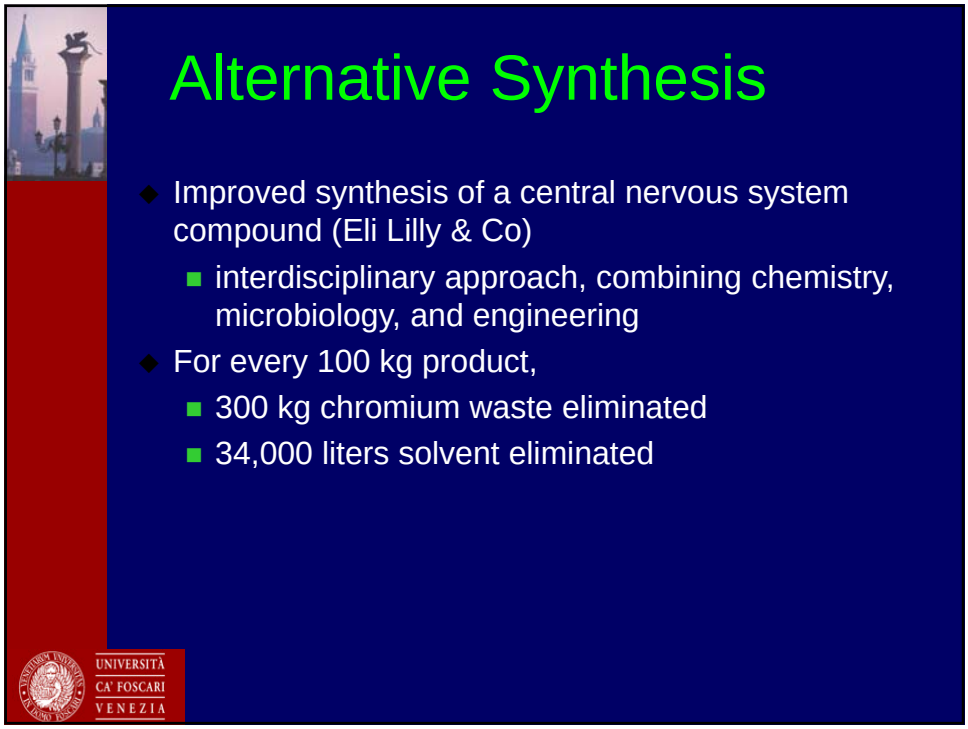
Alternative Synthesis
Improved synthesis of a central nervous system compound (Eli Lilly & Co)
interdisciplinary approach, combining chemistry, microbiology, and engineering
For every 100 kg product,
300 kg chromium waste eliminated
34,000 liters solvent eliminated
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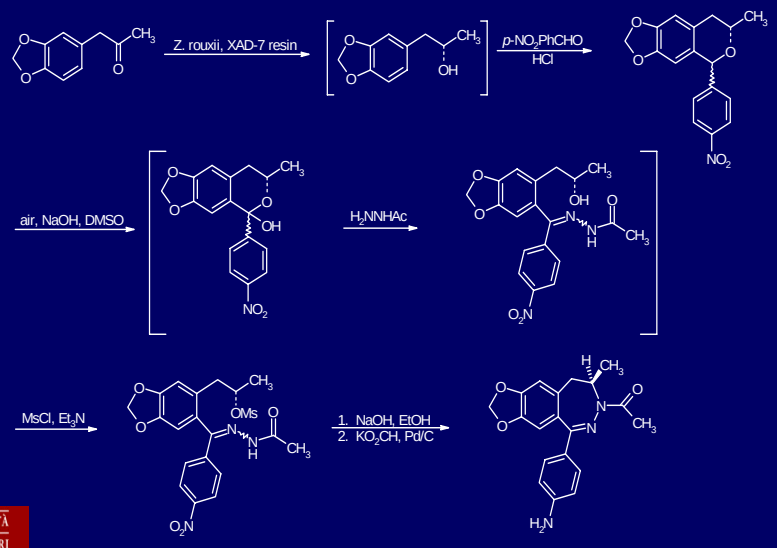
Alternative Synthesis



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UN-GREEN CHEMISTRY

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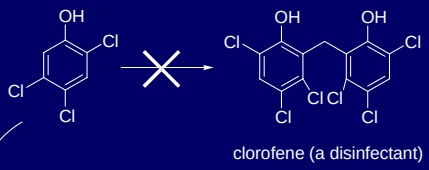
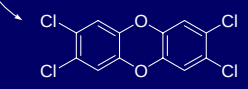
SEVESO: DIOXIN CONTAMINATION



clorofene (a disinfectant)



2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Evacuazione della popolazione di Seveso

Il 10 luglio 1976 presso la ditta ICMESA di Meda, in provincia di Milano, si verificò una fuoriuscita di gas tossico contenente diossina. Fu necessario ordinare la temporanea evacuazione della popolazione di Seveso, un centro situato nei pressi degli stabilimenti.

