

CAL EPA
Department of Toxic Substances
Control
Environmental Chemistry Lab

August 10, 2011

“An overview of Chemicals of Concern- current and future, REACH, toxicology testing, risk assessment and how green chemistry is going to lead the way in the 21st century”

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Contents

- Chemicals of Concern
- Regulatory control
- Toxicology testing
- Risk Assessments
- Green chemistry

Chemicals Data

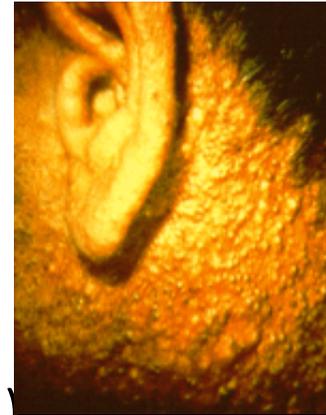
- The U.S. currently has more than 85,000 chemicals in commerce
- There are approximately 3000 “high production volume” (HPV) chemicals (based on US and EU HPV programs), which are manufactured at a rate of more than 1000 Mtons annually
- There are about 1600 additional chemicals that can be considered CMRs (Carcinogenetic, mutagenic or reproductive hazards) and/or R50/53, very toxic to aquatic species based on REACH submissions
- It has been said by many regulators and chemical control advocates state that nearly 45 percent of these HPV chemicals are lacking adequate toxicological studies conducted to evaluate their health effects on humans and the environment
 - **May have been true in 2000, but with REACH submissions (Nov. 2010) it is unlikely HPV chemicals are generally highly tested by now and if you know your chemical is a CRM or R50/53, then you’ve tested your chemical a lot**
 - **Chemicals that likely have toxicology holes are the remaining 80,000 smaller volume chemicals not due to be submitted to REACH by June 2013 (≥ 100 Mtons) and June, 2018 (≥ 1 Mton)**
- Further, about 2,000 new chemicals are introduced into commerce annually in the U.S., at a rate of seven new chemicals a day, but most will have significant tox data, at least a base set

Chemicals whose importance is fading (speakers opinion)

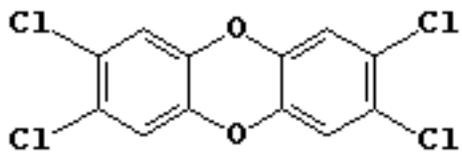
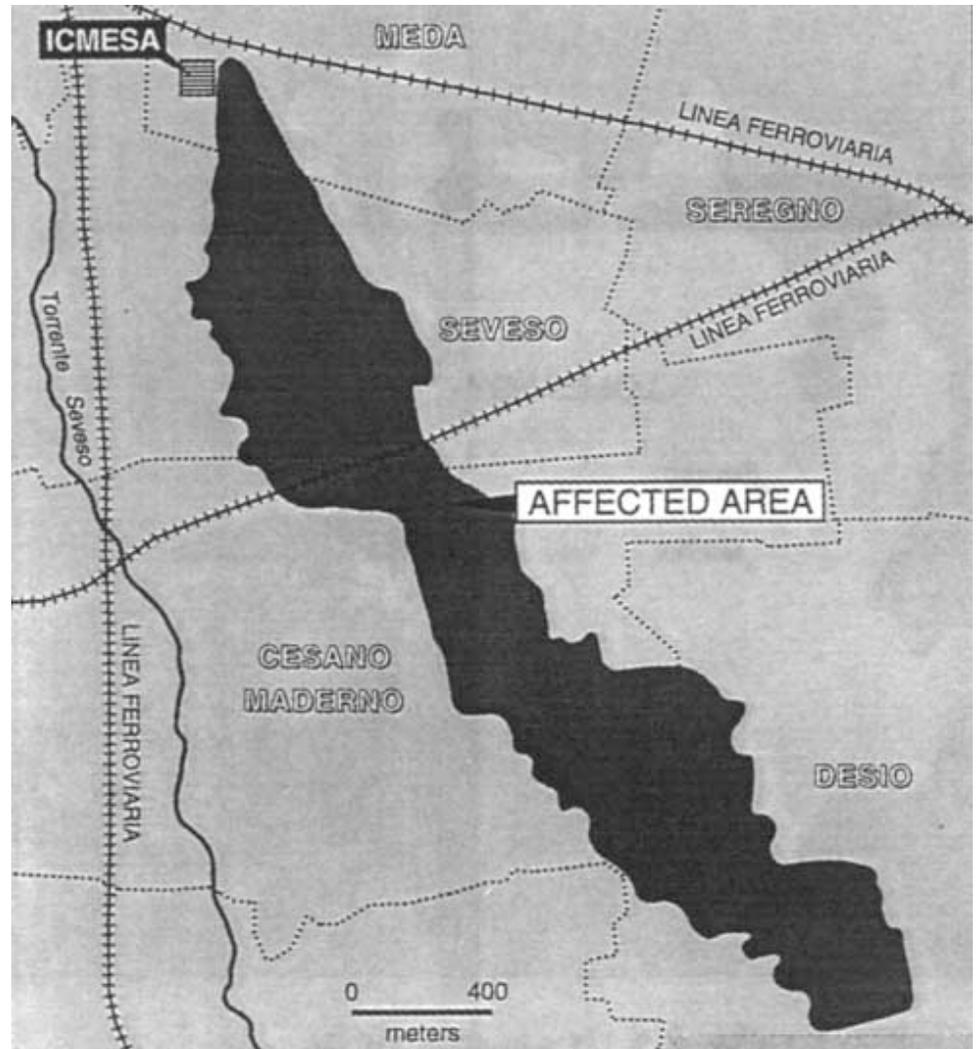
- Dioxin
- PCB
- DDT

