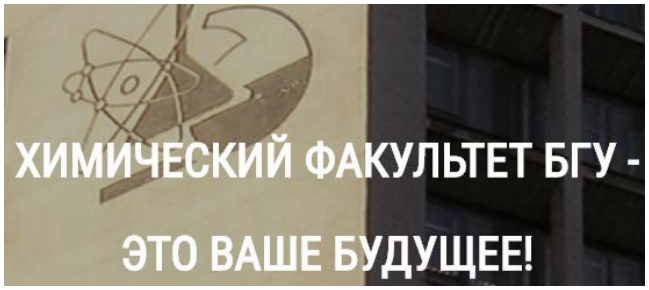


MODULE

Drug Chemistry and Technology Basics, Cleaner Production and Mega-Trends in Pharmaceutical Industry (Chemistry for Drug Substances)

Prof. Tatsiana Savitskaya
Assoc. Prof. Iryna Kimlenka

Lectures1,2

This module will give you a unique complex of interdisciplinary knowledge about:

- Cleaner production strategy;
- Mega-trends in chemistry;
- Management in pharmaceutical industry;

Prof. Tatsiana Savitskaya,
Head of the module

PhD. Iryna Kimlenka

This module will give you a unique complex of interdisciplinary knowledge about:

- Pharmaceutical chemistry basics;
- Terminology of drugs, quality standards, control by pharmacopeias.

Prof. Natallia Loginova

PhD. Anastasiya Sladkova

This module will give you a unique complex of interdisciplinary knowledge about:

- Up-to-date concept of drugs technology;
- Very common basics of drugs technology;

PhD. Evgeni Grinyuk

This module will give you a unique complex of interdisciplinary knowledge about:

- State-of-art strategy for the development of new generations of drugs;
- XXI century drugs and antioxidant protection of the organism.

Prof. Oleg Shadyro

Corresponding Member of NAS Sergey Usanov

Teaching Methods

- Lectures;
- Seminars;
- Labs;
- Group projects;
- Interactive case studies.

Total: 72 hours in class (5 ECTS)

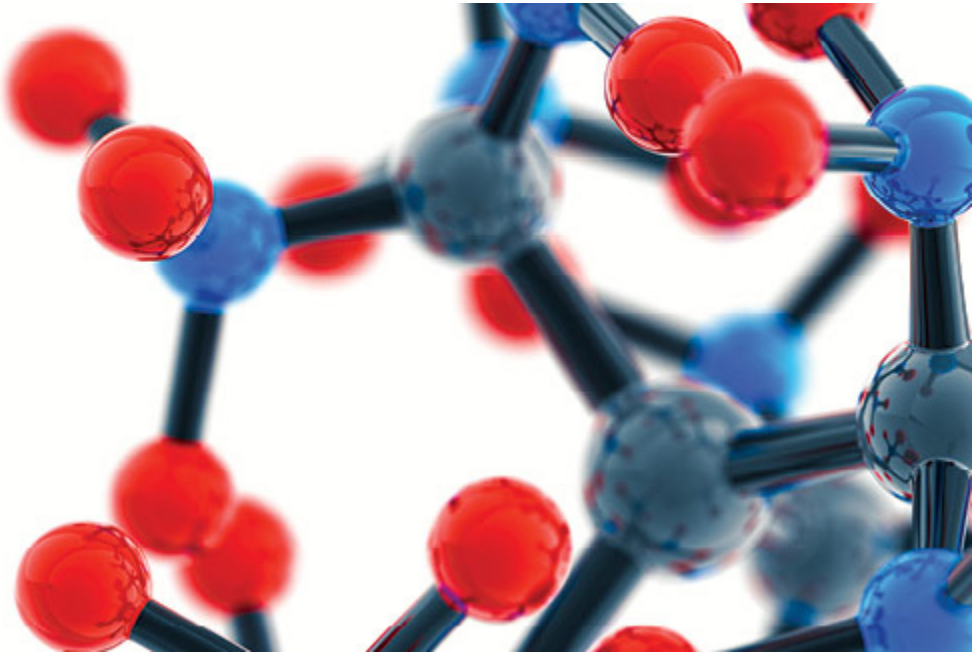
Contents

- What is Chemistry?
- Students' Activity "Chemicals in our Life"
- Sustainable Development Concept
- The New Face of Chemistry
- Up-to-Date Chemical Reactions Metrics
- Students' Activity "Metrics"
- Inherently Safer Design
- Top 10 Countries and Pharmaceutical Companies

Chemistry and Chemicals in Our Everyday Life

CHEMISTRY IS CENTRAL; WITHOUT BONDING WE WOULD FALL APART.

-Anonymous



What is Chemistry?

Chemistry is the study of substances in terms of:

