聲明
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[如本頁取材自○○○○教授演講內容]。
綠色化學在化學與製藥工業之應用

2012 綠色/永續合成化學工作坊
November 30, 2012, 化學會年會，成功大學

國立中正大學  周德璋
Global Sustainability
The most critical challenge of today

“The challenges of global sustainability are most complex and definitionally the most consequential of any that civilization has or can encounter.”

“The three elements of sustainability, environmental, social, and economic must be recognized in the context shown in Fig.1.”

Fig. 1. A sustainable community [3].
“……..., we must understand that the economy exists within society and the society exists within the environment.

“The true long-term goal must be to ensure that the goals of environment, society, and economy are working in concert in a synergistic way.”

Toward→→→ global sustainability

Sustainable Development
Meeting the needs of today without compromising the ability of future generations to meet their needs.

Chemistry is a central science and technology!

Sustainable Chemistry not only includes the concepts of green chemistry, but also expands the definition to a larger system than just the reaction. Also considers the effect of processing, materials, energy, and economics.

Green Chemistry is focused on the design, manufacture, and the use of chemicals and chemical processes that have little or no pollution potential or environmental risk.

Introduction
Sustainable Development

“safeguarding human health and environment to allow for future generations to maintain the necessary resources to sustain life”

[永續發展：守護人類的健康和環境，讓子孫能持有永續其生命的必需資源。]

The challenges to chemists

government

public

industry

The challenges to chemists
"Why did you become a chemist?"
Some are excited by the intellectual challenges of chemistry. Others want to use chemistry and chemical engineering to solve problems and make the world a better place.

Anastas:
"The world needs both. Building a sustainable world is the most taxing intellectual exercise we have ever engaged in. It is also the most important for the future of the world."
Green Chemistry

The design, development, and implementation of chemical products and processes to reduce or eliminate the use and generation of substances hazardous to human health and the environment.

[為縮減或淘汰對人類健康和環境具有危害性的物質的使用與產生，而進行化學產品和製造過程的設計、開發與執行。]


The Twelve Principals of Green Chemistry

1. Prevent waste
2. Design safer chemicals and products
3. Design less hazardous chemical syntheses
4. Use renewable feedstocks
5. Use catalysts, not stoichiometric reagents
6. Avoid chemical derivatives
7. Maximize atom economy
8. Use safer solvents and reaction conditions
9. Increase energy efficiency
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

“Underlying the Green Chemistry approach is the recognition that all we have to work with on Earth is matter and energy.”

“Green Chemistry seeks to design and invent the next generation of matter (material) that is the basis of our society and our economy so that it minimizes adverse consequences to human health and the environment.”


Introduction
Webster’s definition of chemistry, “the study of matter and all of its transformations.”

Transformations are carried out by chemical synthesis.

Green Sustainable Synthesis [綠色永續合成] seeks to reduce and prevent pollution at its source.

Anastas and Warner:
"In virtually every aspect in society, it has long been acknowledged that preventing a problem is superior to trying to solve it once it has been created."
“Synthetic chemistry in the 21<sup>th</sup> century is not just a great intellectual challenge, it is essential for addressing the many challenges that face humanity.”

[21世紀的合成化學並不只是一個重大的智力挑戰，有必要考慮到如何解決人類面臨的種種挑戰。]

# Prof. Peter B. Dervan, California Institute of Technology, 2009 Welch Symposium

Green Sustainable Synthesis

The challenges to all Chemists
Robert H. Grubbs, Richard R. Schrock, and France's Yves Chauvin won the 2005 Nobel Award for their development of the metathesis method in organic synthesis.

“This represents a great step forward for green chemistry, reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of mankind, society, and the environment,……"
To process chemists

Process chemists and engineers in industry generally feel that **green chemistry** is an academic pursuit – until **green chemistry** considerations can lower the cost of goods (COG).