Consequences of Dioxin Exposure

- Acute
 - Chloracne (skin lesions)
 - Darkening of skin
 - Decreased liver function
- Chronic
 - Cancer (TCDD is a known human carcinogen)
 - Dioxins do not alter DNA directly, so there is a level below which cancer risk is considered negligible
 - High risk groups include fetuses, infants, industrial workers
 - Other associated disease processes include: heart disease, diabetes and damage to the CNS/PNS, immune system, and thyroid



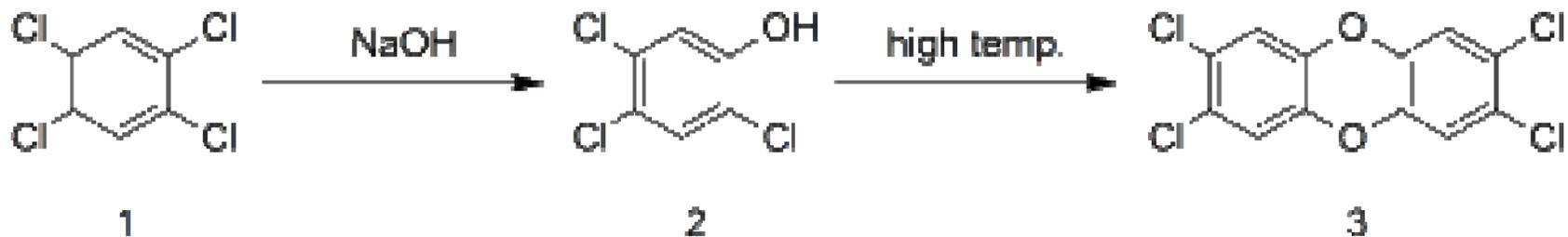
Seveso, Italy



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

Seveso, Italy

- Industrial accident in 1976
- Storage tank holding TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) ruptured
- Resulted in highest known community exposure to TCDD