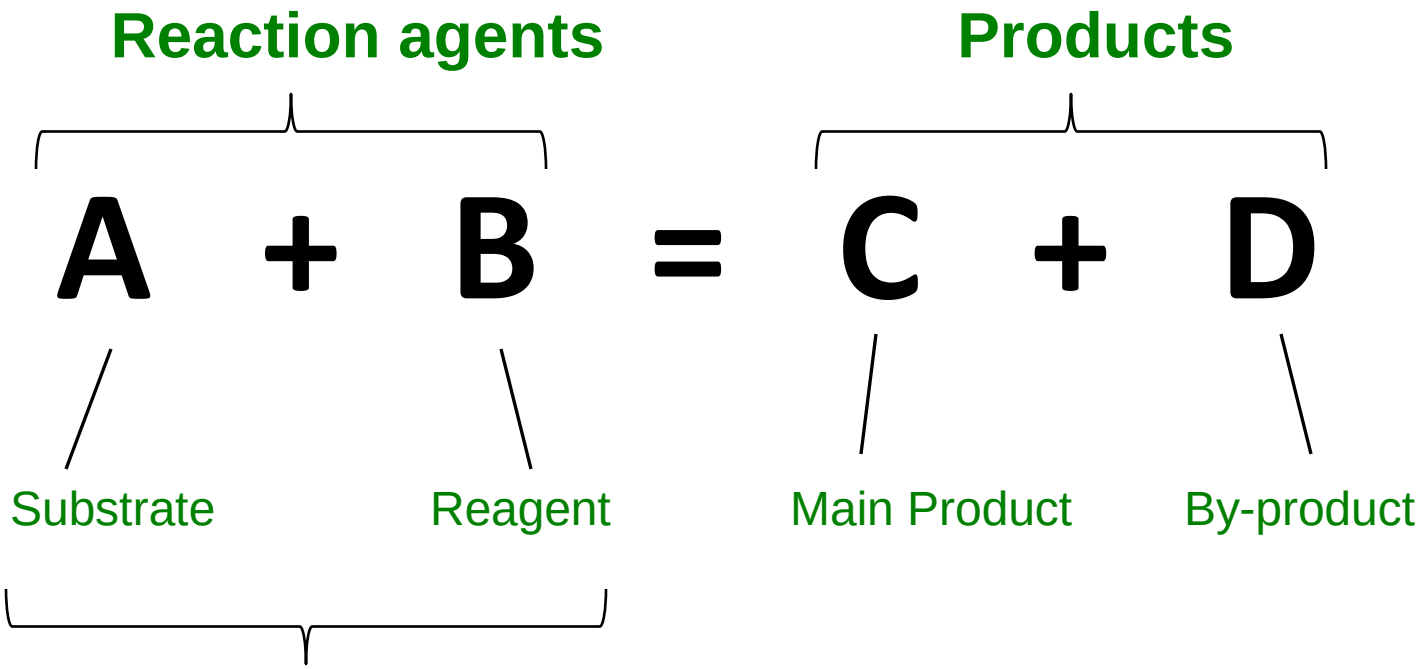
Composition What a material is made of;

Structure How the elementary particles are put together;

Properties The characteristics of the material;

Reactions How it behaves with other substances.

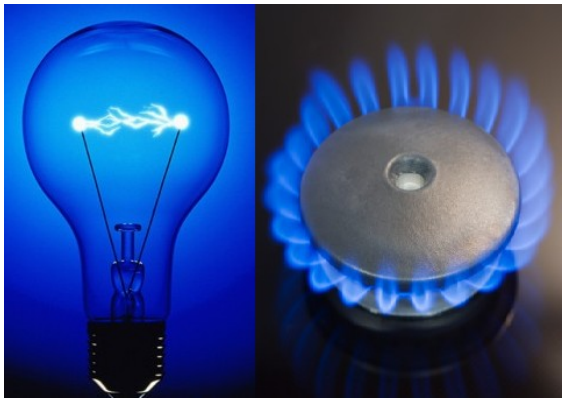
Chemical reactions



conditional division, it is not always possible definitely identify the substrate and reagent

Chemical reactions happen when:

- tarnish is removed from silver;
- electricity is produced from burning natural gas;
- fertilizer is added to help plants grow;
- food is digested;
- rust is formed on iron nails.

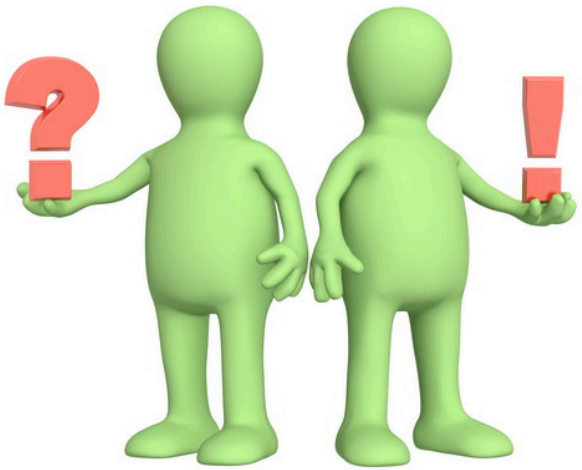


Drugs: More Than Chemical Reactions

Two main opinions on Chemistry:

✓The benefits of chemicals are difficult to overestimate;

✓ Chemistry causes the enormous damage for environment and human health.



Opinion 1

- The chemical industry is one of the most important in the world, worth a staggering US$3.6 trillion a year (according to the American Chemistry Council, ACC).

- It has dramatically changed and improved our lives. It is impossible to think of modern-day civilization without ChI.

Chemicals in Our Life

Chemicals Commonly Used in Toothpaste

Chemical	Function
Calcium Carbonate	Acts as an abrasive to remove plaque
Sorbitol	Prevents loss of water and hardening of toothpaste
Carrageenan (seaweed extract)	Keeps toothpaste from hardening or separating
Glycerin	Makes toothpaste foam in the mouth
Sodium lauryl sulfate	Acts as a detergent used to loosen plaque
Triclosan	Inhibits bacteria that cause plaque and gum disease
Titanium dioxide	Makes toothpaste base white and opaque
Sodium fluorophosphate	Prevents formation of cavities by strengthening tooth enamel with fluoride
Methyl salicylate	Gives a pleasant flavor of wintergreen

Chemicals in Our Life

- Rapidly soluble film strips Listerine Pocket Paks (Bio Film Holdings Limited Company);
- Edible Films (Japan Company PIP Health).

Chemicals used:

Essential oil: thymol and eucalyptus
Methyl salicylate
Mint

What kind of characteristics of chemicals are useful in our lives?

Characteristics	Main Living Environment
Flammable	?
Sticking	?
Elastic	?
Lightweight and strong	Plastic
Grease-cutting	?
Flavored	?
Scented	?
Exterminating harmful insects	?

Opinion 2

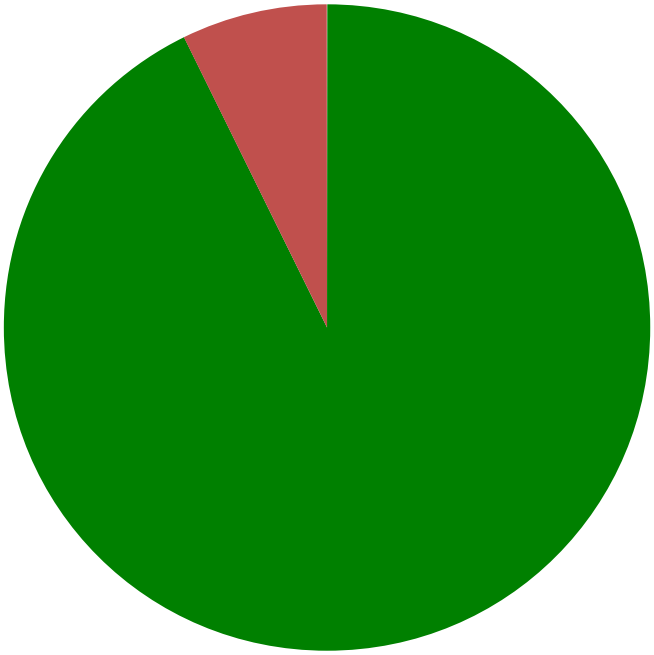
- For decades Chemistry was not interested in sustainability or protecting the environment.