And provide good **business opportunity**:

Enhance Reputation; Prevent Product Liability; Increase Profitability; Ensure Compliance; Freedom to Innovate/Operate

---

**Editorial:** Organic Process Research & Development 2008, 12, 1019.
John C. Warner

Research chemist at Polaroid (1988)
Professor at the UMass, Boston (1996),
-- established first doctoral program in green chemistry Professor at UMass Lowell (2004)
-- founded Center for Green Chemistry

Chief technology officer and chairman of the board of Warner Babcock Institute for Green Chemistry (2007)

“Green chemistry is the mechanics of doing sustainable chemistry,”

Warner:
“By focusing on green chemistry, it puts us in a different innovative space. It is a science that presents industries with an incredible opportunity for continuous growth and competitive advantage.”

Chemical & Engineering News, 88(40), October 04, 2010
<table>
<thead>
<tr>
<th><strong>Atom Economy</strong></th>
<th><strong>Convergence</strong></th>
<th><strong>Reagent Optimization</strong></th>
<th><strong>Solvent Reduction</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Green Chemistry is Cost Efficient</strong></td>
<td><strong>環境思維</strong></td>
<td><strong>經濟思維</strong></td>
<td><strong>環境思維</strong></td>
</tr>
<tr>
<td><em>Minimal by-product formation</em></td>
<td><em>increased process efficiency</em></td>
<td><em>Catalytic, low stoichiometry, recyclable reagents minimize usage,</em></td>
<td><em>Less solvent waste,</em></td>
</tr>
<tr>
<td>減低環境負擔</td>
<td>減低環境負擔</td>
<td>減低環境負擔</td>
<td>減低環境負擔</td>
</tr>
<tr>
<td><strong>More from less – incorporate total value of materials</strong></td>
<td><strong>Higher efficiency – fewer operations</strong></td>
<td><strong>Higher efficiency - higher selectivities</strong></td>
<td><strong>Higher throughput, less energy,</strong></td>
</tr>
<tr>
<td>降低成本</td>
<td>降低成本</td>
<td>降低成本</td>
<td>降低成本</td>
</tr>
</tbody>
</table>
## Green Chemistry is Cost Efficient

<table>
<thead>
<tr>
<th>環境思維</th>
<th>經濟思維</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy Reduction</strong></td>
<td><strong>reflects increased efficiency, shorter process, mild conditions</strong></td>
</tr>
<tr>
<td><em>from power generation, transport, and use</em></td>
<td><strong>降低成本</strong></td>
</tr>
<tr>
<td>減低環境負擔</td>
<td><strong>降低成本</strong></td>
</tr>
<tr>
<td><strong>In-situ Analysis</strong></td>
<td><strong>Real-time data increases throughput and process efficiency, fewer reworks</strong></td>
</tr>
<tr>
<td><em>Reduced possibility for exposure or release to the environment</em></td>
<td><strong>降低成本</strong></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td><strong>Worker safety and reduced down time, Reduced time on special control measures.</strong></td>
</tr>
<tr>
<td><em>Non-hazardous materials reduce risk of exposure, release, explosions and fires</em></td>
<td><strong>降低成本</strong></td>
</tr>
</tbody>
</table>
Lower the Cost of Goods (COG) and the Environment

● **Minimize waste**
  
  ★ Achieving higher yields reduces the environmental quotient (EQ) of waste production.
  
  ★ Processing using fewer unit operations and under more concentrated conditions reduce waste, cycle times, and labor costs.

● **Designing routes that require fewer steps**

require smaller quantities of starting materials, solvents, and reagents and less labor; less waste and reduced costs for waste disposal.
● Review and consider older approaches and replaced by new reactions and new technologies.

● Support new synthetic initiatives and encourage unbiased researchers from academia to invent new approaches to existing compounds.

● Provide feedback to drug discovery.
  ▶ Is the most potent or bioavailable compound selected?
  ▶ Can the compound be prepared in the fewest steps?
  ▶ Is the chiral center of the prodrug really necessary?