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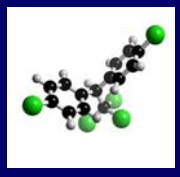
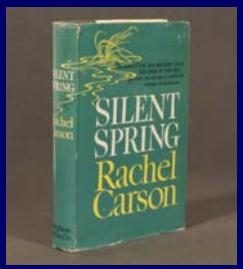
Dichloro-Diphenyl-Trichloroethane

DDT





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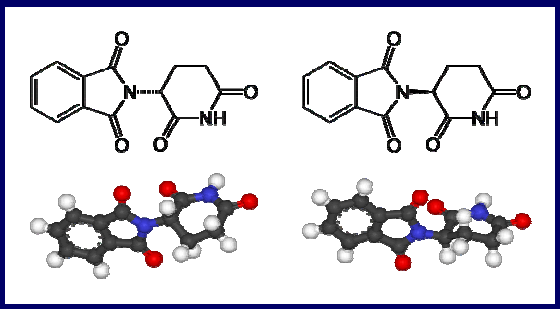
Thalidomide

Thalidomide was used by pregnant women in Europe to lessen the effects of morning sickness'. About 10000 children were born with acute birth defects, in many cases in the form of missing or deformed limbs.

One enantiomer is active as a drug, the opposite one is teratogenic.



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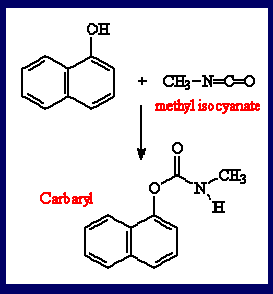
BHOPAL disaster



December 3rd 1984, the Union Carbide plant in Bhopal (India) discharged 42 tons of methyl isocyanate into the atmosphere exposing over 500,000 people.

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13 November 2005
China National Petroleum Co. in Jilin.

An explosion dumped in the Songhua river 100 tons of benzene, along with 2 ton. of nitrobenzene, aniline, and xylene.

13 November: accident
24 November: in Harbin drinking water supplies are closed

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Paracelsus

Paracelsus who was born Philippus Aureolus (1493-1541) took the pseudonym of Theophrastus Bombastus Von Hohenheim. He became a renown physician, alchemist and occultist.

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

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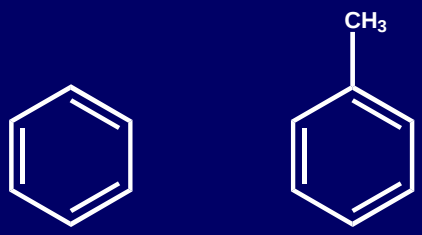
Solvents

Green chemistry principle no. 8: Use safer solvents and reaction conditions.

An old example: benzene vs. toluene:



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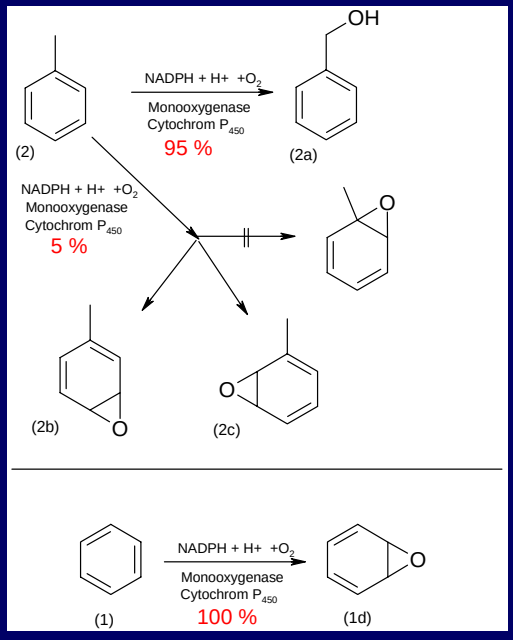
toluene

