MATERIE PRIME RINNOVABILI E BIOTRASFORMAZIONI PER L'ECONOMIA CIRCOLARE

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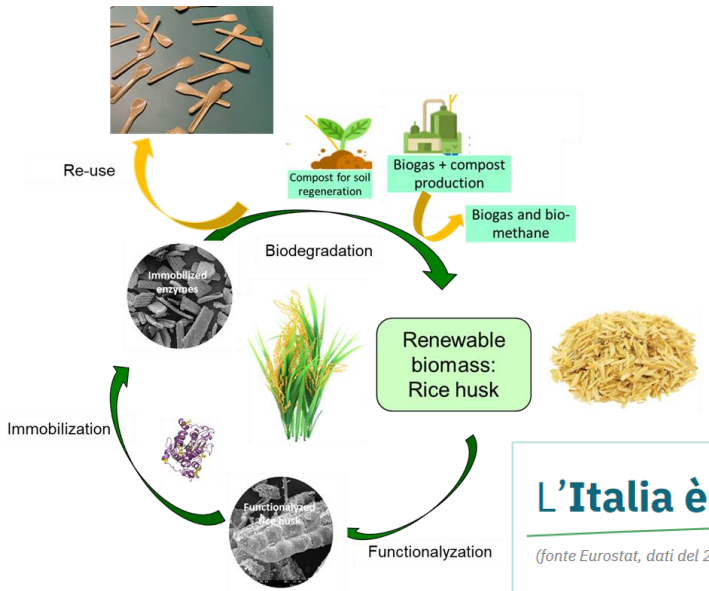
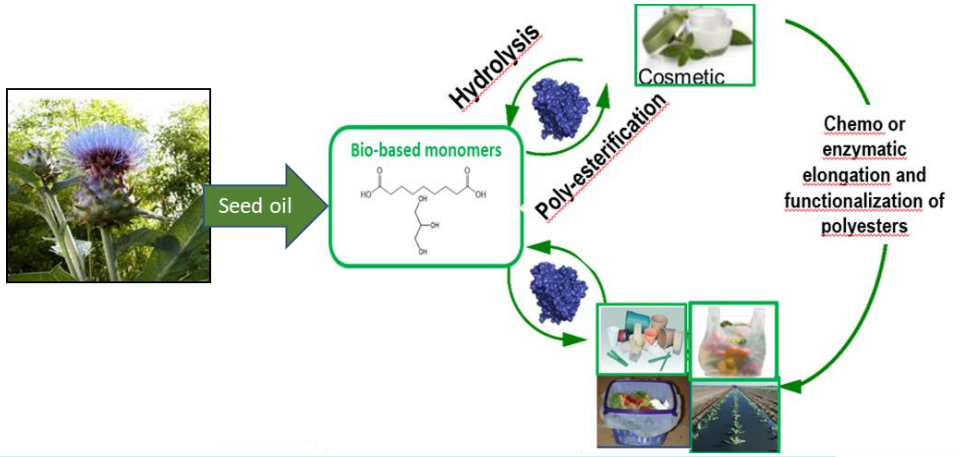
Dipartimento di
Scienze Chimiche e Farmaceutiche

Sostenibilità e Bio-economia Circolare: il contributo delle biotecnologie integrate con la chimica

Bioeconomia circolare per materiali, prodotti chimici e plastiche sostenibili e rinnovabili





L'**Italia è leader europeo** dell'economia circolare

(fonte Eurostat, dati del 2020)

- **Guida la classifica europea della produttività delle risorse** con 3,5 euro di pil per ogni kg di risorse utilizzate, il 60% in più della media europea;
- **È leader per il tasso di utilizzo circolare dei materiali** del 21,6%, a fronte di una media europea del 12,8% e di quello della Germania fermo al 13,4%;
- **È leader nel tasso di riciclo di tutti i rifiuti**, urbani e speciali, con il 67,5% a fronte del 40,9% della Germania.

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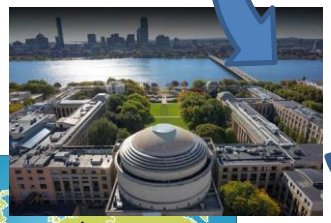
AREA SCIENCE PARK

2007

SPRIN technologies

1989



Boston/MIT

1991

2009

European Commission

SPRING
Sustainable Processes and Resources for Innovation and National Growth
Italian Cluster of Green Chemistry

2017

2019

Gruppo di Coordinamento Nazionale per la bioeconomia

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Available for meeting students upon appointment via e-mail

Scientific literature and relevant documents will be provided on moodle

- optional

Pablo Domínguez de María "Industrial Biorenewables" Wiley (http://eu.wiley.com/WileyCDA/WileyTitle/productCd-111884372X,subjectCd-EG30.html).

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"Ricerca ed innovazione per la transizione sostenibile: dall'idea alla start-up"

La prima giornata vedrà un intervento introduttivo della prof. Gardossi e a seguire dei seminari di ricercatori, alcuni dei quali laureati e dottori di ricerca di UNITS, che hanno fondato aziende nel settore delle biotecnologie. Sono stati invitati
la Dr Claudia Cusan (BEST srl)
il Dr Nicola De Zordi (SAM, Fitoterapica delle Dolomiti)
il Dr Mattia Lazzarotto (Enzyan Biocatalysis)
la prof. Cinzia Pezzella (Biopox)

Nella seconda giornata il prof. Guido Bortoluzzi (DEAMS) introdurrà le attività del *Contamination* lab di UNITS. Successivamente animerà dei lavori di gruppo durante i quali gli studenti analizzeranno dei modelli di business e trend settoriali.

Green chemistry: integrating sustainable processes with renewable products

Green chemistry

- The chemistry sector, its impact on economy and society
- Evolution of chemistry to meet environmental urgencies

What chemical industry produces: definitions

Commodities:

A basic good used in commerce that is interchangeable with other commodities of the same type. Most often used as inputs in the production of other goods or services. The quality of a given commodity may differ slightly, but must meet specified minimum standards.

Specialty chemicals

low volume–high value products that constitute raw materials for the production of pharmaceuticals, auxiliaries for industry, crop protection and pigments among others.

Consumer chemicals

products such as detergents, perfumes and cosmetics sold directly to consumers.

Chemistry is the manufacturing sector that delivers products with the highest added value in Europe

15% of EU GDP

20% of global production

Italy:

-ranked 10 globally

-ranked 3 in EU (excellence in fine chemistry and specialty chemistry)

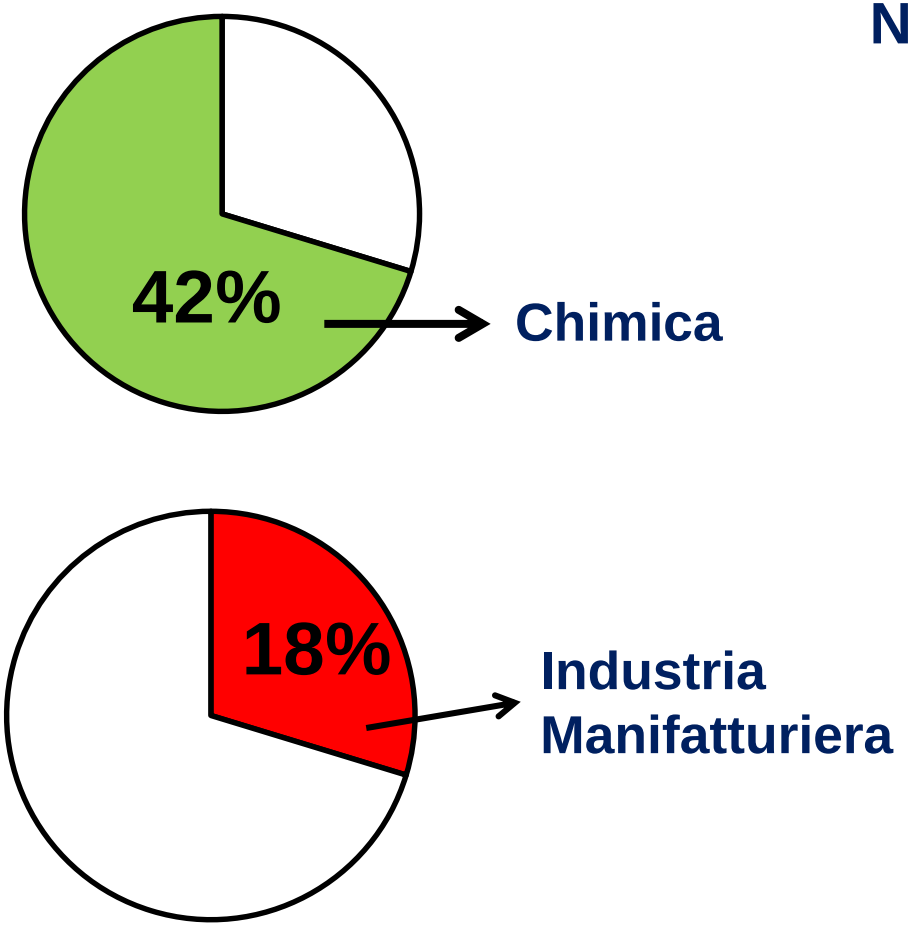
During economic crisis of 2008-2009 the world consumption of chemical products has increased by +3.9% per year
Projections: +4.5% growth in 2011-2020.

L'Industria chimica in cifre, Federchimica, 2014.

Centralità di Ricerca e Innovazione

Imprese con R&S interna in Italia

(% sul totale imprese)



Imprese con R&S interna in Europa

(% sul totale imprese)

Numero di imprese con R&S interna nella chimica europea

Germania	1.278
Italia	683
Spagna	548
Francia	541
Olanda	224

Note: imprese con più di 10 addetti

Fonte: Eurostat - Community Innovation Survey, 201

Dall'elevata produttività maggiore difesa dai concorrenti emergenti

Innovazione basata sulla ricerca

+

Impianti e tecnologie complesse

+

Intensità di capitale

Elevata qualifica e produttività consentono maggiori remunerazioni

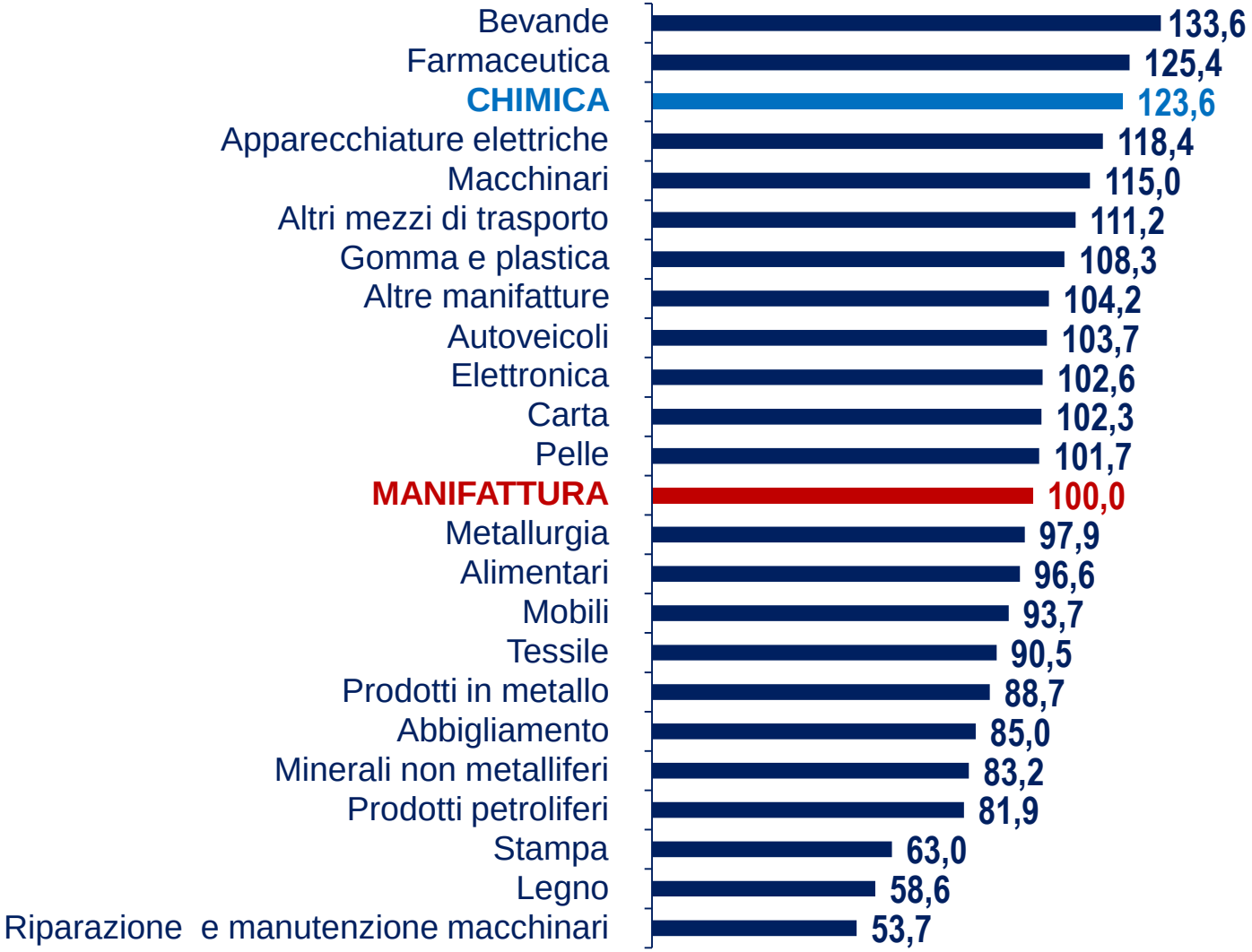
Valore aggiunto per addetto
(indice manifattura =100)