● Selecting different starting materials through designing and redesigning routes to lower the COG

緑色化學在化學與製藥工業之應用

November 30, 2012
**E-Factor** [Environmental factor]

\[
E = \frac{\text{Total Waste (kg)}}{\text{Product (kg)}}
\]

**Products:** target compounds (goods) and materials that are recovered.

**Waste:** Anything that enters and causes “burden” to the environment.

### E Factors in Chemical Industry

<table>
<thead>
<tr>
<th>Industry Sector</th>
<th>Product Tonnage</th>
<th>E factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil refining</td>
<td>(10^6 - 10^8)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Bulk chemicals</td>
<td>(10^4 - 10^6)</td>
<td>&lt;1 - 5</td>
</tr>
<tr>
<td>Fine Chemicals</td>
<td>(10^2 - 10^4)</td>
<td>5 - 50</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>(10 - 10^3)</td>
<td>25 - 100</td>
</tr>
</tbody>
</table>

Green Chemistry in the Chemical and Pharmaceutical Industry

Examples of Success
Case 1. **Pregabalin (Lyrica®)**
   A Drug for the treatment of Neuropathic Pain

Case 2. **Sildenafil Citrate**
   The Active pharmaceutical ingredient (API) in the PDE$_5$ Inhibitor Viagra™

Case 3. **Ibuprofen**
   One of core non-steroidal anti-inflammatory medicines

Case 4. **Disodium iminodiacetate (DSIDA)**
   A key intermediate in the production of Roundup® herbicide
Pregabalin (Lyrica®)

普瑞巴林

A Drug for the treatment of Neuropathic Pain

(S)-3-(aminomethyl)-5-methylhexanoic acid
What is Pregabalin (Lyrica®)?

- An anticonvulsant drug used for neuropathic pain.
- Marketed by Pfizer under the trade name Lyrica®.
- Was invented by medicinal chemist Richard Bruce Silverman at Northwestern University in the United States.

(S)-3-(aminomethyl)-5-methylhexanoic acid

(Silverman, R. B.; Andruszkiewicz, R. U. S. Pat. 6,197,819 B1 -- "Gamma Amino Butyric Acid Analogs and Optical Isomers." (March 6, 2001); expires in March 2018
✓ Pregabalin is an analogue of gamma-aminobutyric acid (GABA).

✓ Binds to the $\alpha$–$\delta$ protein subunit of voltage-sensitive calcium channels, modifying calcium transduction and neurotransmitter release.

✓ Pregabalin acts as a agonist of GABA receptors.

✓ Increases GABA levels by increasing glutamic acid decarboxylase (GAD) activity.

✓ GAD is an enzyme that synthesizes glutamate to GABA in one step.
✓ **Lyrica®** launched in the US in September 2005.

- Sales in 2006 $1.16 billion
- Sales in 2007 $1.8 billion
- Sales in 2009 $2.84 billion
- Sales reached a record $3.063 billion in 2010.

✓ First drug approved by the US. FDA (2007) for widespread pain of fibromyalgia.


✓ Also treats epilepsy [羊癲瘋] and neuropathic [神經質的] pain disorders.

✓ Classified as a **Schedule V** drug in the U.S.

*(low potential for abuse, and a limited dependence liability if misused)*
Manufacturing Process

- **Launch Process — Malonate route**

\[
\text{CH}_3\text{C(OH)}\text{CO}_2\text{Et} + \text{CO}_2\text{Et} \xrightarrow{3 \text{ steps}} \text{CH}_3\text{CH(COOEt)}\text{CO}_2\text{Et} \xrightarrow{\text{resolution}} \text{CH}_3\text{CH(COOEt)}\text{CO}_2\text{H} \text{NH}_2
\]


- **Chemoenzymatic Process (2006)**

\[
\text{CH}_3\text{CH(COOEt)}\text{CO}_2\text{EtCN} \xrightarrow{\text{Lipolase}} \text{CH}_3\text{CH(COOEt)}\text{CO}_2\text{EtCN}
\]

*Using commercially available Lipolase to resolve rac-2-carboxyethyl-3-cyano-5-methylhexanoic acid ethyl ester*

Pregabalin Manufacturing Process
(Launch Process)

\[ \text{Knoevenagel condensation} \]

\[ \text{cyanation} \]

\[ \text{hydrolysis, reduction, decarboxylation} \]

\[ \text{resolution} \]

\[ \text{(S)-(+) - Mandelic acid} \]

\[ \text{(2 crystallization)} \]

\[ \text{Org. Process Res. Dev. 1997, 1, 26}, \]
Problems

Atom economy: ~40%
Using extremely toxic potassium cyanide

Any synthetic solution??