Phase I of biotransformation of toluene and benzene within mooxidenase system in Cytochrom P450

benzene



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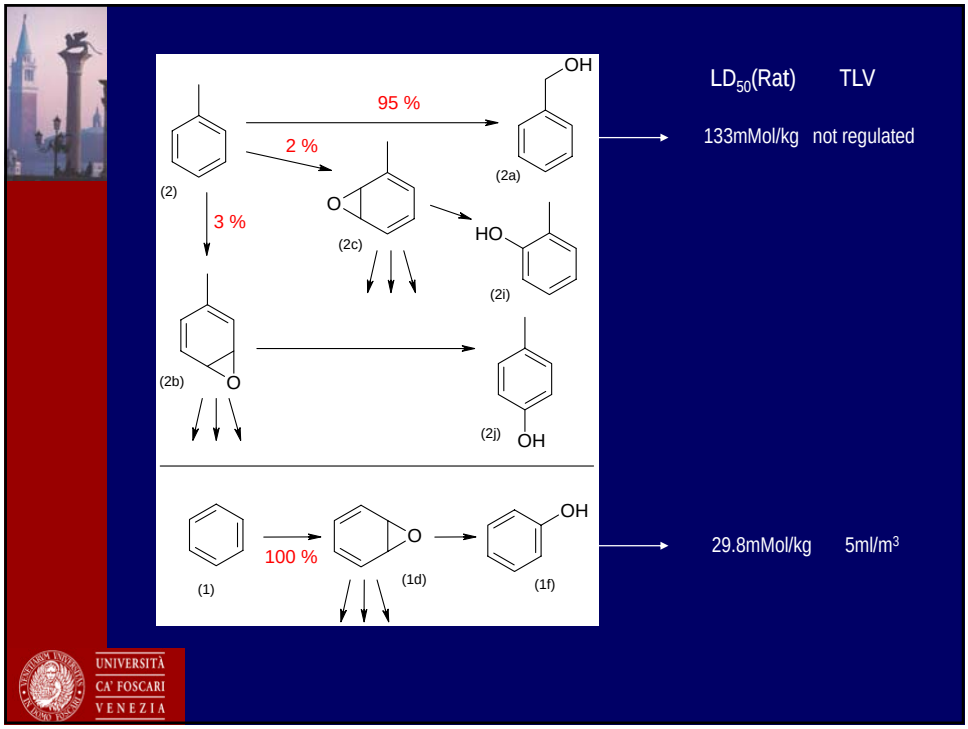
OH
95 %
2 %
(2)
(2a)
O
(2c)
3 %
HO
(2i)
(2b)
O
(2j)
OH
LD50(Rat)
TLV
133mMol/kg
not regulated
100 %
O
OH
(1)
(1d)
(1f)
29.8mMol/kg
5ml/m3
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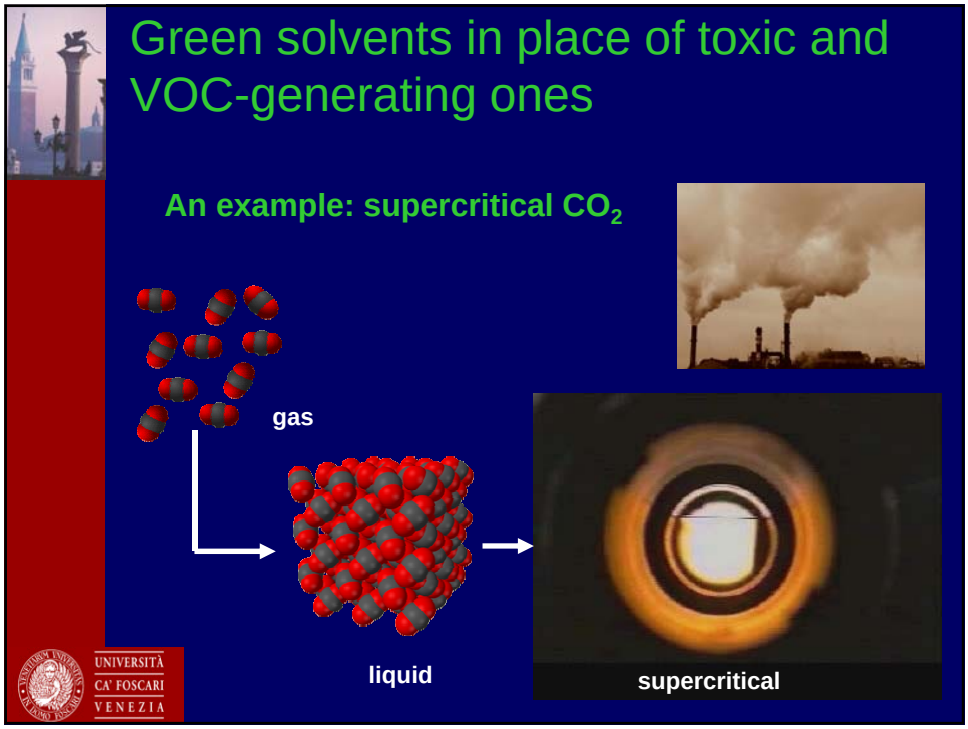
Green solvents in place of toxic and VOC-generating ones
An example: supercritical CO2
gas
liquid
supercritical
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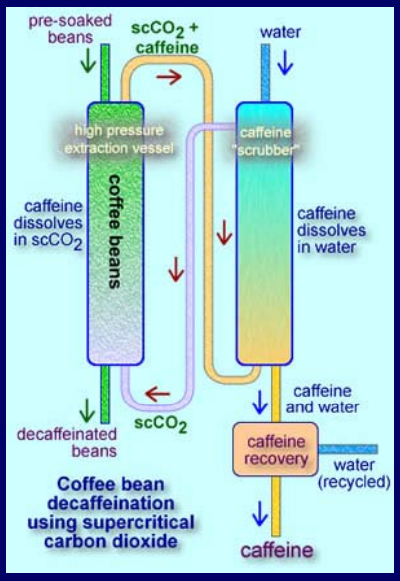
Extraction of organic compounds using supercritical CO_2