Fonte: Federchimica su Istat, 2015

Industria chimica leader in Sostenibilità economica e competitività

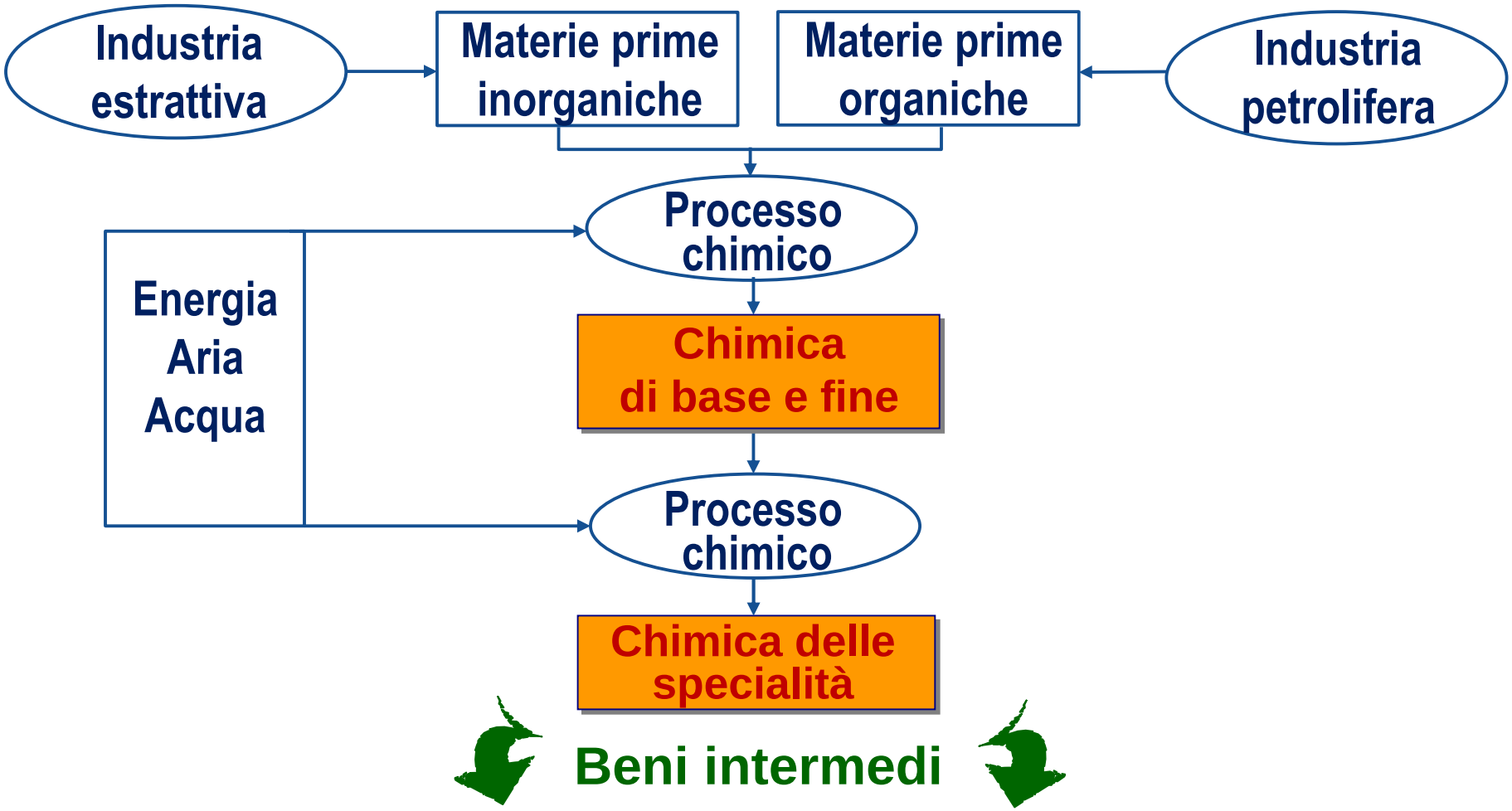
ISCO - Indicatore sintetico di competitività ISTAT

(indice industria manifatturiera =100, anno 2015)



Fonte: Istat

Chimica come infrastruttura tecnologica



Infrastruttura tecnologica per il Made in Italy

La chimica è il turbo del Made in Italy

Innovazione

Personalizzazione

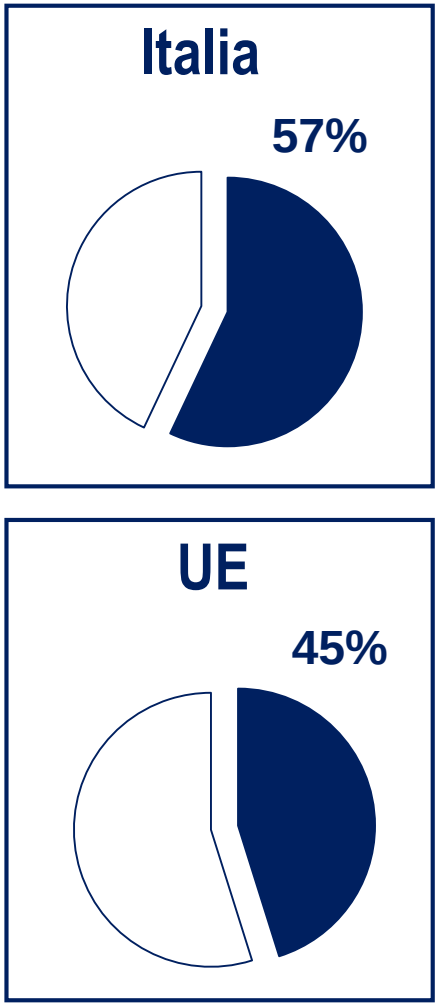
Specializzazione

Flessibilità

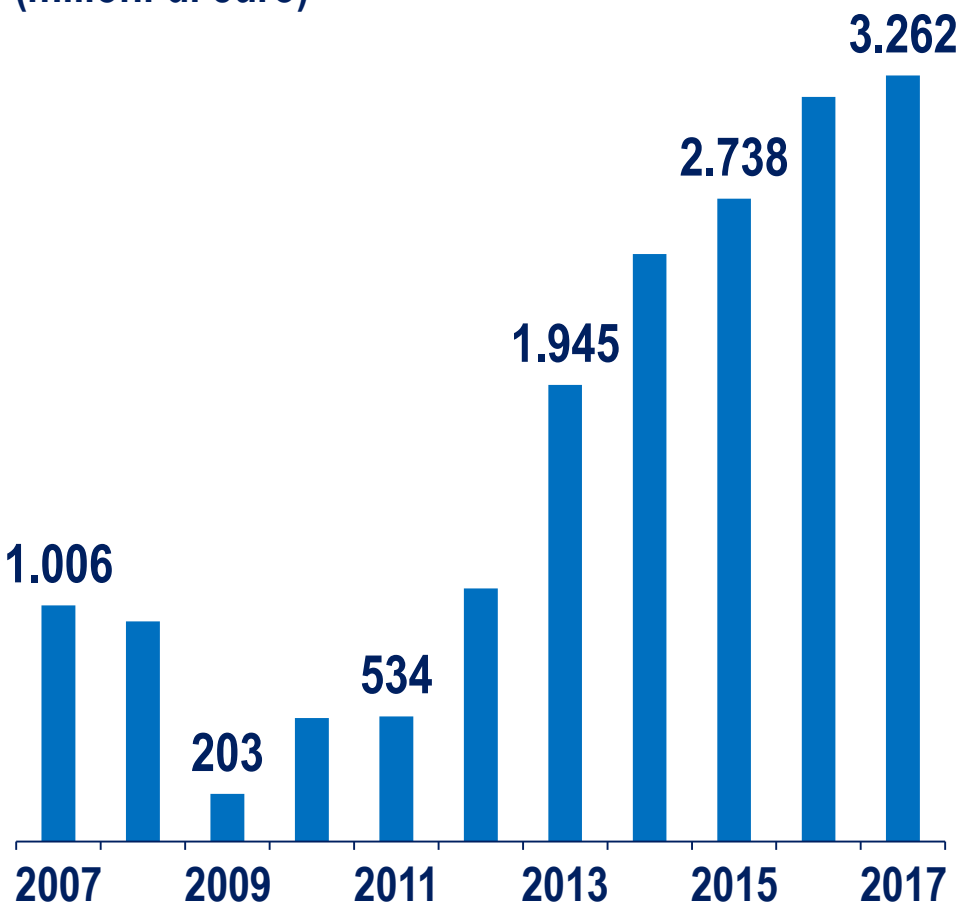
Biella - Prato	tessile
Como	seta
Brianza - Alto Livenza	arredamento
Premana	forbici
Milano - Varese	plastica
Bergamo	bottoni
Sassuolo	ceramica
Castel Goffredo	calze da donna
Vigevano	calzature
Verona - Alpi Apuane	marmi
Rossano Veneto	selle per biciclette
Cadore	ottica
Pesaro	cucine
Solofra Arzignano - S.Croce	concia
Vicenza - Arezzo	oreficeria
Montebelluna	calzature sportive
Rimini - Forlì - Pesaro	mobili
Bologna	imballaggio
Fermo	footwear
Le Murge	divani

Specializzazione italiana nella Chimica fine e delle specialità

Quota della Chimica a valle
(% sul totale del valore della produzione)



Saldo commerciale della Chimica fine e delle specialità
(milioni di euro)



Note: la chimica a valle comprende la chimica fine, specialistica e per il consumo

Da Chimica 1.0 a Chimica 4.0

Chimica 1.0	**Chimica del Carbone**
Chimica 2.0	**Petrolchimica**
Chimica 3.0	**Specialità e Globalizzazione**
Chimica 4.0	**Digitalizzazione? Economia circolare? Bioeconomia?**

“European Chemicals Industry, Enabler of a Sustainable Future”

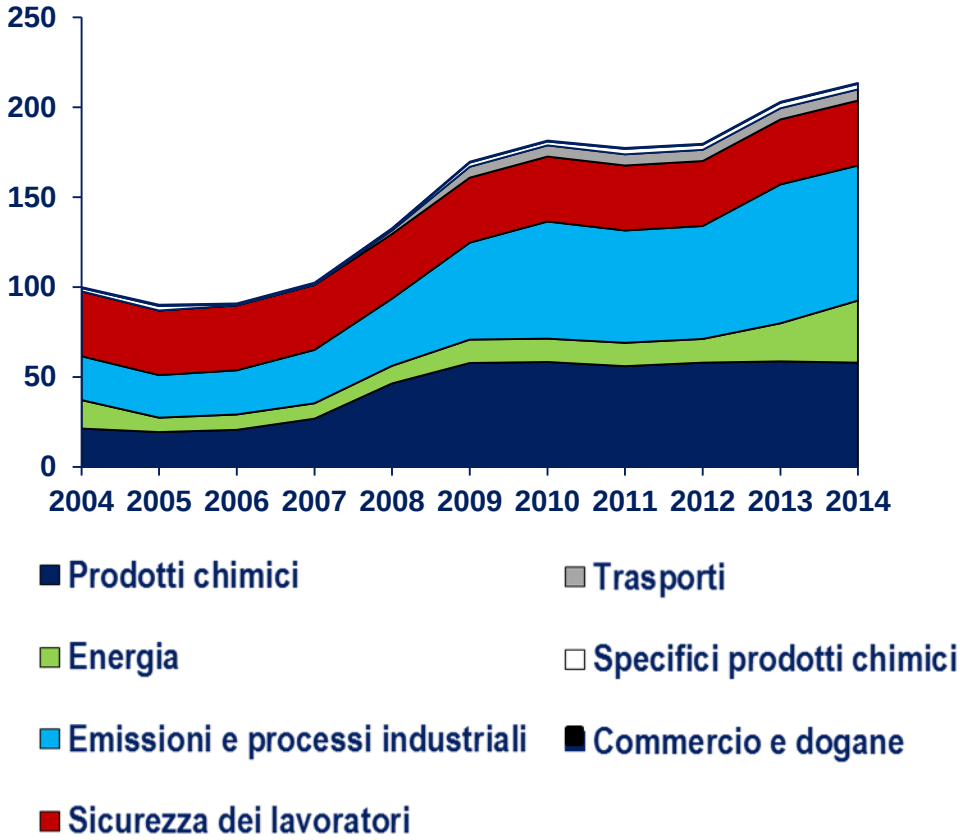
- Sostenibilità alimentare
- Nuove esigenze connesse all’invecchiamento
- Cambiamento climatico
- Uso più efficiente delle risorse

«Le principali sfide dell’umanità
richiedono nuove soluzioni
molte delle quali possono essere implementate
solo grazie a nuovi materiali e sostanze»

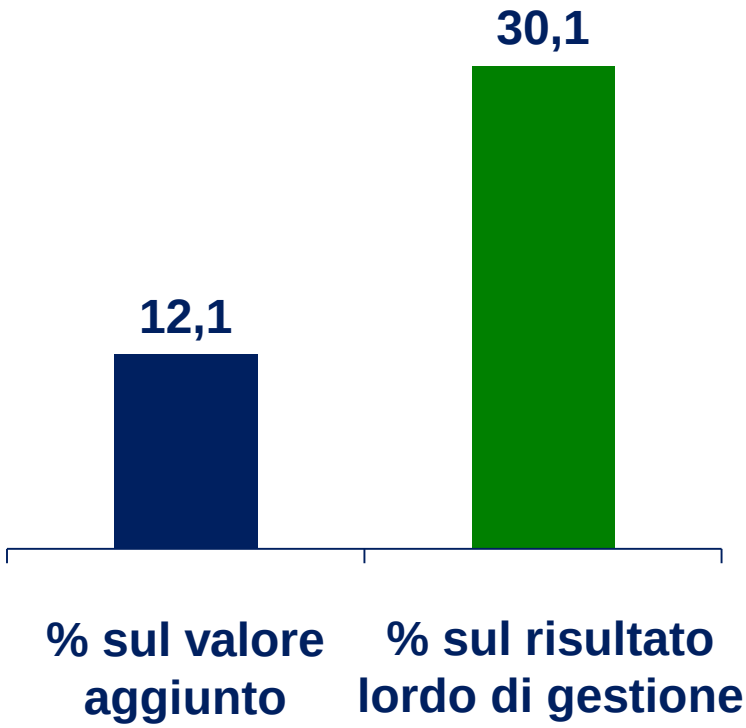
Tanta Chimica negli obiettivi ONU

Crescente costo della regolamentazione

Costi della regolamentazione per l'industria chimica europea
(indici 2004=100)



Costi della regolamentazione per l'industria chimica europea
(%, media 2004-2014)



Fonte: CCA Report, «Cumulative Cost Assestement for the EU Chemical Industry», Technopolis Group, 2015

https://ec.europa.eu/growth/sectors/chemicals/reach_en

REACH is the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals. It entered into force in 2007, replacing the former legislative framework for chemicals in the EU.