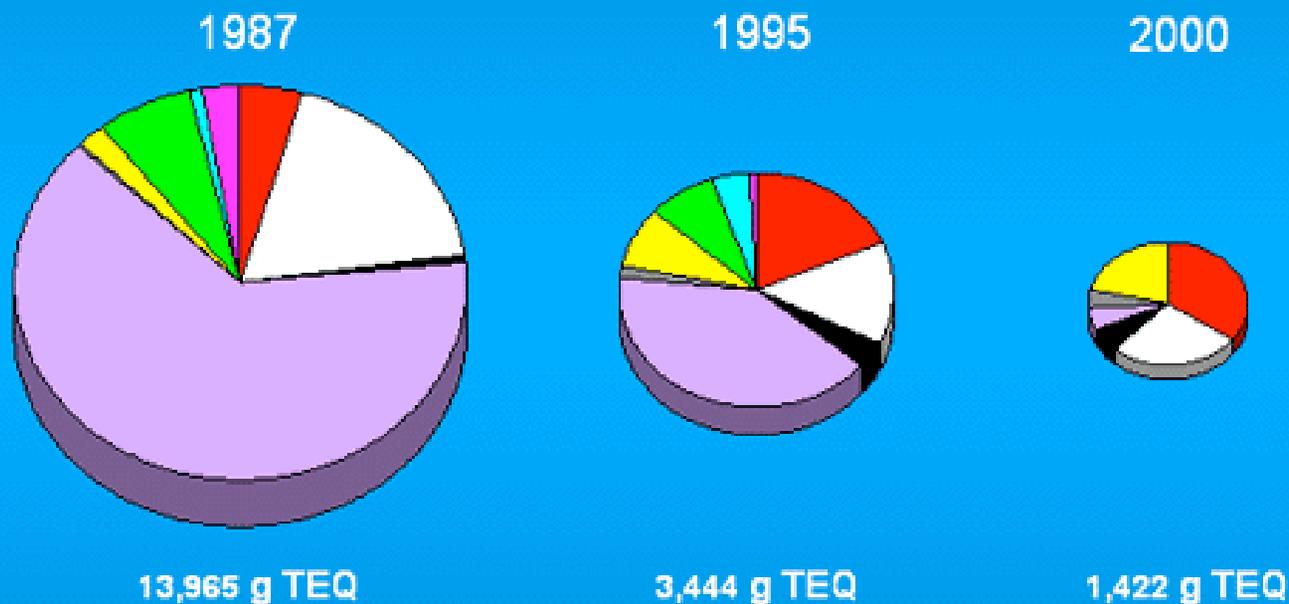


Nucleophilic aromatic substitution followed by combustion

- Contaminated a densely populated area about six kilometers long and one kilometer wide, lying downwind from the site.
- Cleanup was poorly-coordinated
- More than 700 people were evacuated and restrictions were applied to another 30,000
- The controversy behind this event led to increased prevention and control regulations (the Seveso Directive)