Classical resolution

Requires stoichiometric mandelic acid
Undesired enantiomer difficult to recycle
75% of everything becomes waste
Overall low yield, low throughput, and high cost
Solution – Chemoenzymatic resolution

Recycling

Lipolase (8%) activation

\[
\text{Ca(OAc)\textsubscript{2} \cdot H\textsubscript{2}O (150 mM)} \quad \frac{\text{CO\textsubscript{2}Et}}{\text{CO\textsubscript{2}Et}} \quad \text{CN} \quad \text{CO\textsubscript{2}Et} + \text{CO\textsubscript{2}Et} \quad \text{Na} \\
\]

\[
\text{PhMe, 80 °C, 16 h, NaOEt, ~100%} \\
\]

\[
\text{Raney Ni, H\textsubscript{2}, H\textsubscript{2}O, pH 7.0, rt, 24 h} \\
\]

\[
\text{Pregabalin} \quad \text{CO\textsubscript{2}H} \quad \text{CH\textsubscript{2}NH\textsubscript{2}} \\
\]

99.5% pure; 99.75% ee overall 40-45% yields after one recycling

\[
\text{KOH-H\textsubscript{2}O, rt, 1 h} \\
\]

\[
\text{CO\textsubscript{2}Et} \quad \text{CN} \quad \text{CO\textsubscript{2}Et} \\
\]

\[
\text{>99% ee} \quad \text{~100% conversion isolated} \\
\]

\[
\text{Organic Process Research & Development 2008, 12, 392} \\
\]
Environmental benefits

The IChemE Award for Excellence in Green Chemistry and Engineering (2006)

- Biocatalytic with low (~0.5%) protein loading,
- Resolution at first step (wrong enantiomer can be recycled),
- Higher yields (40–45% after one recycle),
- Substantial reductions of waste streams, (the $E$ factor decreased from 86 to 17 to 8)
- All reactions performed exclusively in water!
- Organic solvents (IPA, toluene) used for drying and cleaning only.
Between 2007 and 2020 the new synthesis will eliminate:

- 185,000 tonnes of solvent (water, THF, MeOH, EtOH, IPA), > 90 % reduction
- 4800 tonnes of (S)-mandelic acid, 100 % reduction
- 2000 tonnes of Raney Ni catalyst, 90 % reduction
- 15,000 tonnes of starting material (CNDE), > 50 % reduction

Solvent and Energy savings are the equivalent to saving 413,550 tonnes of CO₂ emissions

Equivalent to taking 69,000 US cars off the road for a year!

😊
Case 2.

Sildenafil Citrate

The Active pharmaceutical ingredient (API) in the PDE$_5$ Inhibitor Viagra™
What is Sildenafil Citrate?

Sildenafil was synthesized at Pfizer's research facility at Sandwich, Kent, in England.

It was initially studied for use in treating hypertension (高血壓) and angina pectoris (心絞痛).

It was approved by the US FDA on 27 March 1998 for use in treating erectile dysfunction (勃起機能障礙) under trade name Viagra™.
In June 2005, it was approved by FDA for treatment of pulmonary arterial hypertension (肺動脈高血壓), marketed as Revatio®.

It has been shown to be useful for the prevention and treatment of high-altitude pulmonary edema (肺水腫) associated with altitude sickness such as that suffered by mountain climbers.

Viagra™ is actually a citrate salt and water-soluble, obtained simply by reacting sildenafil, a base, with citric acid (100% efficient).