REACH shifts the responsibility from public authorities to industry with regards to assessing and managing the risks posed by chemicals and providing appropriate safety information for their users. It impacts on a wide range of companies across many sectors beyond the chemical industry. It requires new forms of cooperation among companies, enhancing communication along the supply chain.

Objectives of REACH
The main aims of REACH are to ensure a high level of protection for human health and the environment.

NO DATA NO MARKET!

Register information in the data-base of the European Chemical Agency

REACH - Chemicals - Environment - European Commission http://ec.europa.eu/environment/chemicals/reach/reach_en.htm

European Commission

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REACH

REACH (EC 1907/2006) aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. This is done by the four processes of REACH, namely the registration, evaluation, authorisation and restriction of chemicals. REACH also aims to enhance innovation and competitiveness of the EU chemicals industry.

"No data no market": the REACH Regulation places responsibility on industry to manage the risks from chemicals and to provide safety information on the substances. Manufacturers and importers are required to gather information on the properties of their chemical substances, which will allow their safe handling, and to register the information in a central database in the European Chemicals Agency (ECHA) in Helsinki. The Agency is the central point in the REACH system: it manages the databases necessary to operate the system, co-ordinates the in-depth evaluation of suspicious chemicals and is building up a public database in which consumers and professionals can find hazard information.

Sostenibilita: dall'innovazione di processo all'innovazione di prodotto

-80% emissioni in acqua dal 1989

-95% emissioni in aria dal 1989

-62% emissioni di gas serra dal 1990

1 tonnellata di CO_2 emessa per la produzione chimica evita 2,6 tonnellate di gas serra da parte dei clienti industriali o dei consumatori finali

FEDERCHIMICA CONFINDUSTRIA

Fonte: Federchimica - Responsible Care ®, ENEA – ODYSSEE Project, ISPRA, Istat, ICCA - McKinsey

Production of waste by various branches of chemical industry

Industry	Product scale (t/year)	Kg waste / Kg product (*E* factor)
Oil refining	10^6-10^8	<<0.1
Bulk chemicals	10^4 - 10^6	1-5
Fine chemicals	10- 10^4	5 - 50
Pharma	1- 10^3	25 - > 100

Sheldon R.A., Green Chemistry, 2007, 9, 1273-1283.

CHEMISTRY ENVOROMENTAL IMPACT!

Green Chemistry

The U.S. Pollution Prevention Act of 1990 led to a fundamental shift in the strategy for environmental protection from "end-of-pipe" waste treatment to waste prevention and led to the emergence of the term "**green chemistry**" at the U.S. Environmental Protection Agency (EPA) in the early 1990s

(Summary of the Pollution Prevention Act. http://www.epa.gov/laws-regulations/summary-pollution-prevention-act)

A succinct definition of green chemistry is as follows: ***Green chemistry*** *efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.*

(Sheldon, R. A. Atom utilisation, E factors and the catalyticsolution. C. R. Acad. Sci., Ser. IIc: Chim. 2000, 3, 541–551)

http://www.sheldon.nl/bi/EFactor.aspx

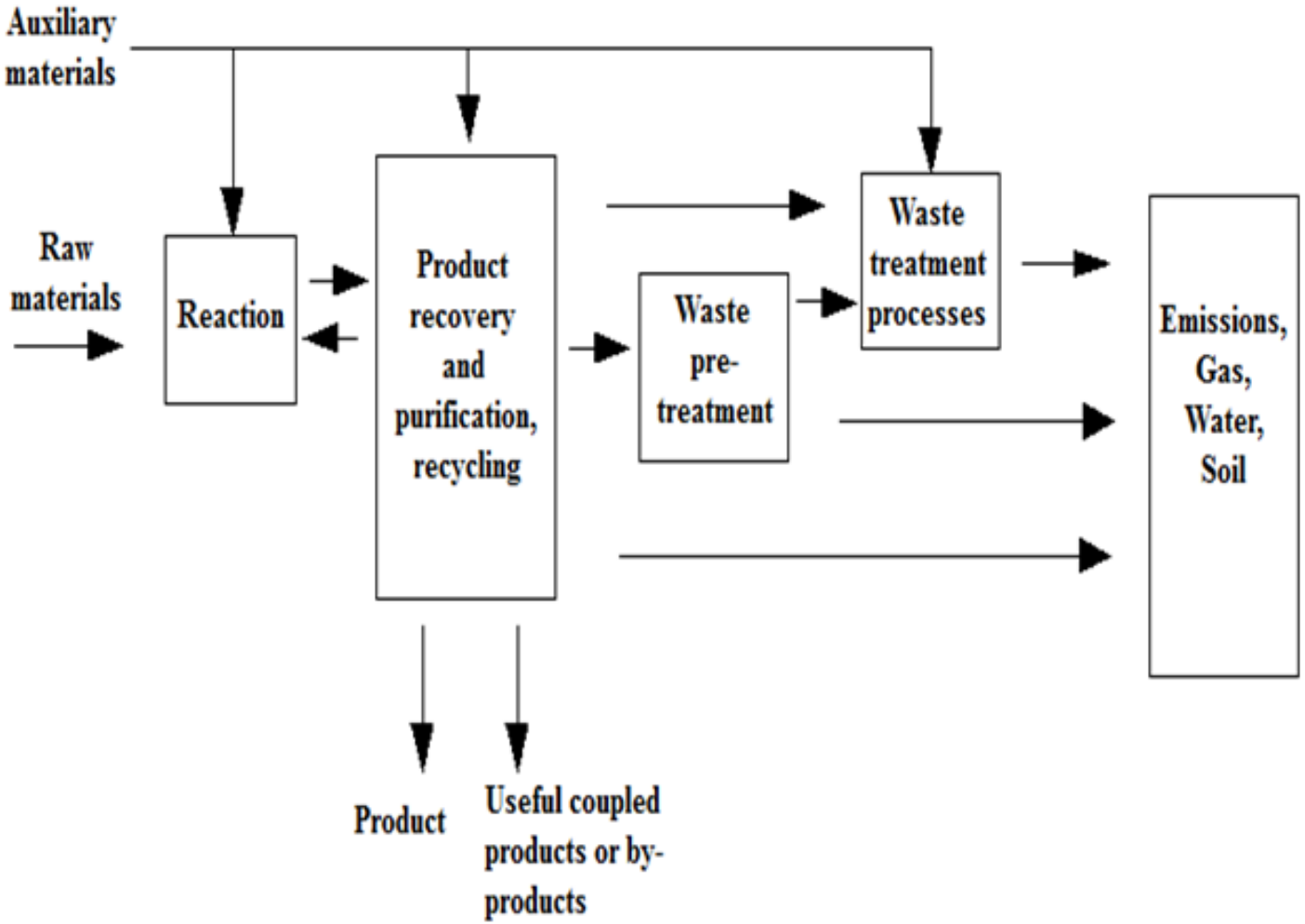
Environmental quotient, EQ,

EQ = Environmental Factor × Q

What is important is the environmental impact of this waste, not just its amount. One kg of sodium chloride is obviously not equivalent to one kg of a chromium salt.

EQ, is obtained by multiplying the E factor with an arbitrarily assigned unfriendliness quotient, Q. For example, one could arbitrarily assign a Q value of 1 to NaCl and, say, 100-1000 to a heavy metal salt, such as chromium, depending on its toxicity, ease of recycling, etc. The magnitude of Q is obviously debatable and difficult to quantify but, importantly, ‘quantitative assessment’ of the environmental impact of chemical processes is, in principle, possible.

The efficiency and sustainability of a process depend on all steps taken as a whole



12 Principles of Green Chemistry

Developed by Paul Anastas and John Warner:
the list outlines an early conception of what would make a greener chemical, process, or product.

Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30. B

1. ***Prevention***
   It is better to prevent waste than to treat or clean up waste after it has been created.
2. ***Atom Economy***
   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. ***Less Hazardous Chemical Syntheses***
   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. ***Designing Safer Chemicals***
   Chemical products should be designed to affect their desired function while minimizing their toxicity.

Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30. B

5. ***Safer Solvents and Auxiliaries***

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

6. ***Design for Energy Efficiency***

   Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. ***Use of Renewable Feedstocks***

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

Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30. By permission of Oxford University Press.

8. ***Reduce Derivatives***

Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. ***Catalysis***

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

Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30. By permission of Oxford University Press.

10. ***Design for Degradation***

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

11. ***Real-time analysis for Pollution Prevention***

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

12. ***Inherently Safer Chemistry for Accident Prevention***

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

Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30. By permission of Oxford University Press.

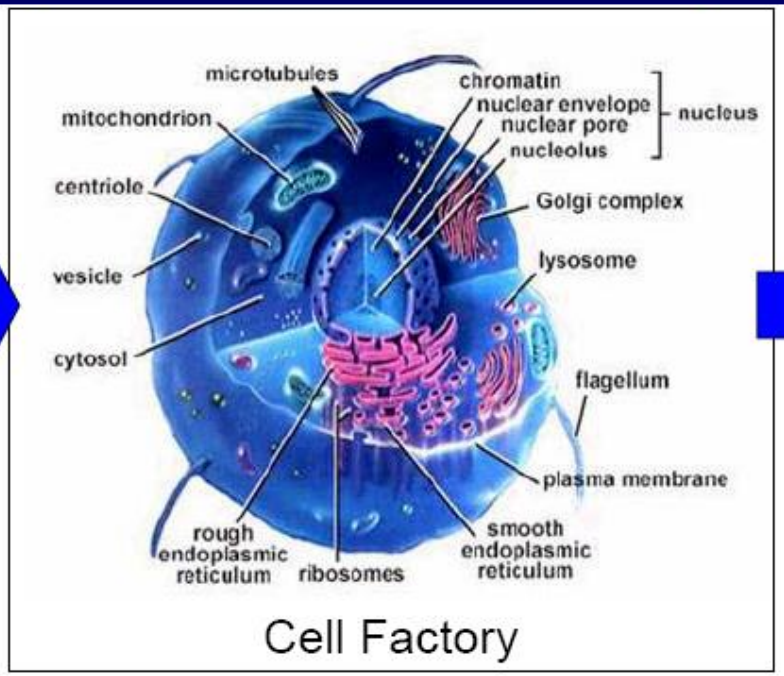
Comparison between stoichiometric and catalytic reactions

STOICHIOMETRIC	CATALYTIC
Reduction:	
$4\ PhCOCH_3 + NaBH_4 + 4\ H_2O$	$PhCOCH_3 + H_2$
↓	↓
$4\ PhCH(OH)CH_3 + NaB(OH)_4$	$PhCH(OH)CH_3$
120/145 = 82%	100%

Atom Utilisation: catalyst is regenerated

The cell:
The most complex and efficient chemical laboratory at low environmental impact

Sugar
Fats
Aminoacids
Etc…



Chemicals

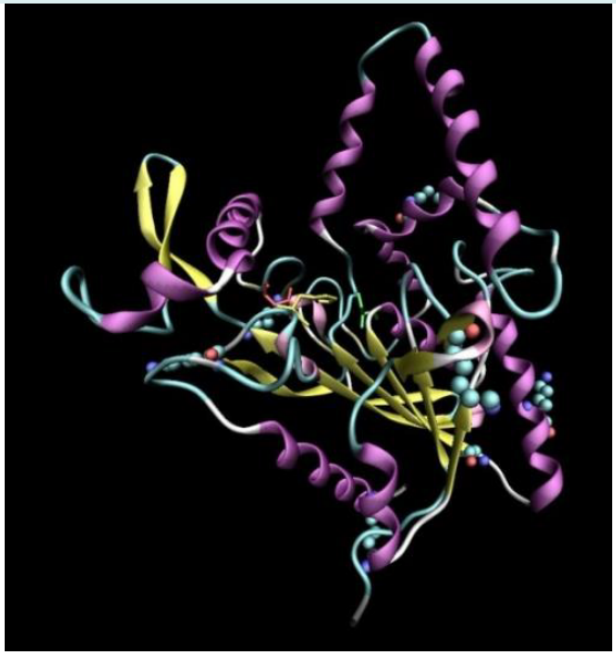
Materials

Drugs

Fuels

bioconversion

Chemical reactions in cells are enabled by enzymes: biocatalysts



They have evolved under the conditions found on Earth to satisfy the metabolic demands of an extensive range of cell types, such as:

1) Chemical reactions take place under mild conditions
2) Specific action according to enzyme class
3) Very fast reaction rates
4) Numerous enzymes for different tasks

Biocatalysis: biological catalysis

Biocatalysis is the general term for the transformation of natural and non-natural compounds by enzymes.