- By the 1970s and 80s the image of the chemical industry was as dirty as its origins.

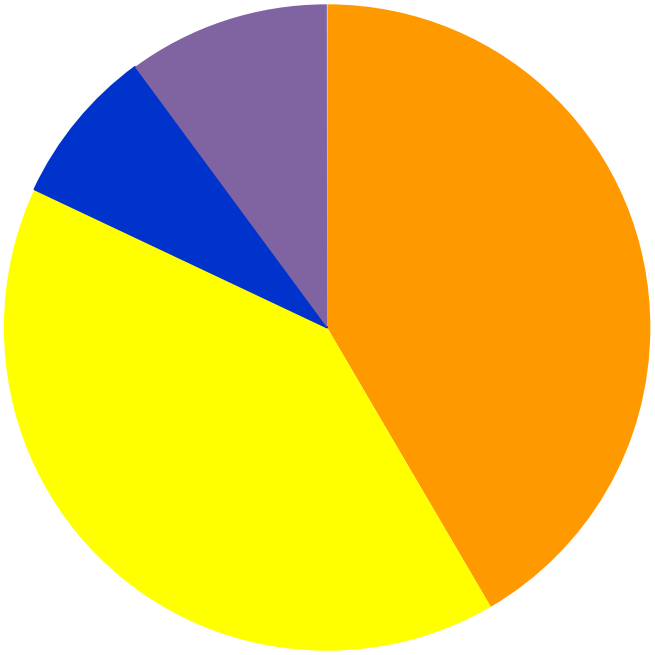
Global pollution = F (chemistry)

What is the Sciences color?

BIOLOGY



CHEMISTRY



2010 Public opinion poll results, Moscow State University, Russia

Transforming our world:
the 2030 Agenda for Sustainable Development
United Nations Summit 2015, New York

Sustainable development :

two meanings

Linguistic

Sustainable steady growth.

Conceptual

Continuing development that is not contrary to the continued existence of mankind and its development in the same direction.

Sustainable Development

1987

A United Nations Commission on Environment and Development (Bruthland Commission)

"Sustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs. It contains within it two key concepts:

*the concept of **needs***

*the idea of **limitations***

WE DO NOT INHERIT THE EARTH FROM OUR ANCESTORS, WE BORROW IT FROM OUR CHILDREN (LEE TALBOT)

Triunique Sustainable Development Concept

Planet

People

Profit

NOT “Back to the Nature” BUT “Back to the Future”

Traditional Way of Ecological Problems Solving

“END-OF-PIPE” STRATEGY

Methods used to remove already formed contaminants from a stream of air, water, waste or similar. These techniques are normally implemented as a last stage of a process.

The most popular color is

Generate less waste

Recycle everything that cannot be reused

Educate the community on eco-friendly options

Evaluate the environmental impact of actions

Nourish discussions and activities that integrate environmental education into existing curriculum

Green Economy

- United Nations Environment Programme (UNEP) defines a green economy as one that results in “improved human well-being and social equity, while significantly reducing environmental risks and ecological scarcities” (UNEP 2010).

- A green economy is low-carbon, resource efficient, and socially inclusive.

Green Economy

Irina Bokova, UNESCO Director-General, looking back on 2011 and setting some priorities for 2012, emphasized that it's necessary to build up not only green economy, but also **green society**. Even though little time has passed, there's no doubt the green strategy affected all spheres of life and our world is well on the way towards the new **green civilization**.

“Going green”

- This phrase often carries a negative connotation in the business world, because business owners and managers often associate making changes to become more environmentally friendly with increased costs. However, businesses that go green can improve quality.

- **Going green can be expensive in the short term, but in the long term, many changes often pay for themselves.**

“Going green”

A company that makes environmentally friendly changes may boost its reputation with its customers, which may lead to more business.

Being environmentally friendly may also help a business to attract better employees, which may make it more efficient and also produce a better work environment.

Cleaner Production, CP

- The concept was introduced by **UNEP** in 1989.

CP is the continuous application of an integrated preventive environmental strategy applied to processes, products and services to increase eco-efficiency and reduce risks for humans and the environment.

It applies to:

- ***production processes*:** conserving raw materials and energy eliminating toxic raw materials and reducing the quantity and toxicity of all emissions and wastes;
- ***products*: reducing negative impacts along the life cycle of a product** from raw materials extraction to its ultimate disposal

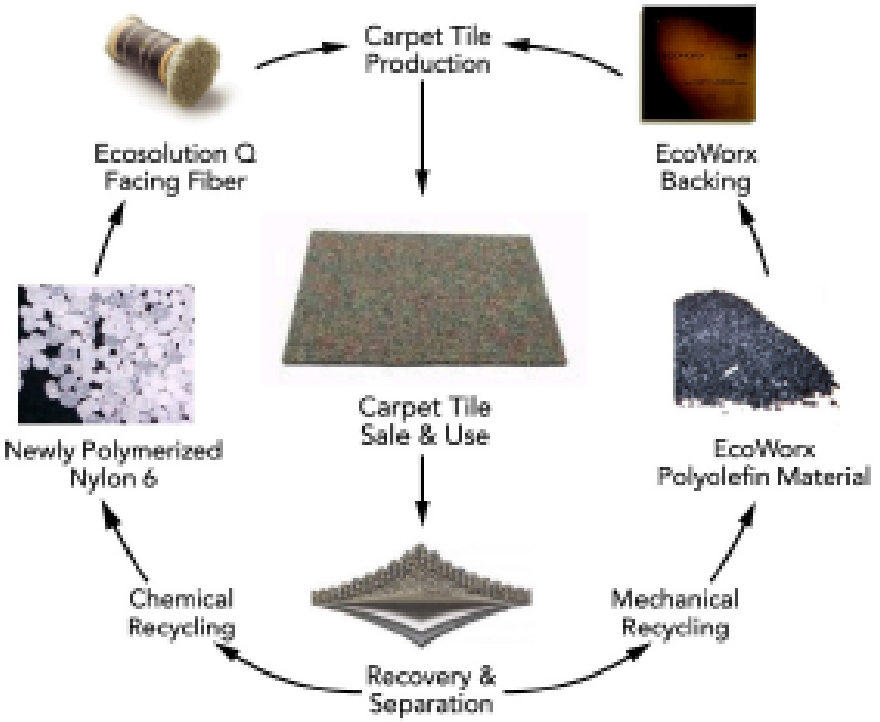
Lifecycle from “cradle to grave”