In 2003 Pfizer received the UK IchemE Crystal Faraday Award for designing the green sildenafil process.
Sildenafil is a potent and highly selective inhibitor of PDE5 (phosphodiesterase type 5), acting as a molecular impostors of cGMP.

How sildenafil acts in the body.

* Sildenafil works by inhibiting the enzyme PDE5 by occupying its active site. This means that cGMP is not hydrolysed as fast and this allows the smooth muscle to relax.

Nitric Oxide (NO) → guanylate cyclase → guanosine triphosphate (GTP) → cyclic guanosine monophosphate (cGMP) → smooth muscle to relax → an inflow of blood → an erection.

Viagra → phosphodiesterase type 5 (PDE5) → hydrolyzed.
Chemical Synthesis of Sildenafil

2-ethoxybenzoic acid

chlorosulfuric acid

pyrazole-derivative

1-methylpiperazine

Sildenafil Citrate
**Chemical Synthesis** – original, basic (academic)


\[
\begin{align*}
1. & \text{ Me}_2\text{SO}_4 \\
2. & \text{ NaOH/H}_2\text{O} \\
3. & \text{ HNO}_3/\text{H}_2\text{SO}_4 \\
4. & \text{ SOCl}_2 \\
5. & \text{ NH}_4\text{OH} \\
6. & \text{ SnCl}_2 \\
\end{align*}
\]

**Pyrazole-ring formation**

**Methylation**

**Hydrolysis**

**Nitration**

**Carboxamide formation**

**Reduction**

Sildenafil Citrate
Sildenafil
Citrate

9 process steps
overall yield: 27.6%.
Chemical Synthesis – Patent, Manufacturing Process (Industry)

P. J. Dunn *Organic Process Research & Development* 2005, 9, 88-97

The United Kingdom Award for Green Chemical Technology ("Best Process" category). -- 2003

\[
\text{EtO}_2\text{C} = \text{CO}_2\text{H} \rightarrow \text{EtO}_2\text{C} = \text{CO}_2\text{H}
\]

chlorosulphonation

\[
\begin{align*}
\text{ClSO}_3\text{H} & \quad \text{(4 equiv.)} \\
\text{SOCl}_2 & \quad \text{(1 equiv.)}
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{N} \\
\text{N} & \quad \text{Me}
\end{align*}
\]

*N*-sulphonation of 1-ethylpiperazine

1. \text{EtOAc}

2. \text{EtOAc} (5% excess)

Sildenafil Citrate
(1) under neutral conditions: heated with or without a solvent or a dehydrating agent; or
(2) under acidic conditions: a protic or Lewis acid with or without a solvent.

Significant achievements:

(i) a convergent, efficient synthetic route
(ii) 8 process steps, no extractive work-up in any step
(iii) implementing efficient solvent recovery early in the product's commercial lifetime.
a convergent vs. a linear synthetic route.

overall yield 51.7% vs. 27.6%.

In a typical production year Pfizer (worldwide) produces 300 tons of organic waste in the preparation of sildenafil citrate. vs. 4300 tons.

The overall environmental impact is low with $E = \sim 6$. (industry average 25 ~100).
The last three key steps of the reaction make use of only one solvent (EtOAc).

In a typical production year Pfizer (worldwide) eliminates 3900 tons of aqueous waste.

Green Chem. 2004, 6, 43–48
Case 3.

Ibuprofen

US Presidential Green Chemistry Challenge Awards: 
**Greener Synthetic Pathways Award** 1997
What is ibuprofen?

(S)-2-(4-isobutylphenyl)propanoic acid, (S)-ibuprofen, is active form both *in vitro* and *in vivo*.

(S)-ibuprofen  (R)-ibuprofen

2-arylpropionyl-CoA epimerase (isomerase)

marketed as *racemic mixtures*. 