Because of this, the term biocatalysis is also referred to the application of enzymes in chemistry (Bommarius and Riebel, 2004).

Solid to solid:

Organic solvent

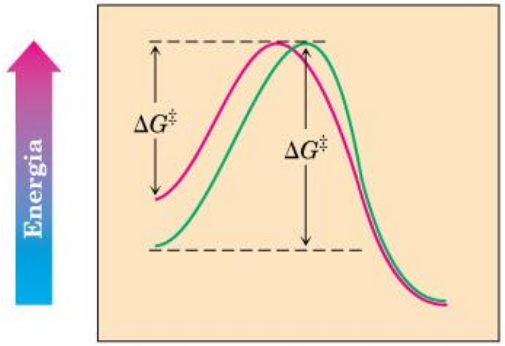
Bulk –solventless - transformation

Some comparison between chemical and biocatalyzed processes

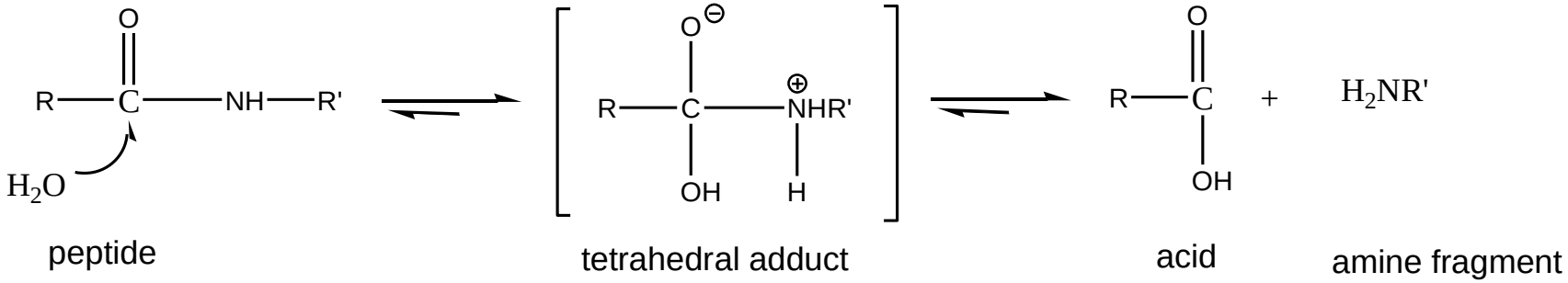
Chemical *vs* enzymatic reactions: Peptides and proteins are hydrolyzed chemically at very harsh conditions:

Options:
a)Aqueous HCl 6M, 100 °C for several hours

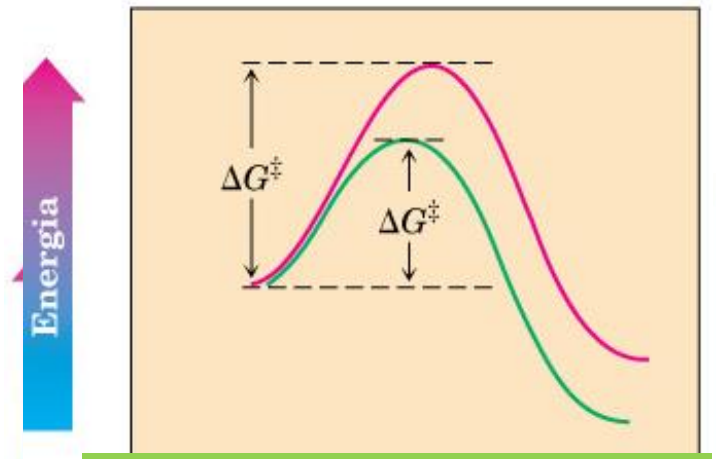
b)Sodium hydroxide



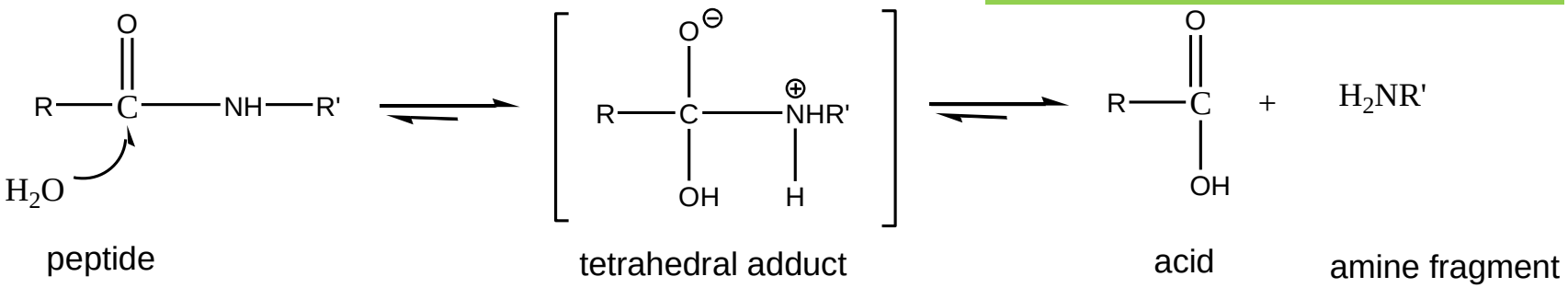
Increasing the energy of the system: Highly active reactants



Enzymes make reactions happen at mild teperature and pH



Decreasing energy by stabilization: CATALYSIS



Subtilisine from *Bacillus specie*: digests proteins under mild conditions

900/y tons for additives in detergents

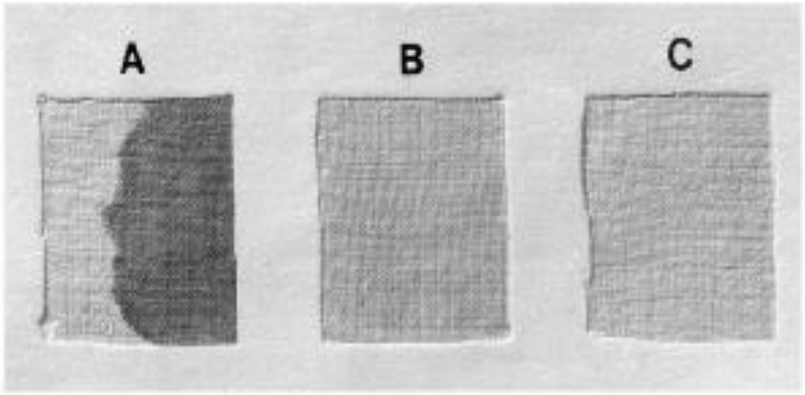


Fig. 6. Washing performance of alkaline protease from *B. brevis* in presence of detergent. (A, Cloth stained with blood; B, blood stained cloth washed with detergent only; and C, blood stained cloth washed with detergent and enzyme.)

A serine protease

Also known as *Subtilisin Carlsberg*

Why traditions matter!

"Jacobson specifically wanted a laboratory that expanded science for the benefit of society," Its charter declares that "the principal task of The Carlsberg Laboratory shall be to develop as complete a scientific basis as possible for malting, brewing and fermenting operations." And on the wall of the building's central grand staircase, the following mantra is inscribed in gold leaf: "No result of the Laboratory's activities which is of theoretical or practical importance shall be kept secret."

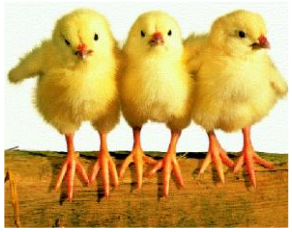
A statue of company founder Jacobson. C. Carlsberg stands outside the Carlsberg Laboratory in Valby, Copenhagen.

Carlsberg Foundation was founded in 1876 and owns 30.3% of the shares in Carlsberg Group and has 74.2% of the voting power.

World leaders in enzymes & microorganisms

Technical enzymes

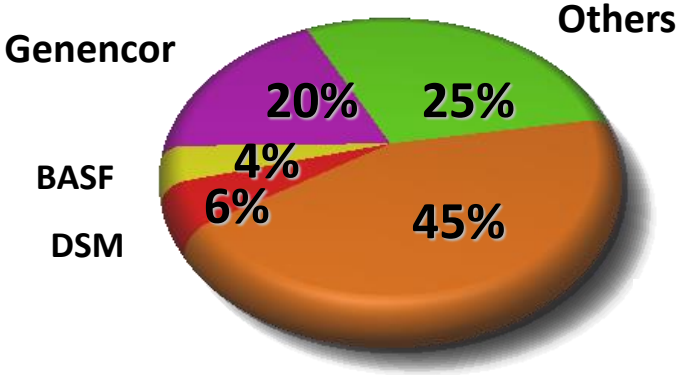
Food enzymes

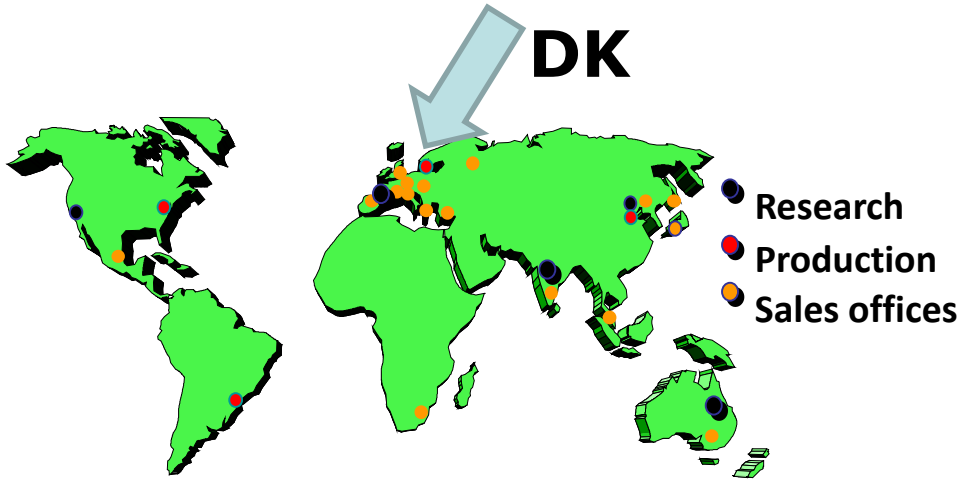


Feed enzymes

Microorganisms

Biocatalysis
Small part to increase





novozymes
Rethink Tomorrow



The global market for enzymes was estimated at about 4.5 bln dollar in 2012 and 8 bln dollar in 2020. Europe is the world leader in key industrial biotechnologies such as enzyme technologies, with Novozymes from Denmark holding a market share of >45% worldwide.

Source. Festel G., Detzel C. and Maas R., Industrial Biotechnology – Markets and industry structure, Journal of Commercial Biotechnology, Volume 18, No. 1, 2012

http://www.novozymes.com

ATTUALITÀ

DOI: http://dx.medra.org/10.17374/CI.2018.101.1.22

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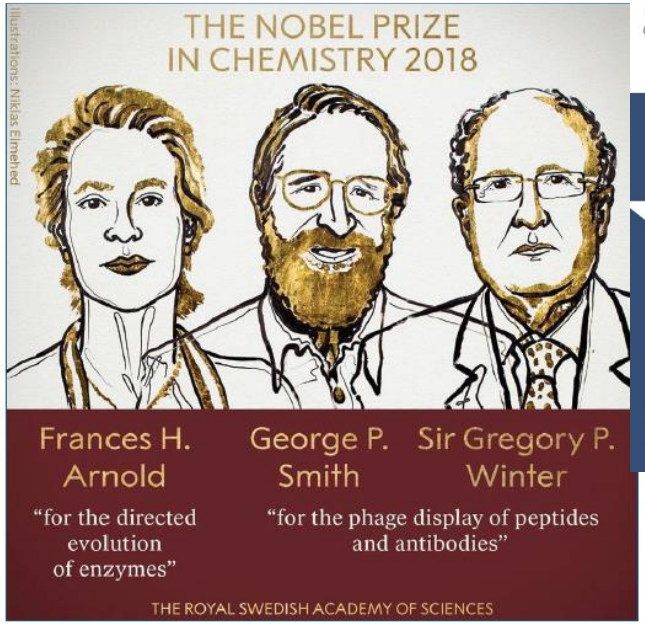
IL NOBEL 2018 PREMIA L'EVOLUZIONE DELLA CHIMICA ATTRAVERSO LE BIOTECNOLOGIE

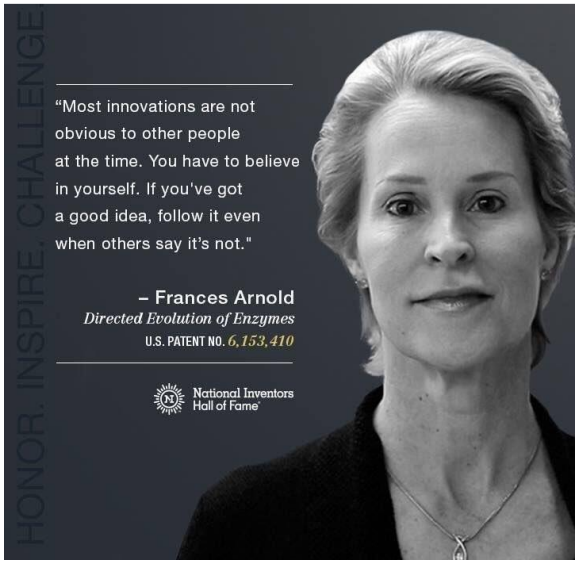
Il premio Nobel per la Chimica nel 2018 è andato agli scienziati che hanno sviluppato strumenti biotecnologici per accelerare e controllare in vitro l'evoluzione delle proteine. Queste metodologie, ideate da Arnold, Winter e Smith, hanno fornito biocatalizzatori di utilità pratica per l'industria chimica ma anche una nuova generazione di agenti terapeutici per cancro e malattie del sistema immunitario.