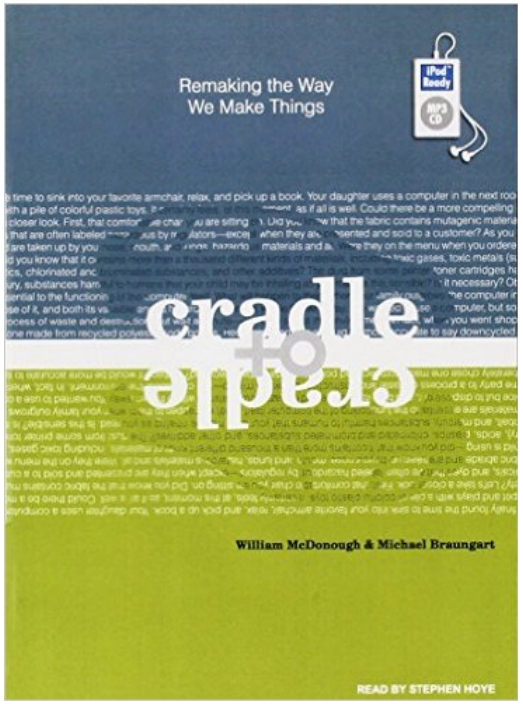
Cradle to Cradle (C2C)

Cradle to grave pattern ➡ Cradle to cradle pattern

Cradle to Cradle: Remaking the Way We Make Things. 2002

William McDonough and Michael Braungart





The New Face of Chemistry

- **Sustainable Chemistry**
- **Green Chemistry**

Important: Definitions (terms)!

R.S. Kaplan, 1997
Emeritus Professor of Harvard Business School

Theorem 1. 50% of all problems we have because of people use the same definitions for different things.

Theorem 2. The rest 50% of the problems we have because of people use the different definitions for the same things.

Green Chemistry…

…has been recognized as **a fundamental tool for design and attainment of sustainable development** through the use of multi-disciplinary scientific know-how, such a discipline produces benefits in all areas concerning sustainable development: environment, economy and society.

Green Chemistry = Sustainable Chemistry?

- To differentiate **Green Chemistry** and Sustainable chemistry or we take the risk of confusing purpose and **procedure.**

Joaquin Barroso

Green Chemistry is oriented towards the way we perform chemistry in order to achieve a *sustainable* chemical industry.

Green Chemistry = Sustainable Chemistry?

Sustainable Chemistry is the philosophical approach with which the ongoing transformations can still be performed while the damage to the environment, namely our ecosystems, is brought to a minimum in order to maintain our industry and the benefits there from for generations to come and spread to a larger scale. But this is **not only a mater of environmentalist nature, it is also an economical matter**.

Qing-shi Zhu, a physical chemist and manufacturer of methanol automobile fuel from biomass sources, during a press conference said:

“The ‘green’ in green chemistry is also the color of money.”

The Royal Society of Chemistry in UK

The International Journal GREEN CHEMISTRY

The American Chemical Society

The Institute of GREEN CHEMISTRY

The International Union of Pure and Applied Chemistry (IUPAC)