November 30, 2012
One of core non-steroidal anti-inflammatory medicines (非類固醇消炎藥) in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic health care system ---- Over-the-Counter (不需處方可出售的) medicine. [others: aspirin, paracetamol (acetaminophen)]

Discovered by S. Adams, with J. Nicholson, A. R. M. Dunlop, J. B. Wilson & C. Burrows (Boots Company), and was patented in 1961. Dr. Adams initially tested the drug on a hangover (宿醉).
It was launched in 1969 as a medication for the treatment of rheumatoid arthritis [風濕性關節炎] in the UK and in 1974 in the USA.

The Boots Group was awarded *Queen's Award for Technical Achievement* for the development of ibuprofen in 1987.

具解熱、消炎和鎮痛的作用，可治療發燒、疼痛和發炎。

減輕關節炎(arthritis)，原發型痛經( primary dysmenorrhea)，發燒(fever)，等症狀；作為止痛劑 (analgesic)；具抑制血小板凝集效應 (antiplatelet effect)。

Active ingredient in “Motrin”, “Advil”, Medipren”….，“炎熱消”（水液），“普服芬” (錠劑), 宜痛炎錠, 伊普®鎮痛, ….。
Synthesis

The industrial synthesis was developed and patented by Boots Company of England in 1961. --- brown synthesis

A new greener industrial synthesis was developed and implemented by the BHC Company (now BASF Corporation) in 1991. --- green synthesis

BHC won Presidential Green Chemistry Challenge Awards (USA) ---- Greener Synthetic Pathways Award in 1997.

BHC = Boots + Hoechst Celanese
Boots synthesis of ibuprofen

--- brown synthesis

Developed and patented by Boots Company of England in the 1960s.
<table>
<thead>
<tr>
<th>Reagent</th>
<th>Used in ibuprofen</th>
<th>Unused in ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formula</td>
<td>Mw</td>
</tr>
<tr>
<td>1</td>
<td>C₁₀H₁₄</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td>C₄H₆O₃</td>
<td>102</td>
</tr>
<tr>
<td>2</td>
<td>C₄H₇ClO₂</td>
<td>122.5</td>
</tr>
<tr>
<td></td>
<td>C₂H₅ONa</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>H₃O</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>NH₃O</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>H₄O₂</td>
<td>36</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Ibuprofen</strong></td>
<td><strong>Waste products</strong></td>
</tr>
<tr>
<td>C₂₀H₄₂NO₁₀ClNa</td>
<td>514.5</td>
<td>C₁₃H₁₈O₂</td>
</tr>
</tbody>
</table>

▶ = (206)/(514.5) x 100 = 40%

Table 1. Atom economy in the Boots’ synthesis of ibuprofen
Problems with Boots synthesis of ibuprofen

**Friedel-Crafts acetylation**

- Reactants: \( \text{H}_3\text{C}-\text{COO}-\text{CH}_3 \) and \( \text{AlCl}_3 \)
- Products: \( \text{HCl} \) and \( \text{AcOH} \)
- Catalyst: \( \text{Al} \)

Aluminium trichloride, \( \text{AlCl}_3 \), is not a true catalyst. It is changed into a hydrated form, \( \text{Al(OH)}_3/\text{H}_2\text{O} \), that has to be disposed of – usually in landfill sites.

**Darzens condensation**

- Reactants: \( \text{Cl}-\text{COO} \) and \( \text{NaOC}_2\text{H}_5 \)
- Products: \( \text{NaCl} \) and \( \text{C}_2\text{H}_5\text{OH} \)
- Atom economy: 71.6%

Atom economy = 74.5%
Hydrolysis

\[ \text{H}^+ / \text{H}_2\text{O} \]

Atom economy = 67.6%

Dehydration

\[ \text{C} \_2\text{H}_5\text{OH} \]

Atom economy = 91%

Atom economy = 92%

\[ \text{H}_2\text{O} \]

Atom economy = 92.4%

\[ \text{NH}_3 \]

\[ \text{CO}_2 \]

\[ \text{C}_2\text{H}_5\text{OH} \]

\[ \text{H}_2\text{O} \]

\[ \text{ibuprofen} \]
6 steps!
If 90% yield for each step, then overall yield is 53%.