Directed evolution of enzyme catalysts

Olga Kuchner and Frances H. Arnold

Directed enzyme evolution has emerged in the past few years as a powerful alternative to rational approaches for engineering biocatalysts. Prerequisites for successful directed evolution are functional expression in a suitable microbial host, a rapid screen for the desired feature(s) and a well-thought-out working strategy for navigating protein landscapes. The rapidly growing body of literature on enzyme evolution *in vitro* includes techniques for creating and searching combinatorial enzyme libraries, as well as several successful examples of different evolutionary strategies being used.



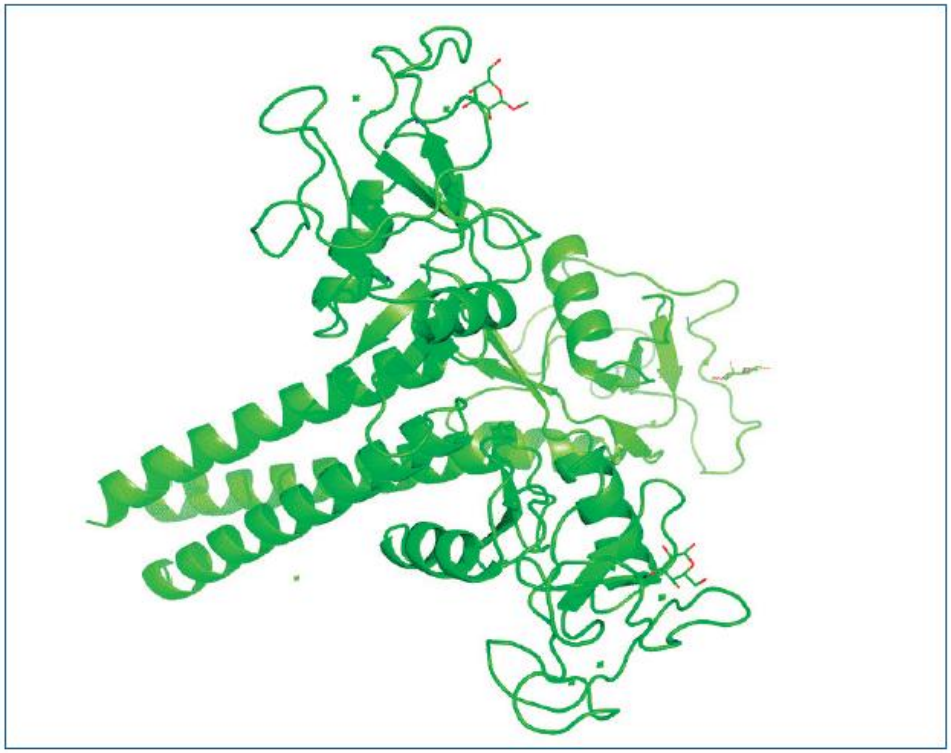


Fig. 2 - Modello tridimensionale del cristallo dell'enzima Subtilisina Carlsberg da *Bacillus licheniformis*, (EC 3.4.21.14) ottenuto in diossano anidro (PDB 1aFA) dal gruppo di A.M. Klibanov (**https://www.ncbi.nlm.nih.gov/Structure/mmdb/mmdbsrv.cgi?Dopt=s&uid=55177**). Questa serin idrolasi entra nella formulazione dei comuni detergenti per il bucato ma è anche utilizzata come biocatalizzatore dall'industria chimica per risolvere miscele racemiche di amminoacidi, ammine e alcoli grazie anche alla sua stabilità in mezzi non acquosi. La famiglia delle subtilisine è caratterizzata dalla conservazione della sequenza Asp^{32}-His^{64}-Ser^{221} (numerazione riferita alla Subtilisina Carlsberg)

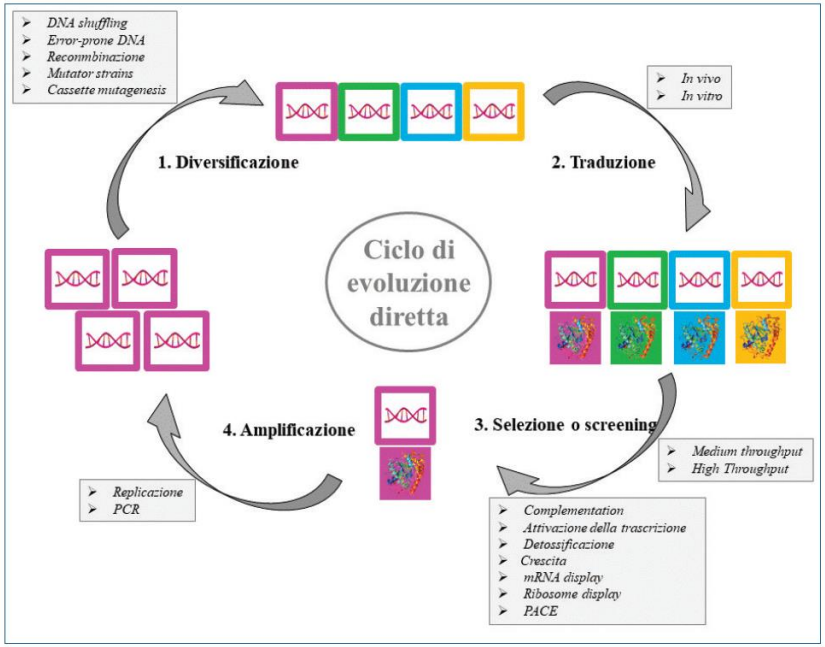
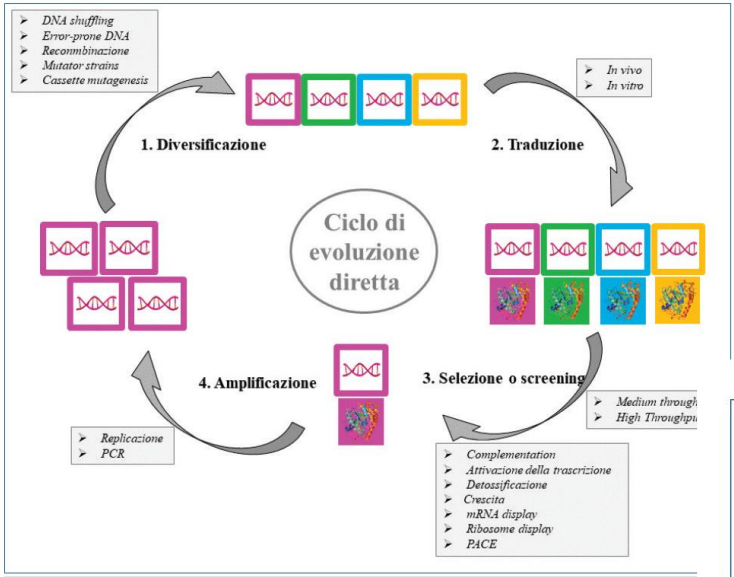


Fig. 1 - Strategia generale per l'evoluzione diretta. I catalizzatori proteici sono ottimizzati mediante cicli iterativi di 1) diversificazione dei geni mediante mutagenesi, 2) traduzione dei geni in prodotti proteici (biocatalizzatori), 3) Selezione delle proteine migliorate con la funzionalità di interesse, 4) amplificazione genica. Abbreviazioni: PACE = phage-assisted continuous evolution; PCR = polymerase chain reaction



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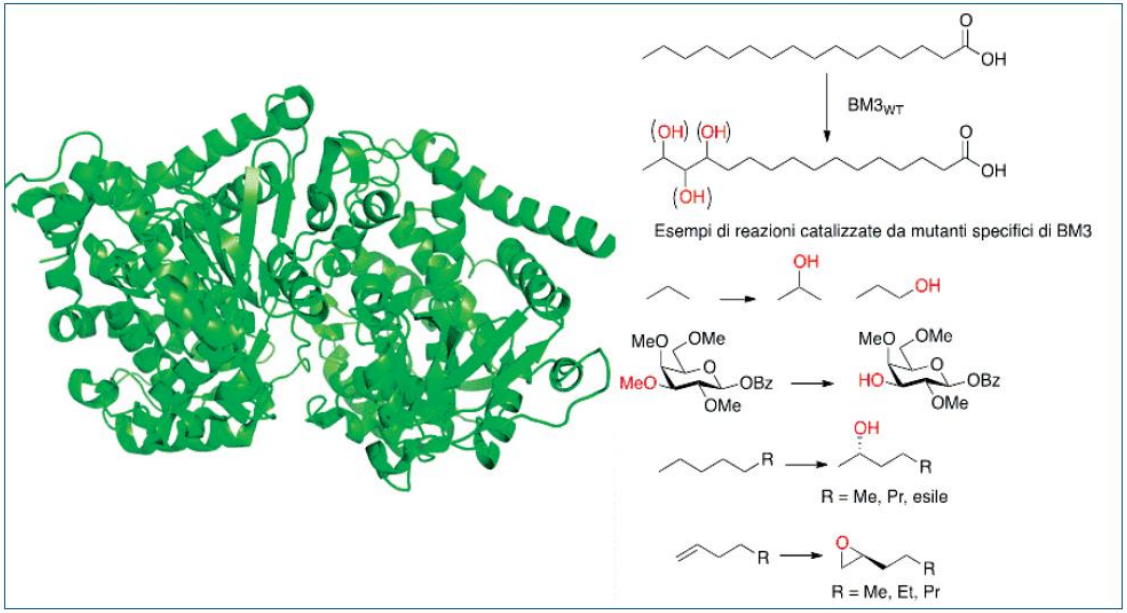
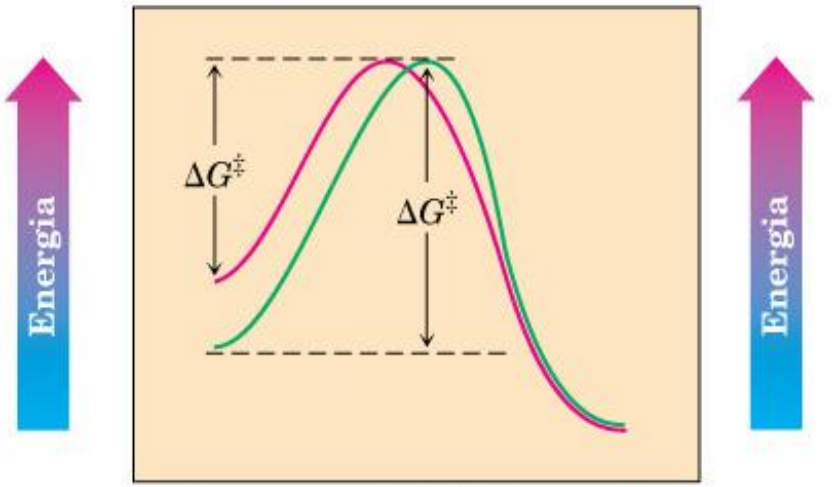


Fig. 3 - Modello della struttura tridimensionale del citocromo P450 BM3 (CYP102A1) da *Bacillus megaterium*. Questo enzima presenta delle caratteristiche ottimali per essere sottoposto a cicli di evoluzione diretta: è una proteina solubile e si può produrre facilmente in *E. coli*. È un citocromo estremamente efficiente, con un numero di turnover pari a 17.000 min^{-1} per la trasformazione dell'acido arachidonico. Il gruppo di ricerca di Frances Arnold ha sviluppato numerosi mutanti di questo citocromo in grado di catalizzare nuove reazioni (riquadro a destra), tra le quali l'idrossilazione di alcani gassosi a catena breve per la sintesi di alcoli, la deprotezione selettiva di zuccheri, la sintesi *in vitro* di metaboliti di farmaci che vengono fisiologicamente prodotti nell'organismo e l'epossidazione stereoselettiva di alcheni.