Dioxin Sources Over Time

Dioxin Source Contributions 1987, 1995 and 2000



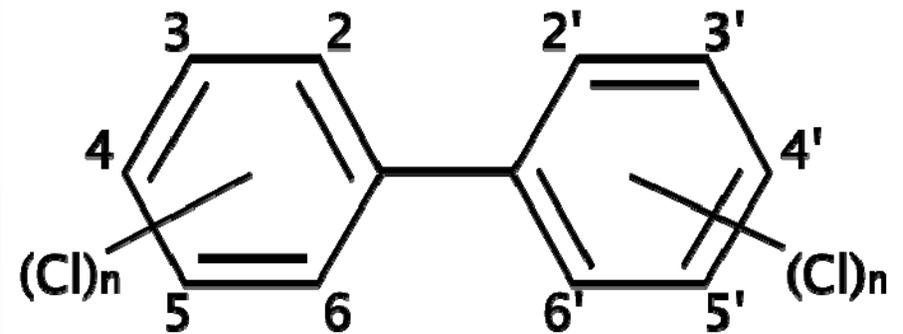
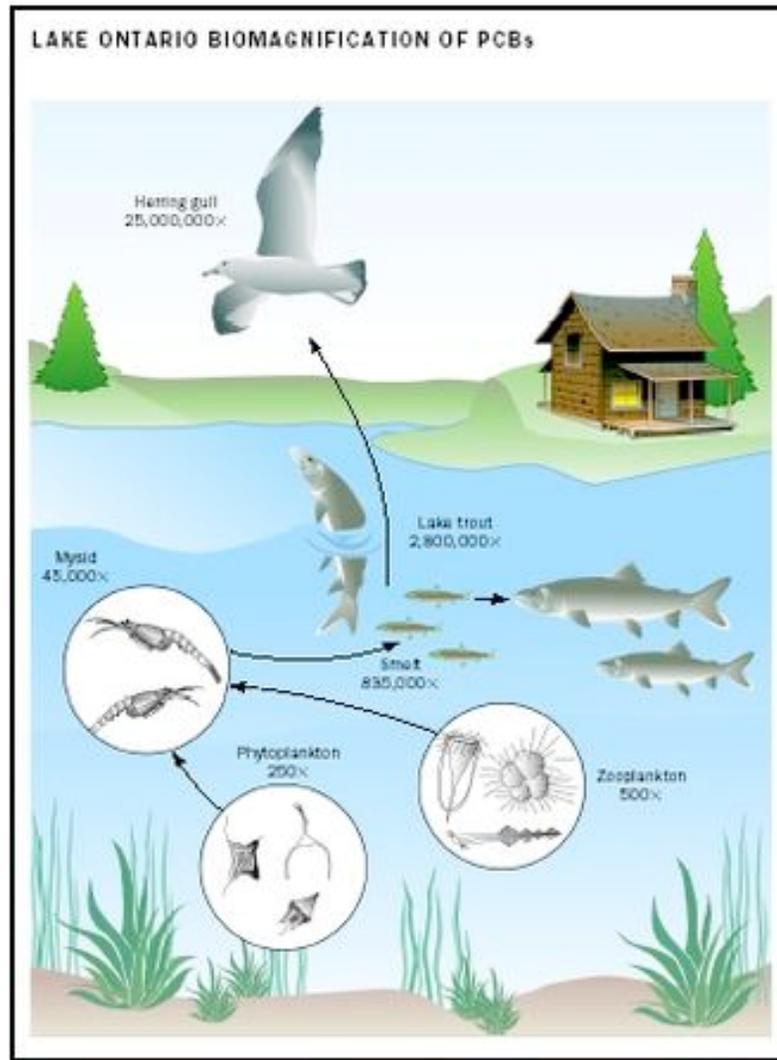
US EPA Regulations –Failure?

- The Natural Resources Defense Council (NRDC) pushed the EPA to regulate dioxin contamination in 2003
 - They claim failure to do so violates the Clean Water Act
- The EPA’s Research Council was split on whether adequate evidence was available to conclude dioxins are “carcinogenic”
 - Issue was semantics

Potential Progress?

- In recent months, the EPA has begun to enforce cleanup requirements for chemical plants
- After much criticism, the EPA is re-evaluating its assessment (expected to be delayed beyond 2010) started in 1991

Polychlorinated Biphenyl



Health Effects

- PCBs have been demonstrated to cause cancer, as well as a variety of other adverse health effects on the immune system, reproductive system, nervous system, and endocrine system.

PCB Concentrations

- In outdoor air-the average PCB concentration measured in a series of North-American cities (5 ng/m³) was 5 to 20 times higher than at two rural locations
- In the Arctic and the Antarctic, which are relatively far from any PCB source, the average PCB concentration was 0.2 ng/m³
- Since the early 1980s, there has been a slight but continuous decrease in the levels of PCBs in air observed in urban, rural, and coastal areas
- By the early 90s, PCB concentrations in rainwater from continental areas had dropped to one quarter or less of their levels in the late 70s, with values decreasing from 20 to 5 ng/litre [0.02-0.005 ng/m³] in rural areas and from 50 to 10 ng/litre [0.05-0.01 ng/m³] in cities. That trend has continued
- In indoor air PCB concentrations in the early 1980s were typically at least ten times higher than in the surrounding outdoor air
- This may be due to the fact that PCBs are emitted by certain electrical appliances and devices (such as fluorescent lighting ballasts) and building materials (such as elastic sealants)