Symposia on GREEN CHEMISTRY

The Father of Green Chemistry, Prof. Paul Anastas

Green Chemistry is a New Solution of Ecological Problems

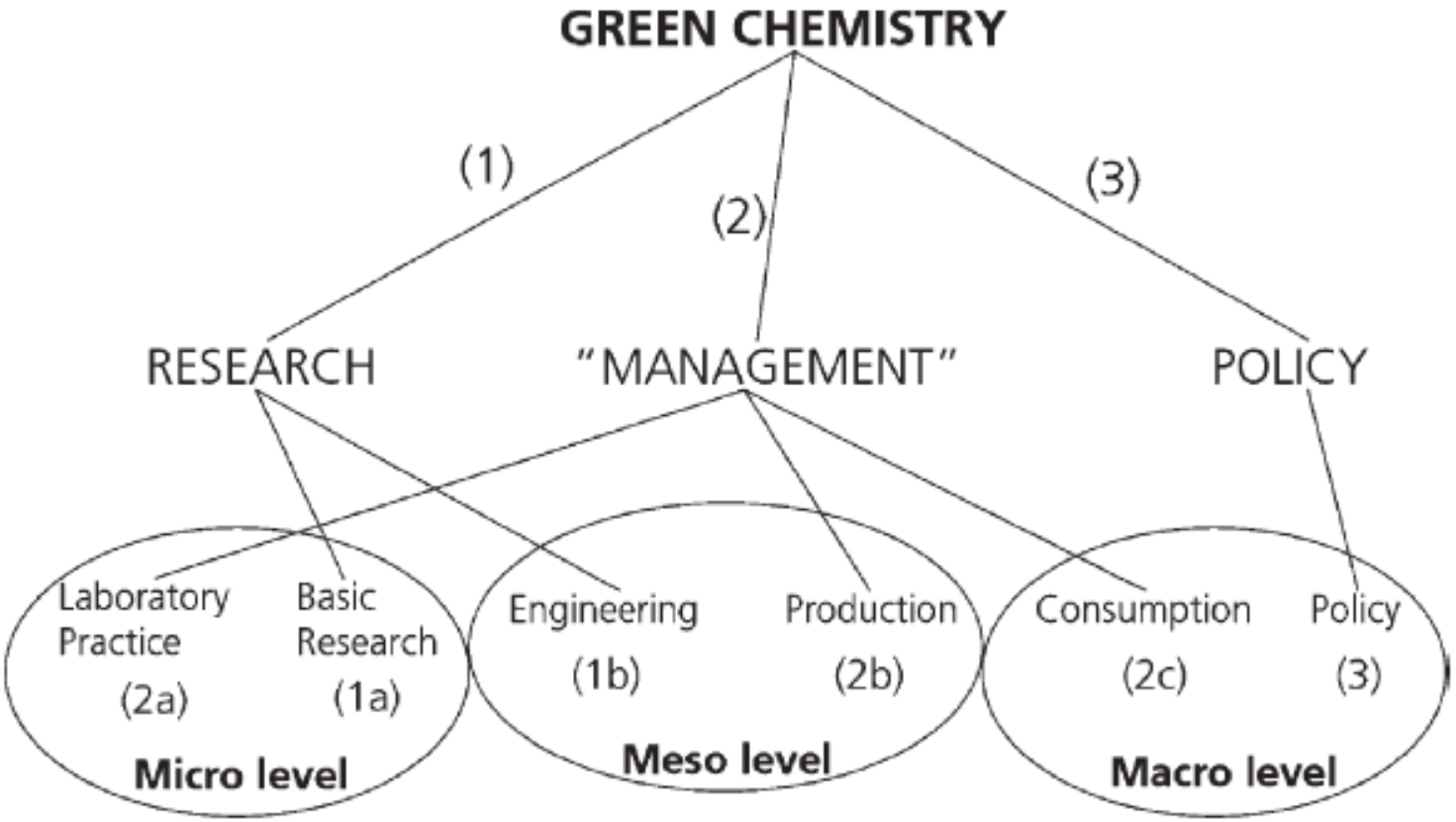
POLLUTION PREVENTION STRATEGY

P^2 focuses on the reasons of the environmental pollution

The Green Chemistry message is simple:

Seek prevention, not cure!

Green Chemistry Activities



Old and New Metrics of Chemical Reactions

Traditional

$$\text{Reaction Yield} = \frac{\text{quantity of product isolated}}{\text{theoretical quantity of product}} \times 100\%$$

Alternative

$$\% \text{ Atom Economy} = 100 \times \frac{\text{Relative molecular mass desired products}}{\text{Relative molecular mass of all reactants}}$$

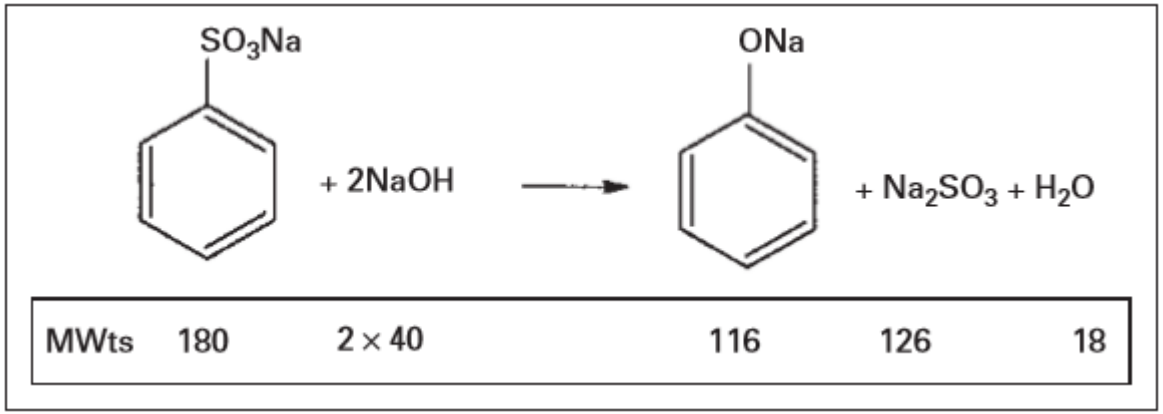
Rotating Chair

The ground Rules:

1. The Lecturer gives the definition of the first metric.
2. The first student will repeat it.
3. The Lecturer gives the definition of the second metric.
4. The second student summarizes what has been said before then develops the idea further (i.e. two definitions together)
5. And so forth.

Atom efficiency or atom economy (AE)

- **Barry Trost**
- **Benzene sulfonate route to phenol**

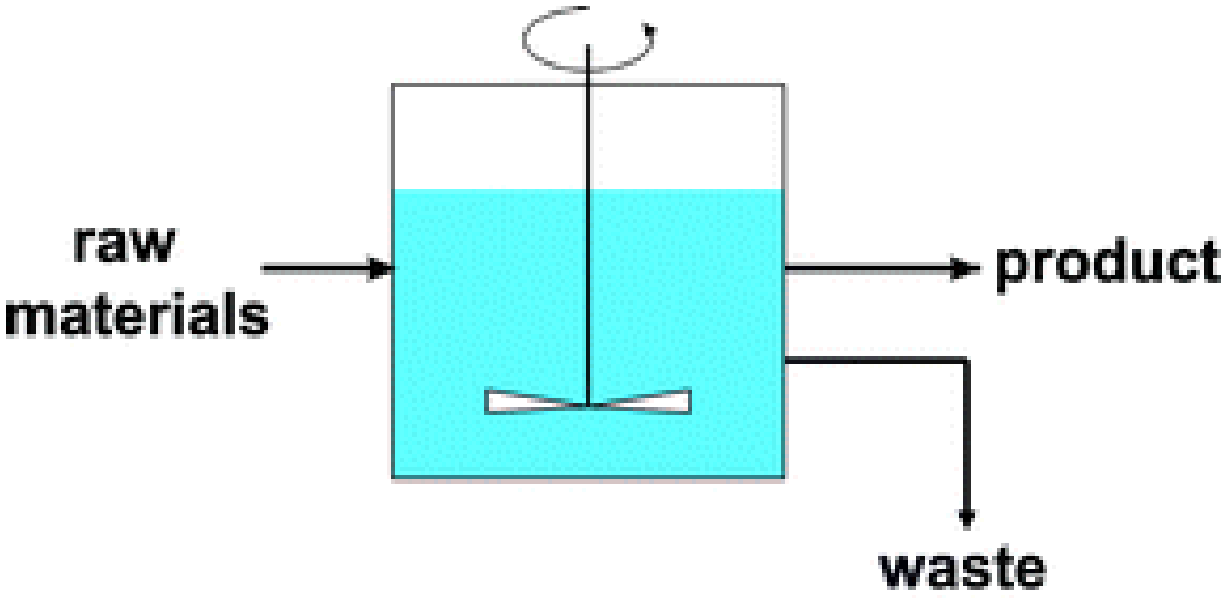


Total AE = 116/260 or **44.6%**

A carbon AE is 100%,

A sulfur AE is 0%.