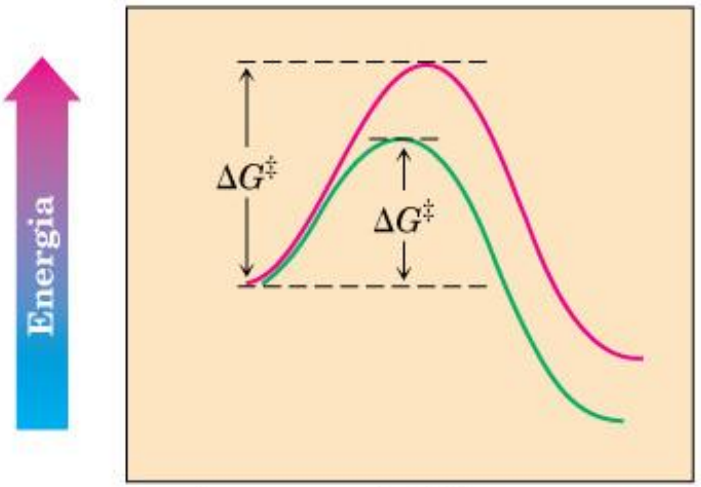
How can we accelerate chemical reactions?

-using more reactive substrates (high energy, low selectivity, side products)

-decreasing the energy of the transformation path through stabilization of the highest energy state.

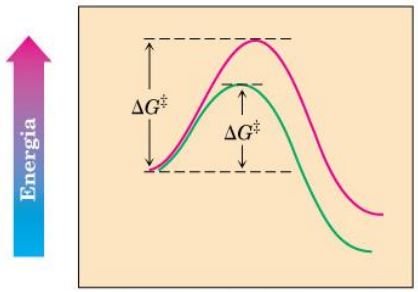


Increasing the energy of the system: Highly active reactants



Decreasing energy by stabilization: CATALYSIS

How can enzyme hydolyse the peptide bond at room temperature and neutral pH?
Why enzymes are more efficient than «chemists»??



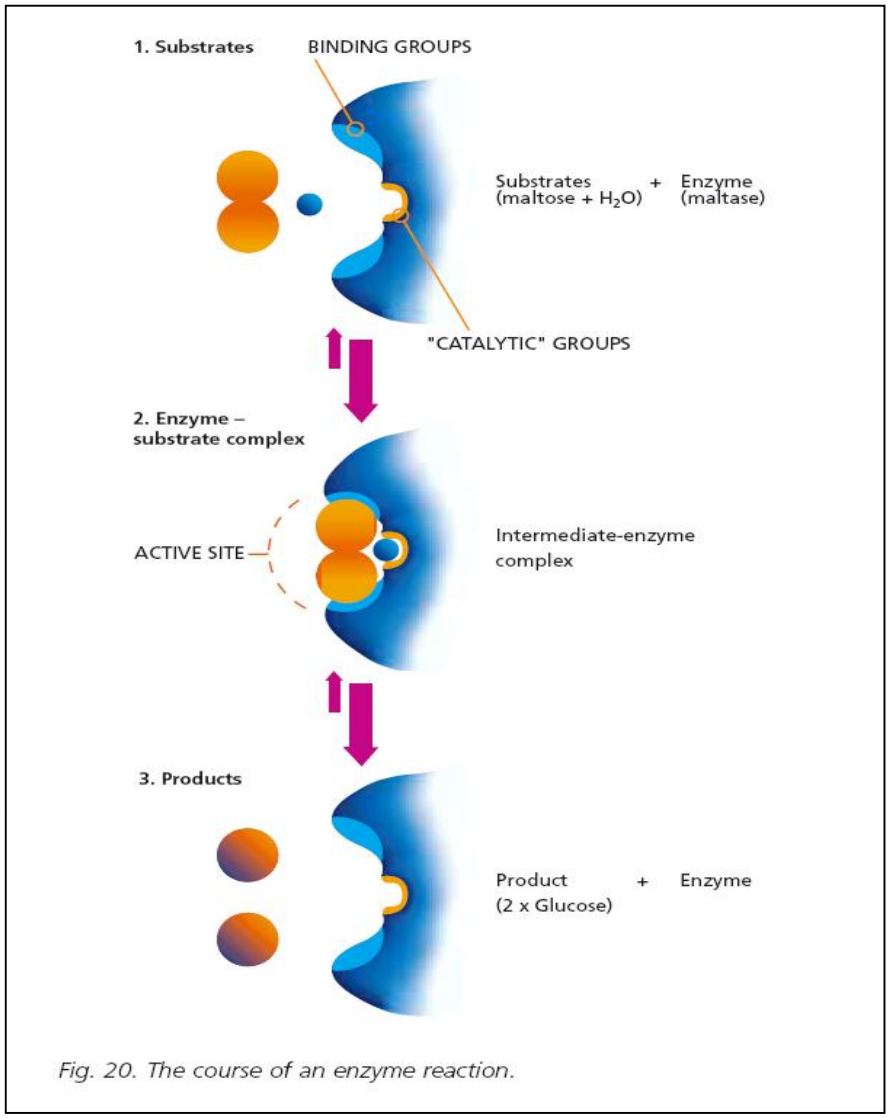
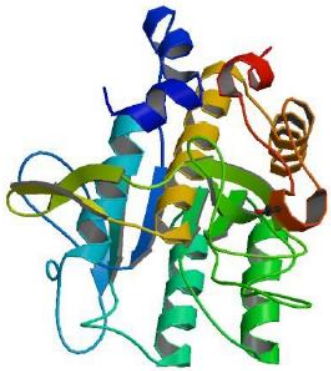
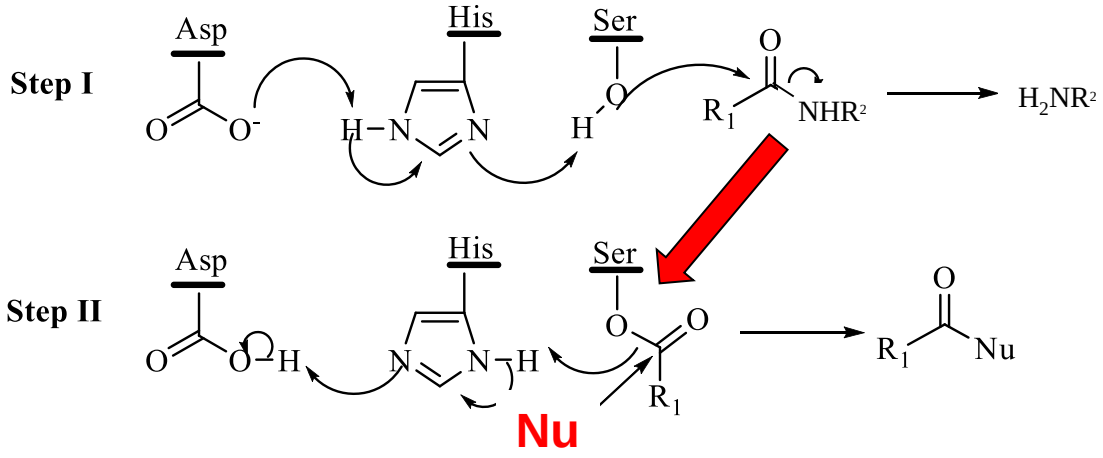


Fig. 20. The course of an enzyme reaction.

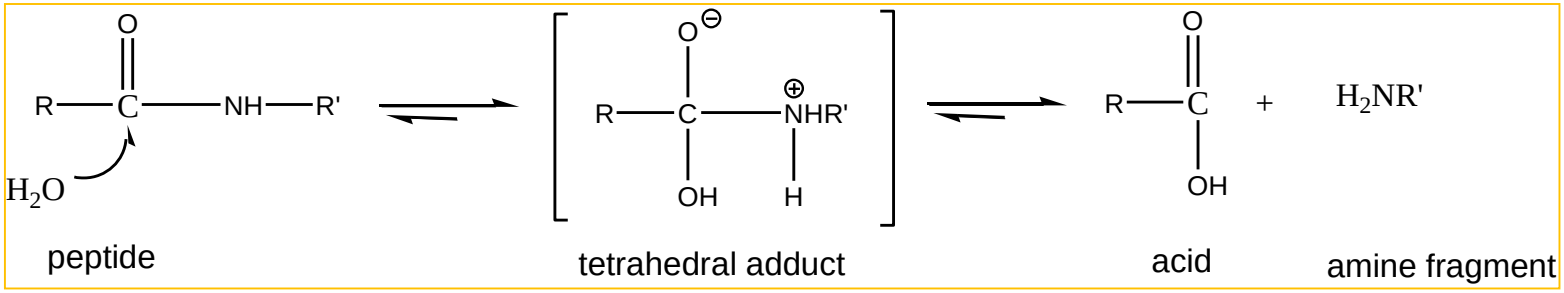
Enzymatic reaction



A serine protease mechanism .



Chemical reaction

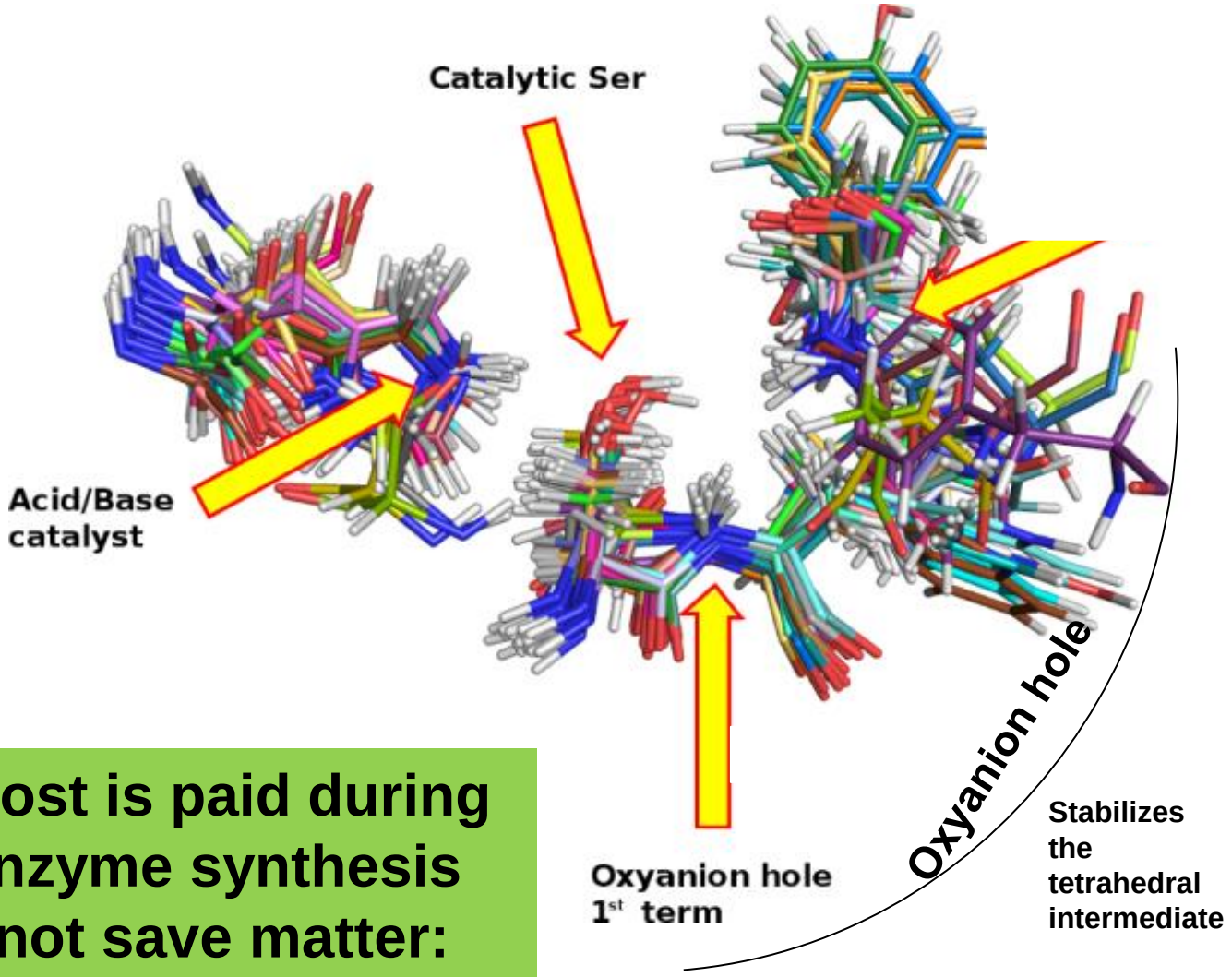


«……the catalytic power of enzymes is largely due to the preorganized electrostatic environment of their active site»

A Warshel et al, Chem Rev, 2006, 106, 3210.