PCB Concentrations

- In seawater, in industrial areas, PCB levels were observed to be at least 100 times higher than further off-shore, based on samples of water taken from the upper few millimeters of the surface- (early 1970's)
- Particularly high concentrations were reported in the North Sea (0.3–3 ng/litre) and in Galveston Bay, a highly industrialized area in Texas, USA (3.1 ng/litre between 1978 and 1979)
- Daniel Carrizo and Orjan Gustafsson of Stockholm University analyzed 13 of the more abundant congeners of PCBs in ice and in surface waters extending to 30 m in depth in the Arctic, published in May 2011. They found that the concentrations of congeners of PCBs ranged from 0.13 to 21 pg/L. A recent north-to-south cruise in the Atlantic Ocean found similar but lower PCB concentrations, ranging from 0.071 to 1.7pg/L in surface waters
- In river sediments, PCBs levels have been measured at different depths
- Sediment samples showed the highest PCB concentrations in sediment layers buried during the time of maximum PCB manufacture
- PCB concentrations are much lower in sediment layers that have formed following the ban on production and use of PCBs.
- In fish, reported PCB levels have dropped significantly
- PCB concentrations in trout from Lake Ontario decreased by 80% between 1976 and 1994
- For several fish species from the Great Lakes, the PCB concentrations in samples collected in the 1990s were generally below 1 µg/kg wet weight

DDT and the Environmental Movement

- *Silent Spring* (1962)
 - Outlined key environmental impacts of DDT use
 - Especially effects on birds
 - Questioned widespread usage of DDT
 - Especially without knowledge of ecological impact and effects on human health
 - Publication was integral to birth of modern environmental movement

The Cautionary Tale of DDT

The lesson (which we'll see a lot):

Even chemicals designed with the best of intentions can have dramatic and unforeseen consequences on the environment and the biosphere

Green Chemists believe that it is the responsibility of chemists to take these possible outcomes in to consideration when designing chemicals, drugs, processes, technologies...

DDT Levels in the Environment

- The literature indicates DDT levels in breast milk and fish have declined significantly since the peak concentrations of the 1970's
- Literature references suggests DDE might be more of a problem than DDT itself and DDE may be a unique problem for the condor, that eat seals that inhabit and feed in the ocean near the old Montrose Chemical facility in SoCal

Can a Chemical be banned because of political, emotional and for non-scientific reasons?

Bisphenol-A: uses

- **~12 billion lbs/year**
- **~74% in polycarbonate ~9 billion lbs/yr**
discovered by GE (Lexan) and Bayer in the 1950's
 - **baby & sports bottles** (disappearing)
 - **food processing equipment**, e.g. milking machines
 - CDs & DVDs, cell phones, computers
 - appliance parts, car headlights
- **~20% in epoxy resins -- primarily food cans, water storage tanks**
 - e.g. baby formula, soft drinks, acidic foods, large community water storage tanks are lined with epoxy resins

Dietary Exposure to BPA

FDA limit: 50 microgm/kg-bw/day

Adapted from *FDA Draft Assessment*, Aug. 2008

Age	Food/Beverages	Conservative Exposure microgram/kg/day
3 month infant	Breast milk only	0.2
3 month infant	Infant formula / glass or non-PC bottle	2.3
3 month infant	Infant formula / PC bottle	<11
Adult	3 kg commercial foods	1.5

Safety factor: >2000x for infants and >27,000x for adults

Minor exposure via soil, dental implants, cash register receipts
(WHO – Nov. 2010)

Conclusions on the Toxicity of BPA (Industry)

- The low-dose hypothesis for BPA has been thoroughly tested with a series of comprehensive, carefully conducted studies
- Included are definitive large-scale studies as well as studies aimed at replicating the results of studies reporting low-dose effects
- The consistent lack of low-dose effects found in these studies demonstrates that the low-dose hypothesis is not valid
- The weight of scientific evidence provided by these studies clearly supports the safety of BPA and provides strong reassurance that there is no basis for human health concerns from exposure to low doses of BPA

Conclusions on the Toxicity of BPA (US Gov't)

- The NTP has some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A
- The NTP has minimal concern for effects on the mammary gland and an earlier age for puberty for females in fetuses, infants, and children at current human exposures to bisphenol A
- The NTP has negligible concern that exposure of pregnant women to bisphenol A will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring
- The NTP has negligible concern that exposure to bisphenol A will cause reproductive effects in non-occupationally exposed adults and minimal concern for workers exposed to higher levels in occupational settings