Environmental Factor (E-factor) defined as the mass ratio of waste to mass of desired product (R. Sheldon, 1994).



$$E = \frac{\text{kg waste}}{\text{kg product}}$$

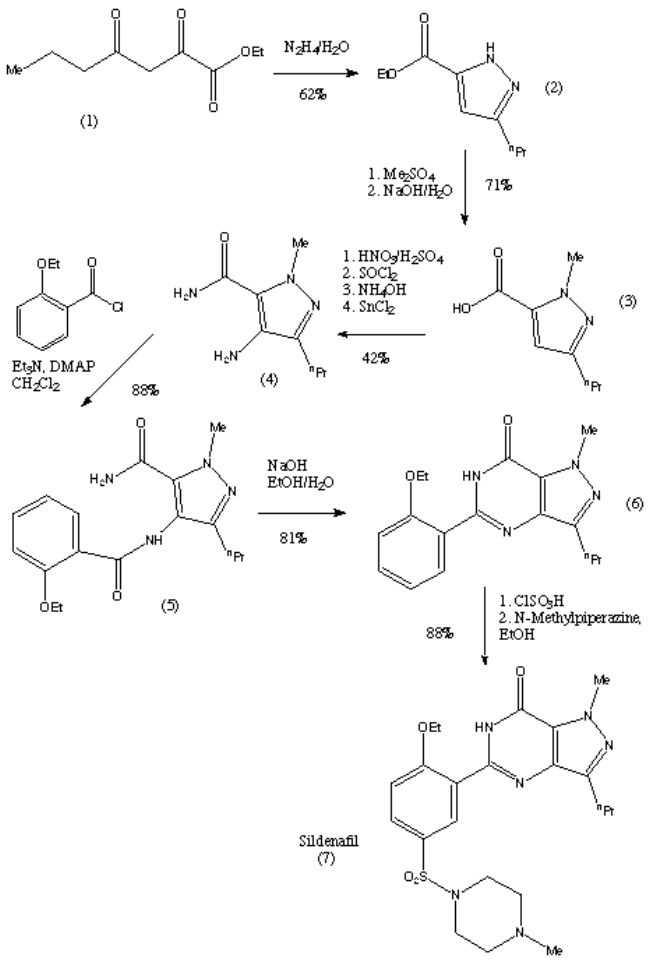
Large scale chemistry	**1- 5**
Pharmaceutical chemistry	**25-100**

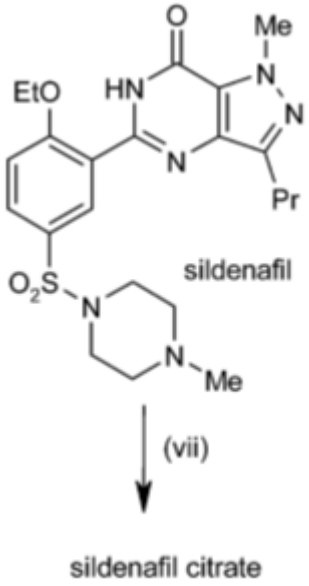
Relative efficiencies of different chemicals manufacturing sectors

Industry sector	Product tonnage	By-product weight / Product weight
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+**