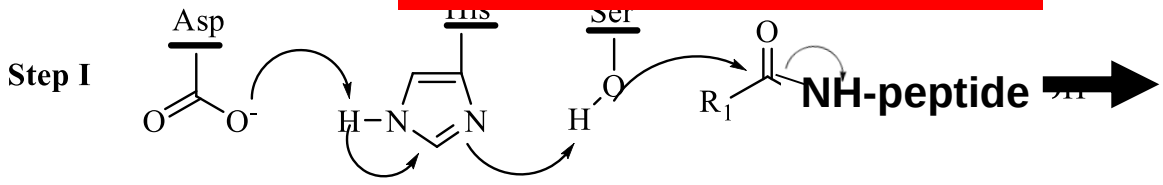
Nobel laureate for chemistry 2013

Serine Hydrolase enzymes active sites: pre-organized reaction environments



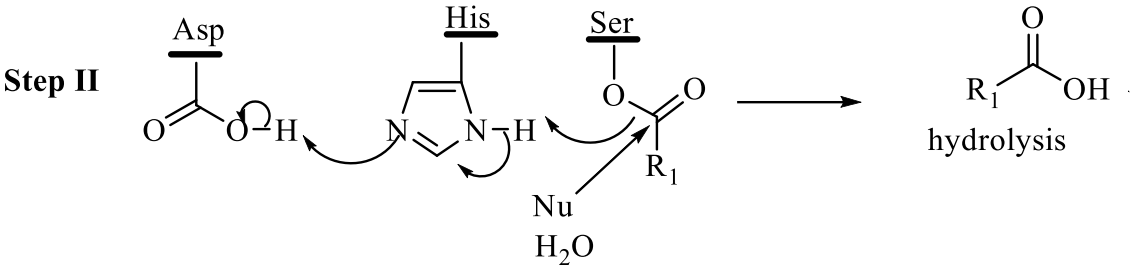
- The energy cost is paid during the protein/enzyme synthesis
- Nature does not save matter: differentiation and selection

Un gruppo alcolico «attivato» della serina funge da nucleofilo ed attacca il legame ammidico: sostituzione nucleofila acilica: alcolisi e formazione di un estere che prende il nome di enzima acilato o acil-enzima



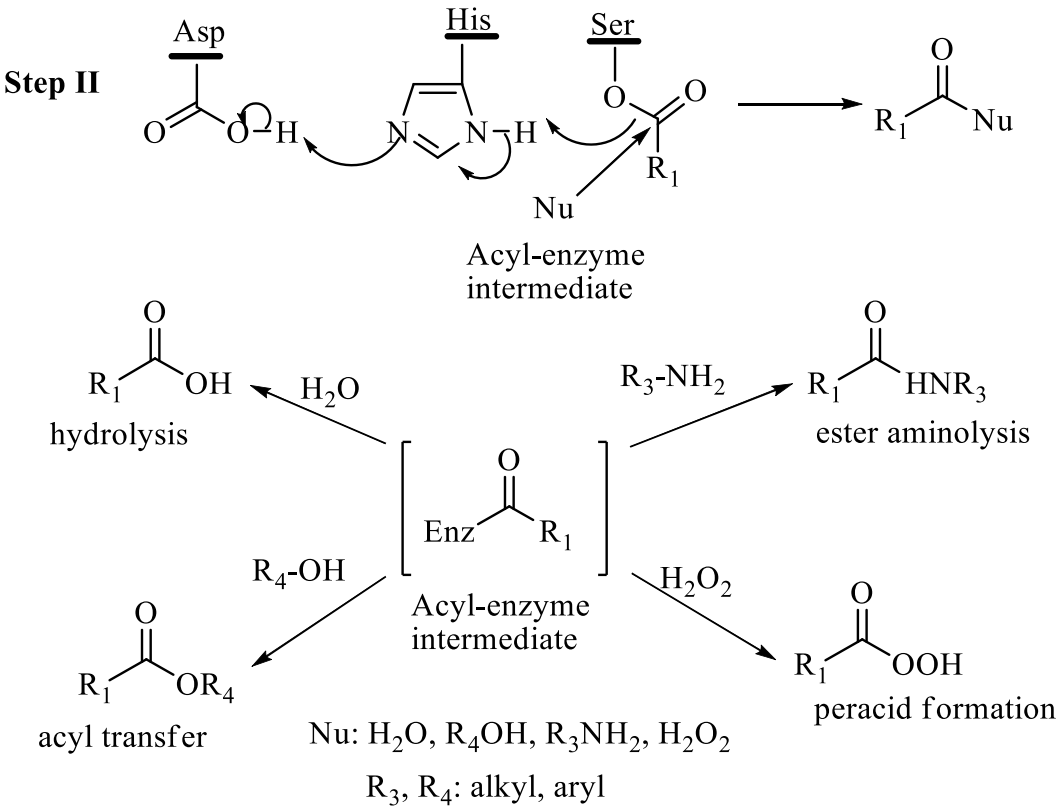
Esce una catena peptidica

H_2N-peptide

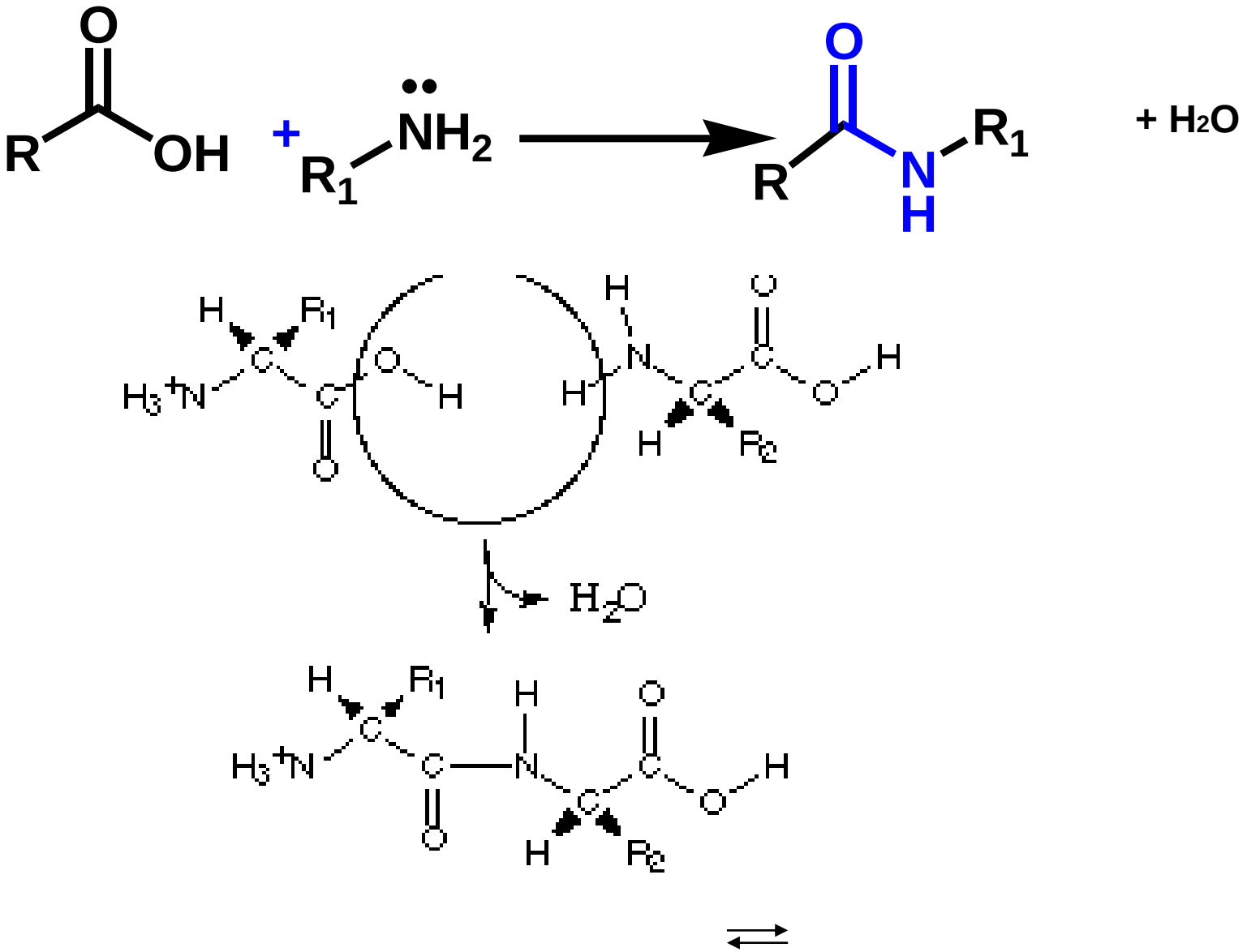


Il nuclofilo acqua attacca l'enzima acilato e mediante sostituzione nucleofila acilica si forma l'acido carbossilico: idrolisi

A serine protease mechanism: different synthetic routes by changing the nucleophile .

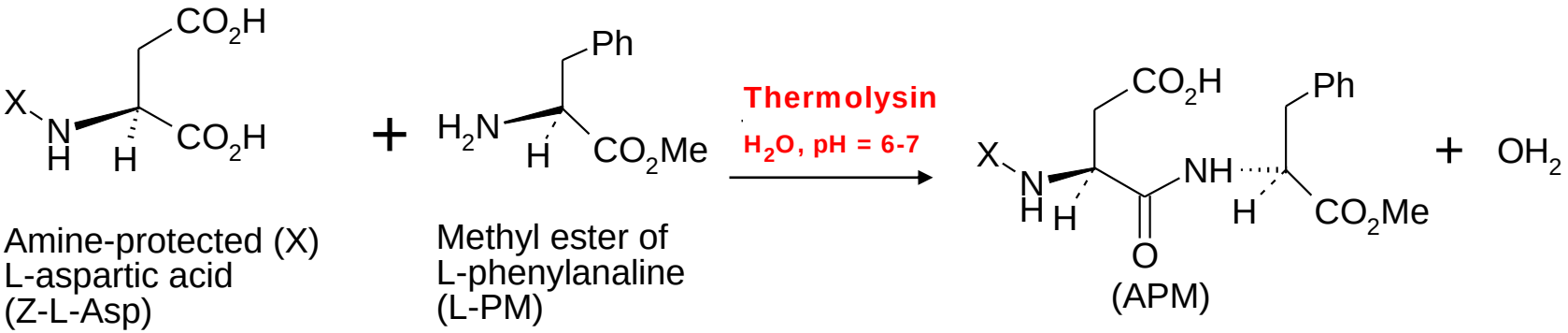


Serin hydrolases can catalyze the synthesis of peptide bond by changing the nucleophile and working under dry conditions



Moving from natural to non-natural substrates: industrial synthesis of dipeptide Aspartame

Enzymatic synthesis of Aspartame in industry

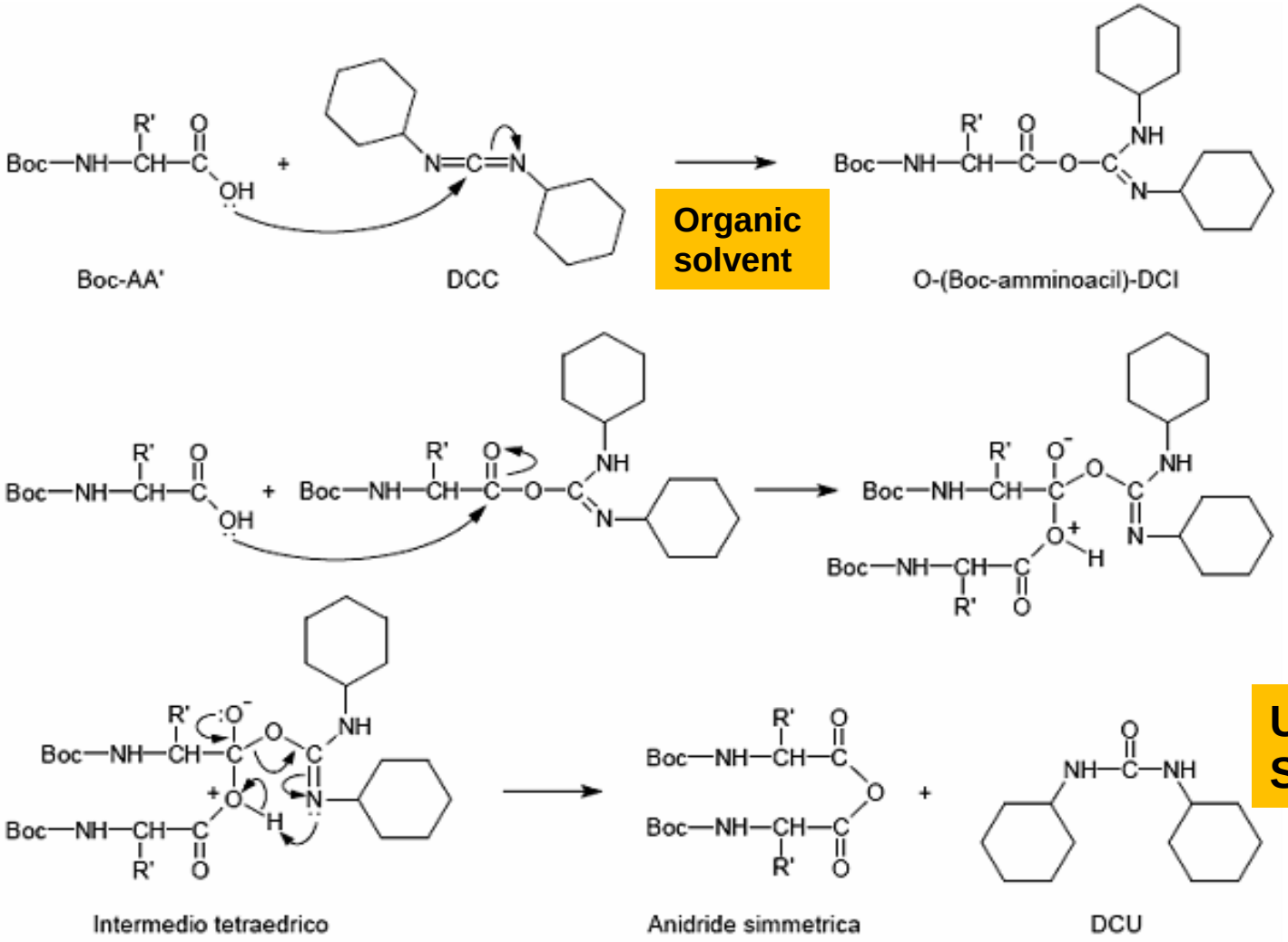


Amine-protected (X) L-aspartic acid (Z-L-Asp)

Methyl ester of L-phenylanaline (L-PM)

Mild conditions: no racemization, less side products

Chemical routes for the synthesis of peptide bonds: Amino and carboxy groups must be protected Acyl group must be activated!! Promotes racemization!!!