Atom economy is 40%!
thus every 1 kg of ibuprofen produced is accompanied with more than 1.5 kg of waste.

UK market for ibuprofen is about 3,000,000 kg per year!

- about 4,500,000 kg of waste are produced.
- a typical tablet contains 200 mg of ibuprofen, then 15,000,000,000 (1.5 x 10^{10}) tablets are produced.

World population on November 2010 is estimated by the United States Census Bureau to be 6.884 billion (0.7 x 10^{10}).
BHC synthesis of ibuprofen
--- green synthesis

(USA) Presidential Green Chemistry Challenge Awards
Greener Synthetic Pathways Award in 1997

Developed and implemented by the BHC Company in 1991

\[
\begin{align*}
\text{Friedel-Crafts acetylation} & \quad \text{H}_2, \text{Raney Ni} \\
\text{hydrogenation} & \quad \text{CO} \\
palladium-catalyzed carbonylation & \quad [\text{Pd}]
\end{align*}
\]
<table>
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<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{10}H_{14}</td>
<td>134</td>
<td>C_{10}H_{13}</td>
</tr>
<tr>
<td>C_{4}H_{6}O_{3}</td>
<td>102</td>
<td>C_{2}H_{3}O</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H_{2}</td>
<td>2</td>
<td>H_{2}</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>28</td>
<td>CO</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>C_{15}H_{22}O_{4}</td>
<td>266</td>
<td>C_{13}H_{18}O_{2}</td>
</tr>
</tbody>
</table>

**Atom economy** = \( \frac{206}{266} \times 100 = 77.4\% \)

Table 2. Atom economy in the BHC synthesis of ibuprofen
Economic and Environmental Advantages of BHC Synthesis

- Greater overall yield (three steps vs. six steps)
- Greater atom economy (77% vs. 40%; uses less feedstocks)
- Fewer auxiliary substances (products and solvents separation agents)
- **Less waste:** greater atom economy, catalytic vs. stoichiometric reagents, recovery of byproducts and reagents, recycling, and reuse, lower disposal costs.

The BHC ibuprofen process is an innovative, efficient technology that has revolutionized bulk pharmaceutical manufacturing.
Case 4.

Disodium iminodiacetate (DSIDA)

US Presidential Green Chemistry Challenge Awards: 
**Greener Synthetic Pathways Award** 1996
What is Disodium iminodiacetate (DSIDA)?

- Disodium 2,2'-azanediyldiacetate
- Sodium 2-[(2-oxido-2-oxoethyl)amino]acetate

A key intermediate in the production of Monsanto’s Roundup® herbicide.

Glyphosate: N-(phosphonomethyl)glycine in the form of its isopropylamine salt (41%)

Roundup® agricultural herbicides are the flagship of Monsanto's agricultural chemicals business.
Strecker amino acid synthesis

Traditionally, the Strecker process has been used to manufacture DSIDA. It requires formaldehyde, ammonia, hydrogen cyanide, and hydrochloric acid.
The Strecker process for synthesizing DSIDA

\[
2 \text{CHO} + \text{NH}_3 + 2 \text{HCN} \rightarrow \text{N} \equiv \text{C} \text{HN} \text{CHCN}
\]

**hydrogen cyanide:**
- extremely toxic;
- requires special handling

**exothermic reaction**
- generating potentially unstable intermediates.

**waste:** 1 kg for every 7 kg of product.
Green process for synthesizing DSIDA

copper-catalyzed dehydrogenation of diethanolamine

\[
\text{diethanolamine} \quad \xrightarrow{2 \ \text{NaOH}} \quad \text{disodium iminodiacetate} + 4 \ \text{H}_2
\]

2,2'-azanediyl diethanol

Greener Synthetic Pathways Award
1996
the dehydrogenation reaction is endothermic; avoid the use of cyanide and formaldehyde; fewer process steps, higher overall yield; no purification or waste cut is necessary; recover catalyst by filtration, ready for subsequent use in the manufacture of Roundup; This catalysis technology is applicable in the production of other amino acids and becomes a general method for conversion of primary alcohols to carboxylic acid salts.