It's important: **E-factor includes solvents, catalysts etc.**

Sildenafil citrate synthesis metrics

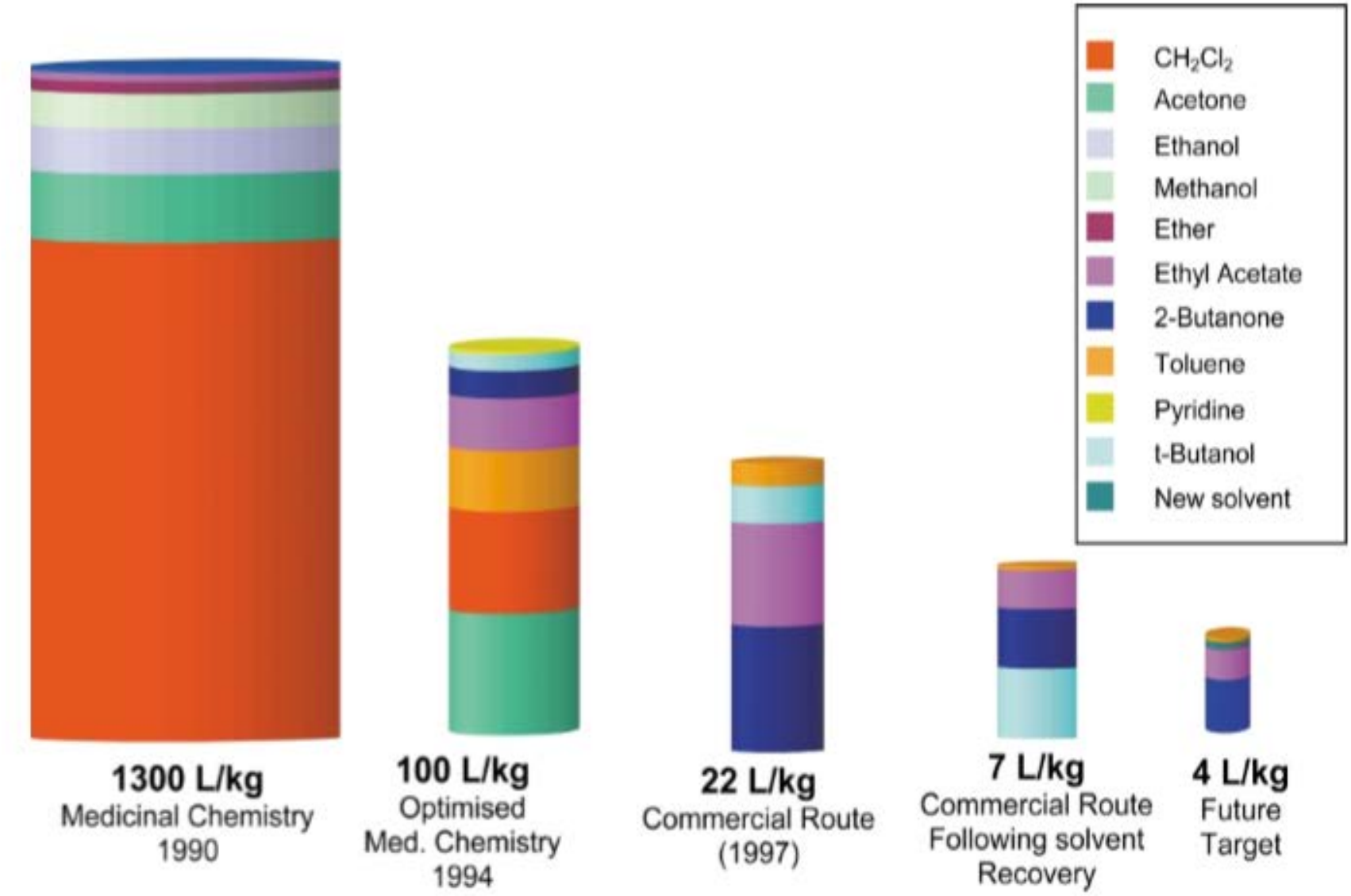




Citric acid, 2-butanone

- ✓ Thionyl chloride
- ✓ Replaced with a simple catalytic hydrogenation reaction
- ✓ KOBut in tBuOH

The amount of organic waste produced by the sildenafil citrate processes at various time points



Measures (Metrics) of the chemical reactions efficiency

$$\text{Reaction mass efficiency} = \frac{\text{Mass of product C} \times 100}{\text{Mass of A} + \text{Mass of B}}$$

Optimised medicinal chemistry process 1994

Reaction type	Step No	RME	Atom econ.	Yield
Amide formation	1	25%	61%	92%
Reduction (nitro to amine)	2a	83%	83%	100%
Activation/acylation	2b	48%	71%	84% from **(2)**
Cyclisation	3	61%	65%	100%
Chlorosulfonation/sulfonamide formation	4 Reaction	73%	90%	71%
	4 Purification	80%	100%	80%
Salt formation	5 Reaction	91%	100%	91%
	5 Purification	90%	100%	90%
Overall process		10%[8]	56%	36% from **(1)**

Measures (Metrics) of the chemical reactions efficiency

Table 5 Comparison of the E-factor of sildenafil citrate with industry norms

Industry segment	Annual product tonnage	E-factor
Oil refining	10^6–10^8	*ca.* 0.1
Bulk chemicals	10^4–10^6	<1–5
Sildenafil citrate	**30–40**	**6**
Fine chemicals	10^2–10^4	5–>50
Pharmaceuticals	10–10^3	25–>100

Pfizer: **Crystal Faraday Award for optimizing the process of manufacturing Sildenafil citrate**

The Presidential Green Chemistry Challenge Awards winners from the pharmaceutical industry (according to EPA)

Greener synthetic pathways award winners
Manufacturing of ibuprofen, an widely used anti-inflammatory drug (BASF, 1997).
Development of biocatalysts for preparing LY300164, a new potential antiepileptic (Lilly, 1999).
Efficient process for the production of Cytovene®, a potent antiviral agent (Roche, 2000).
Application of green chemistry in the new industrial preparation process of sertraline (Zoloft® from Pfizer, 2002).
Development of a green synthesis for the production of Taxol®, by cell fermentation and extraction (Bristol-Myers Squibb, 2004).
New synthesis of aprepitant (Emend®), a potent antiemetic (Merck, 2005).
New green synthesis of β-amino acids used in the production of sitagliptin (Januvia®), an oral anti-diabetic (Merck, 2006).
An efficient biocatalytic process to manufacture simvastatin, an anti-dyslipidemic (Codexis, 2012).
Greener reaction conditions award
Enzymatic process involving a transaminase in the production of sitagliptin (Januvia®), an oral anti-diabetic (Merck and Codexis, 2010).
Optimization of three bio-catalysts for the industrial production of an important chiral intermediate in the synthesis of atorvastatin (Lipitor®), an anti-dyslipidemic (Codexis, 2006).

GC Metrics: what's new?

- ***R.Sheldon:*** **Environment Quotient**

  EQ = E-factor x Harmfulness factor

- **NaCl HF=1**
- **Salts of metals HF=100-1000**

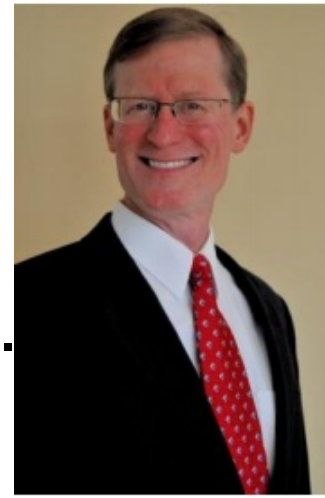
GC Metrics: what's new?

- ***T. Hudlicky :*** **Effective Mass Yield (EMY)** defined as the percentage of product of all the materials used in its preparation. As proposed, it does not include so-called environmentally benign compounds, such as NaCl, acetic acid, etc.

$$\text{Effective mass yield (\%)} = \frac{\text{Mass of products} \times 100}{\text{Mass of non-benign reagents}}$$

GC Metrics: what's new?

• ***D.Constable*:** the use of **Mass Intensity (MI)** defined as the total mass used in a process divided by the mass of product,
Mass intensity takes into account the yield, the solvent, the reagent used in the reaction mixture, and expresses this on a weight/weight basis rather than a percentage.



MI = E-factor + 1 and
The ideal MI is 1 compared with zero for the E-factor.