Caffeine

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Dry-cleaning using $scCO_2$

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Green solvents in place of toxic and VOC-generating ones

Another example: ionic liquids

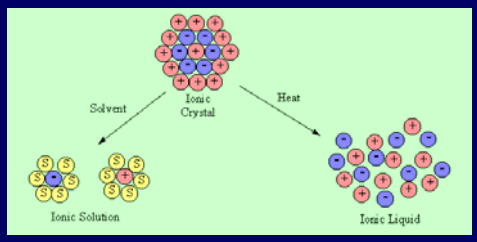

Table salt NaCl
mp = 801 °C

- **Made entirely of ions**
- **Molten at or around room temperature (mp < 100 °C)**
- **No vapour pressure**

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Ionic liquids can be designed to be soluble "as needed".

A triphasic organic - ionic liquid – aqueous system

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The best solvent is no solvent

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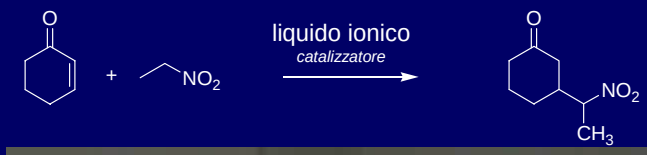
An example of solventless synthesis with an ionic liquid catalyst



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What about water?

"On water" reactions by B. Sharpless (Nobel Prize 2001)

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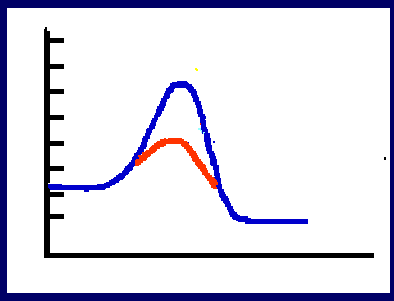
Catalysis

Green chemistry principle no. 5: Use catalysis.