1. Prevent Waste
2. Increase Atom Economy
3. Design Less Hazardous Chemical Syntheses
4. Design Safer Chemicals
9. Use Catalysts
Conclusion

Process chemistry is more than just scale-up

Safe 安全
Cost effective 成本效率
Enviromentally friendly 環境友善
Timely development 適時發展

Green chemistry & engineering offers a system approach to innovating a healthy business and sustainable future!
"The chemical industry plays a key role in sustaining the world economy and underpinning future technologies, yet is under unprecedented pressure from the effects of globalization and change in many of its traditional markets."

"Against this background, what will be needed for the industry to embrace efforts to make it "greener"?"

The best way to predict the future is to create it!

預測未來的最佳方法是創建它！

- - Peter Drucker  an Austrian-born American management consultant, educator, and author.

感謝您的聆聽

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Appendix

12 More Principles of Green Chemistry*
12 Principles of Green Engineering**
9 Principles of Green Engineering ***
(The Sandestin Declaration of Green Engineering Principles)

Some suggested readings

* Winterton N, Green Chemistry 2001, G73
***as developed by more than 65 engineers and scientists at the Green Engineering: Defining the Principles Conference, held in Sandestin, Florida in May of 2003.
Twelve more principles of green chemistry
(Winterton N, Green Chemistry 2001, G73)

1. **Identify and quantify byproducts**
   鑑定並定量所有的副產物

2. **Report conversions, selectivities and productivities**
   記錄所有的轉換率、選擇性和產量

3. **Establish full mass balance for process**
   建立製程中完整的質量平衡

4. **Measure catalyst and solvent losses in air and aqueous effluent**
   測量空氣和水的流出物中催化劑和溶劑的耗損量

5. **Investigate basic thermochemistry**
   查悉基本熱化學

6. **Anticipate heat and mass transfer limitations**
   預估傳熱與傳質的限制

7. **Consult a chemical or process engineer**
   諮詢化學或製程工程師
8. Consider effect of overall process on choice of chemistry
   考量整個製程對選擇化學的影響
   [化學反應和方法的選擇要依據整體製程]

9. Help develop and apply sustainability measures
   協助開發和應用永續發展的措施

10. Quantify and minimize use of utilities
    量化並減少使用通用性器材（水、電、煤氣等）

11. Recognize where safety and waste minimization are incompatible
    認知安全和廢棄物減化在（製程中）何處會是不相容的
    [不能兼顧的]

    監控、記錄和減少實驗室的廢棄物排放
12 Principles of Green Engineering**

1. Inherent Rather Than Circumstantial
2. Prevention Instead of Treatment
3. Design for Separation
4. Maximize Efficiency
5. Output-Pulled Versus Input-Pushed
6. Conserve Complexity
7. Durability Rather Than Immortality
8. Meet Need, Minimize Excess
9. Minimize Material Diversity
10. Integrate Material and Energy Flows
11. Design for Commercial “Afterlife”
12. Renewable Rather Than Depleting
9 Principles of Green Engineering***

1. Engineer processes and products holistically, use systems analysis, and integrate environmental impact assessment tools.
2. Conserve and improve natural ecosystems while protecting human health and well-being.
3. Use life-cycle thinking in all engineering activities.
4. Ensure that all material and energy inputs and outputs are as inherently safe and benign as possible.
5. Minimize depletion of natural resources.
6. Strive to prevent waste.
7. Develop and apply engineering solutions, while being cognizant of local geography, aspirations, and cultures.
8. Create engineering solutions beyond current or dominant technologies; improve, innovate, and invent (technologies) to achieve sustainability.


* The preliminary principles are intended for engineers to use as a guidance in the design or redesign of products and processes within the constraints dictated by business, government and society such as cost, safety, performance and environmental impact.
Some suggested readings


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劉廣定（advocate）
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