David J. Constable is a Director of the American Chemical Society's Green Chemistry Institute

Pre-experimental selection route pro-forma

Atom economy
Expected overall yield
Atom economy × expected yield
Number of individual stages
Number of separation/purification steps
List of VOCs to be used
List of toxic or other environmentally hazardous raw materials
List of toxic or other environmentally hazardous waste products
Significant energy requirements, *i.e.* estimated reaction time at >150 °C or <−15 °C
% Raw materials from renewable resources
List of specialist equipment required
Estimated raw material cost per tonne product

Additional metrics from experimental work

E-factor
Effective mass yield (excluding water)
kg VOC/kg product
kg waste/kg product to be treated on-site
kg waste/kg product to be treated off-site
Additional hazardous by-products identified
Identified options for recycling solvent/by-products on site
Estimated E-factor after on-site recycling

Inherently safer design

- **Inherent** - “existing in something as a permanent and inseparable element...”
  - safety “built in”, not “added on”

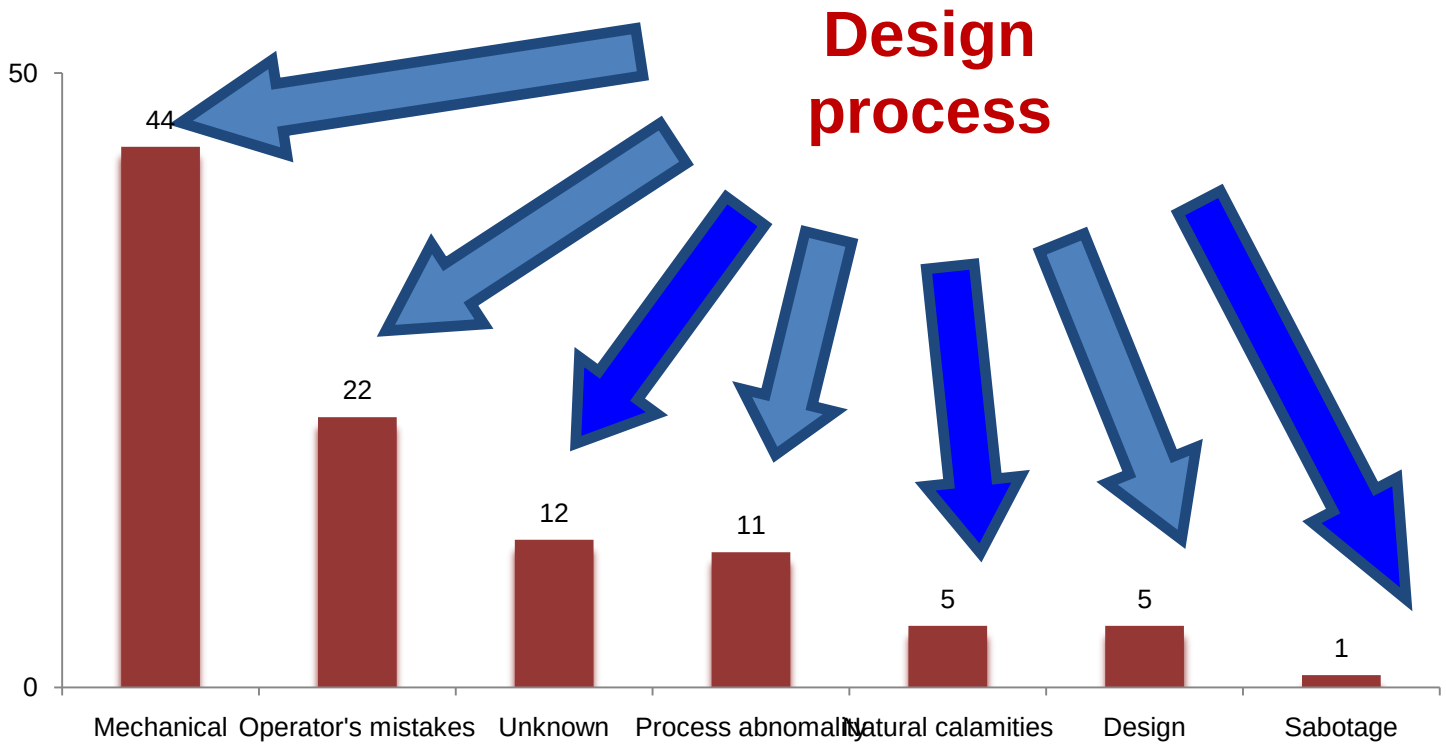
- Eliminate or minimize hazards rather than control hazards

- More a philosophy and way of thinking than a specific set of tools and methods
  - Applicable at all levels of design and operation from conceptual design to plant operations

- ***“Safer,”*** not ***“Safe”***

- **“What you don’t have can’t harm you”** *T.Kletz*

The reasons of accidents in industry



Strategy of ISD

- Minimization
- Simplification
- Substitution
- Moderation
- Limitation

Top 10 Countries with the biggest global pharmaceutical markets

Rank	Country	Value of Pharmaceutical Market (in millions of $)
1	USA	339,694
2	Japan	94,025
3	China	86,774
4	Germany	45,828
5	France	37,156
6	Brazil	30,670
7	Italy	27,930
8	UK	24,513
9	Canada	21,353
10	Spain	20,741

Top 10 Pharma Companies by global sales

2014 | 2013 | 2012

#	Company	2014 ($m)	2013 ($m)	Growth ($m)	Growth (%)
1	Novartis	47101	47468	-367	-1
2	Pfizer	45708	47878	-2170	-5
3	Roche	39120	39163	-43	0
4	Sanofi	36437	37124	-687	-2
5	Merck & Co.	36042	37437	-1395	-4
6	Johnson & Johnson	32313	28125	4188	15
7	GlaxoSmithKline	29580	33330	-3750	-11
8	AstraZeneca	26095	25711	384	1
9	Gilead Sciences	24474	10804	13670	127
10	Takeda	20446	19158	1288	7

Future Chemistry

How does chemistry change the world where we can see a lot of problems: global warming, lack of resources, pollution?

As Nils Bohr said:

“It is difficult to make the exact forecast especially for future”

“We can predict only the perspectives. But I’m absolutely sure it is impossible to overestimate the role of chemistry for sustainable development”

President of the International Union for Pure and Applied Chemistry (IUPAC) Kazuyuki Tatsumi about future of Chemistry.