Major biotransformations at industrial scale 1.

Fine-pharma chemistry

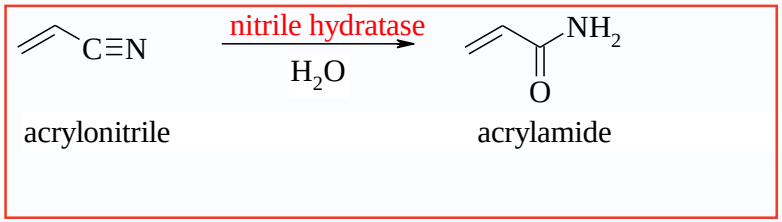
Production scale [tpy]	*Product*	*Enzyme*	*Reactor*	*Company*
> 1 000 000	high-fructose corn syrup (HFCS)	glucose isomerase	fixed-bed, IME	various
> 100 000	lactose-free milk	lactase	fixed-bed, IME	various
> 10 000	acrylamide	nitrilase	batch reactor	Nitto Co.
	cocoa butter*	lipase (CRL)	fixed-bed, IME	Fuji Oil
> 1,000				
	nicotinamide	nitrilase	3-stage batch	Lonza Guangzhou
	D-pantothenic acid	aldonolactonase		Fuji Pharma-ceuticals
	(S)-chloropropionic acid	lipase		Dow Chemical
	6-aminopenillanic acid	penicillin amidase	fixed-bed, IME	various
	7-aminocephalo-sporanic acid	glutaryl amidase	Kundl/Hoechst	
	aspartame®	thermolysin	soluble enzyme	Tosoh/DSM
	L-aspartate	aspartase	fixed-bed, IME	various
	D-phenylglycine	hydantoinase/ (carbamoylase)	resting cells	Kanegafuchi
	D-*p*-OH-phenyl-glycine	hydantoinase/ carbamoylase	resting cells	Recordati

In some cases biocatalyst is the ONLY option

Use of whole cells for the production of acrylamide

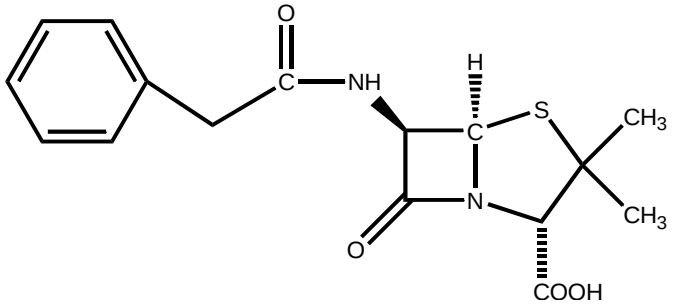
Production of acrylamide by hydration of acrylonitrile using whole bacterial cells (*Pseudomonas chloraphis, Rhodococcus rhodochrous*).

- industrial scale > 30,000 tonnes / year
- Yields >99%
- formation of by-products (acrylic acid) completely avoided

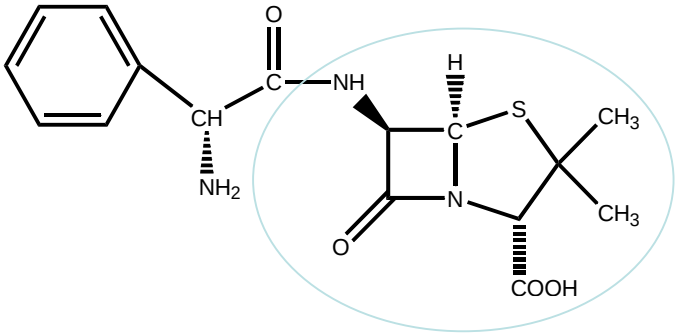


Penicillin G amidase in the hydrolysis of Pen G to 6-APA (precursor of semi-sintetic beta-lactam antibiotics (41% of the whole antibiotic market)

Natural product (secondary methabolite) abtained through fermentation: not used any longer for terapeutic use
Allergenic, degraded when administered by os, narrow spectrum



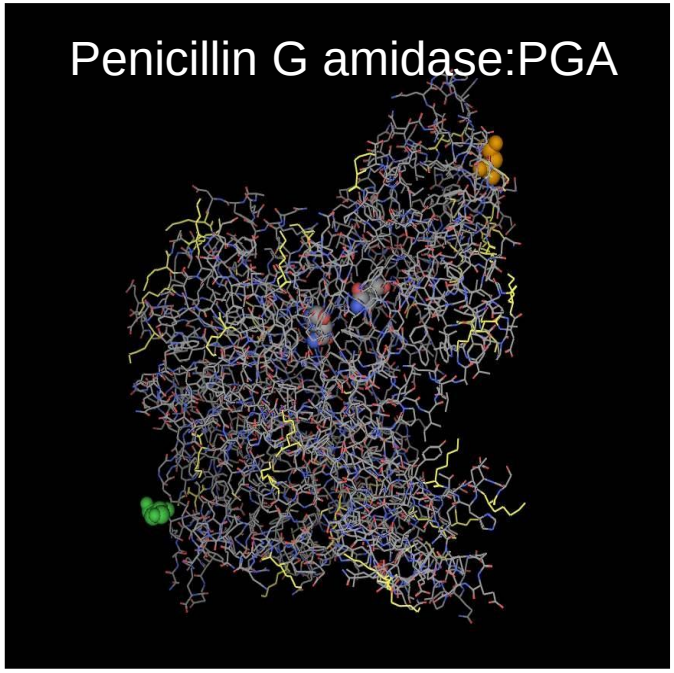
Penicillina G

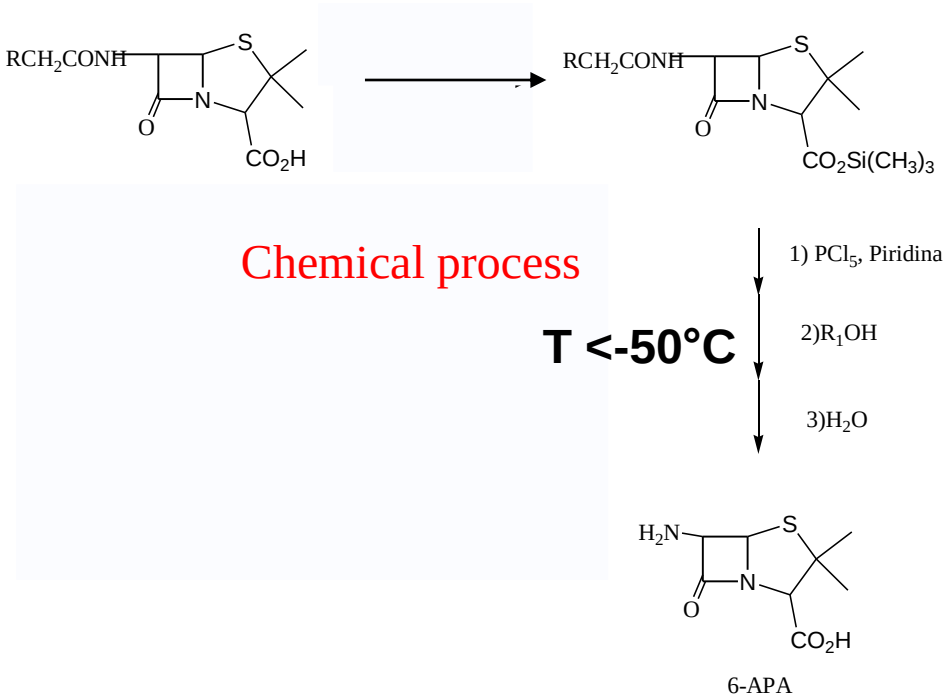


Ampicillin

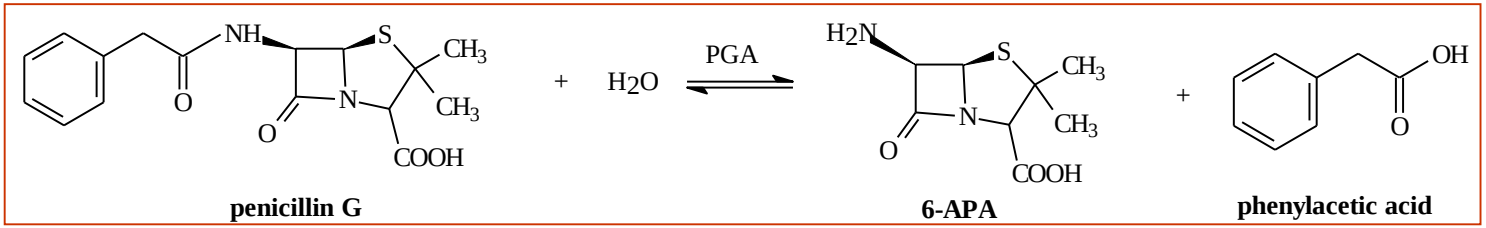
Semisynthetic antiobitic: next generation

Penicillin G amidase in the hydrolysis of Pen G to 6-APA (precursor of semi-sintetic beta-lactam antibiotics





Enzymatic process



Market: 10 - 30 tons of immobilized/insoluble PGA consumed per year

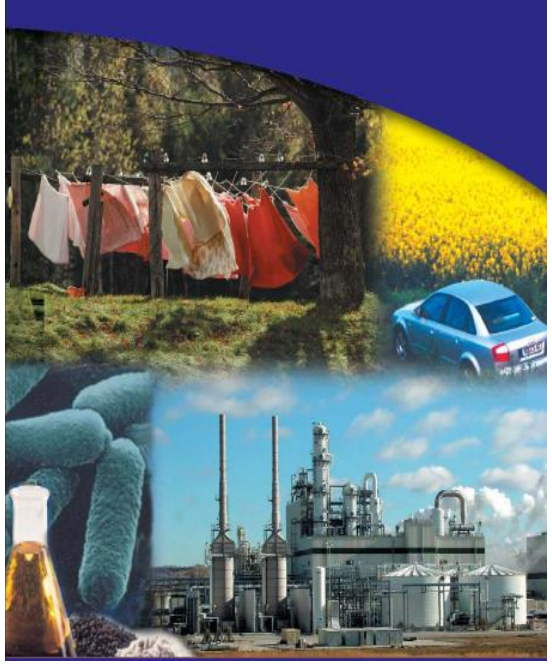
Why biocatalysis? The drivers

Economy

Regulations

Selective + Sustainable

Reduction of process costs



65% of energy saving

Reduction of wastes (1/5)

50% reduction of cost for beta-lactam antibiotics production

Annexes

I dodici principi della chimica verde

1. La prevenzione alla produzione di rifiuti risulta essere più conveniente rispetto al trattare o detossificare i rifiuti dopo che essi siano stati formati.

2. I metodi di sintesi dovrebbero essere messi a punto in modo da poter permettere il massimo utilizzo dei materiali impiegati, consentendo così rese elevate dei prodotti desiderati.

3. Per quanto possibile, le metodologie di sintesi dovrebbero essere ideate per usare o generare sostanze che abbiano minima o nessuna tossicità per la salute umana e l'ambiente.

4. I prodotti chimici devono essere progettati per mantenere l'efficacia della funzione, riducendone la tossicità.

5. L'uso di sostanze ausiliarie deve essere reso innocuo o non necessario.

6. Il fabbisogno energetico dovrebbe essere valutato secondo l'impatto ambientale ed economico, riducendolo al minimo. I metodi di sintesi devono essere condotti a temperatura e pressione ambiente.

I dodici principi della chimica verde

7. Una materia prima rinnovabile dovrebbe essere preferita ad una non rinnovabile, qualora questo sia tecnicamente ed economicamente possibile.

8. Bisognerebbe ridurre i prodotti secondari laddove possibile.

9. I catalizzatori (il più selettivi possibile) risultano essere migliori rispetto i classici reagenti stechiometrici.

10. I prodotti chimici devono essere progettati in modo tale che al termine della loro funzione non persistano nell'ambiente e diano prodotti di degradazione innocui.

11. Le metodologie analitiche devono essere sviluppate per impedire in tempo reale, durante i processi di controllo, la formazione di sostanze nocive.

12. Il tipo di sostanza e lo stato della sostanza, usati durante i processi chimici, devono essere scelti in modo da ridurre il rischio di incidenti, come rilasci, esplosioni ed incendi.

L'utilizzo dei solventi organici costituisce un ulteriore problema nell'ambito della chimica verde:

I solventi non sempre riescono ad essere riciclati. L'impiego di questi in processi costituiti da reazioni multi-stadio causa solitamente delle contaminazioni crociate

- **i solventi sono le sostanze che contribuiscono maggiormente all'ottenimento di valori elevati di E. Factor durante i processi di lavorazione**
- **i solventi costituiscono, nelle sintesi chimiche, l'80% della massa totale delle sostanze coinvolte**

  L'acqua è un buon solvente, essendo non tossica, non infiammabile, disponibile su larga scala ed economica. Nelle reazioni in cui vengono utilizzati i catalizzatori, grazie alla presenza dell'acqua, si possono associare dei sistemi bifasici acquosi. Il catalizzatore risiede nella fase acquosa, mentre il prodotto si trova nella fase organica. In questo modo il catalizzatore può essere recuperato e riciclato attraverso una semplice separazione di fase.
- **OBIETTIVO: USARE ACQUA O SISTEMI CONCENTRATI E POSSIBILMENTE «bulk» senza solvente**