A CATALYST IS SOMETHING THAT MAKES A CHEMICAL REACTION GO FASTER, WITHOUT BEING CONSUMED IN THE PROCESS



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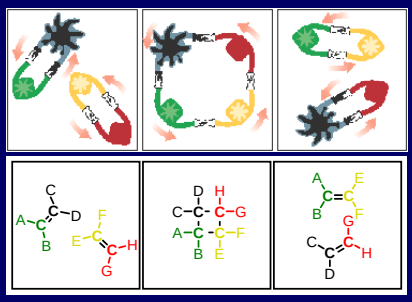
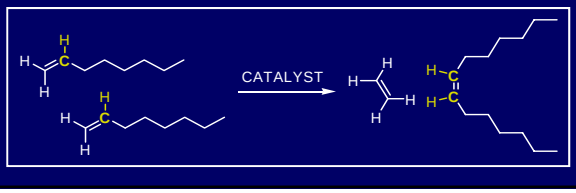
Catalysis



(Chemistry Nobel Prize 2005)

Olefin metathesis



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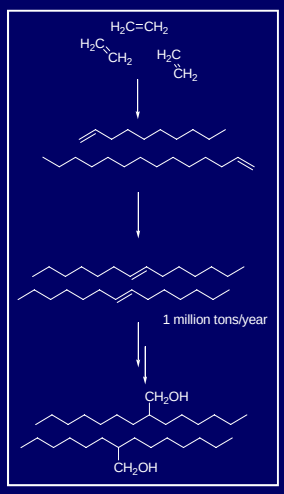
Catalytic metathesis

Shell Higher Olefin Process



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Enantioselective catalysis

Particularly in pharmaceutical chemistry, drugs are often chiral, and only one of the enantiomers is active.

In the best case the other enantiomer is useless (50% waste).
In the worst case its toxic (remember thalidomide).

Why get one for the price of two?

Of the active enantiomer only 50% is used in the body on average.

So we might be producing four times more active ingredient than needed!

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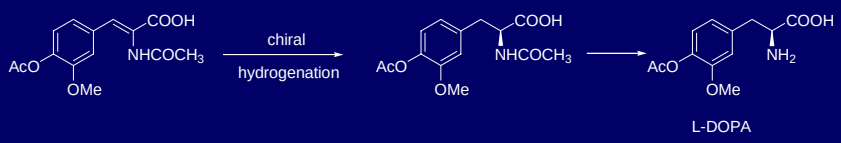
Step 1: Enantioselective catalysis

Example: Monsanto's L-DOPA process



L-DOPA

95 % ee
20000 tons

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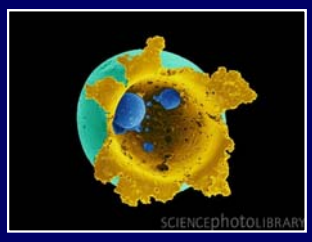
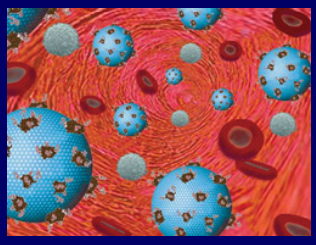
Step 2: Targeted delivery





By coupling enantioselective catalysis with targeted drug delivery 100% of the drug is used.

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So: why do we need Green Chemistry?

Answer: to allow future generations to live at least as well as us, and to live better and save money in the process.

We would need approximately 3.5 earths if all the 6.6 billion people lived with our standards.

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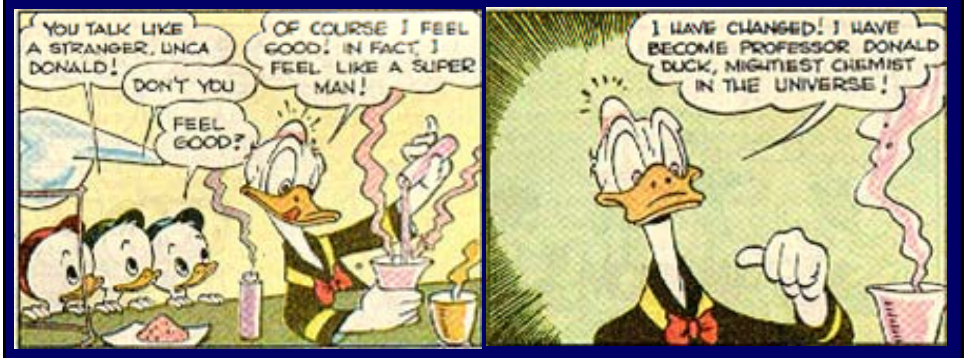
http://sustainability.publicradio.org/consumerconsequences/

Thank you!



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