U.S. Government

- **NIH 2007** – “some concern” for infants/fetus
- **National Toxicology Program 2008**
 - “some concern” for infants (technical classification)
- **FDA – 8/2008 draft report**
 - safe at current exposure limit
- **FDA Science Board 10/2008** – important studies ignored
- **FDA 2010** – supports reduction in BPA exposure for infants
 - Funding in-depth studies to clarify animal effects
- **Senate** – BPA ban not included in food safety bill (2010)

Other Governments

- **Germany, European Union, Japan – 2006-07, 2011**
 - No cause for concern
- **European Food Safety Authority – July 2008**
 - Confirmed safety -- emphasis on infants
 - Low-dose animal studies: “limited in rigor, consistency and biological plausibility”
 - Sept 2010 – expert panels – “no new evidence”
- **World Health Org – Nov 2010 – evidence too weak**
- **European Commission – Nov 2010 -- banned PC baby bottles**
 - Canada (2008), France, Denmark, some U.S. states
 - Canada (2010) – BPA on toxic chemical list

Media, Politics & Science

- **Overblown, inaccurate media reports**
 - Sensational terms: “gender-bending chemical”
 - Confuse “linked” or “associated” with cause
 - “cause liver disease, heart failure, all sorts of things” Katie Lee, CBS Early Show
 - Confuse PC with other plastics (PE, PP, PET)
 - Cherry-pick studies that support conclusions
 - Dismissed other studies and critics as biased
- **Scientists ignore lack of reproducibility**
 - Sharpe – editor *Toxicological Sciences*
- **Politicians bypassing science-based decisions**
- **Impact of Phytoestrogens not known- notion of coevolution vs impact of recent man-made chemicals**
- **\$30 million in additional studies underway- Published in 2011-12**

Practical consequences

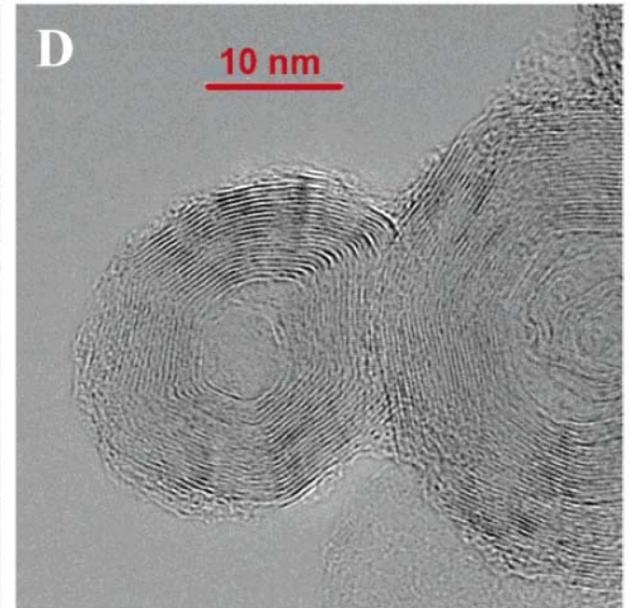
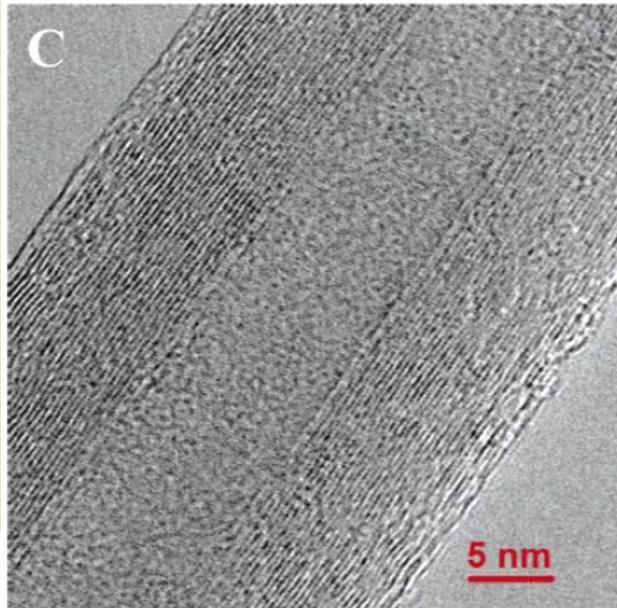
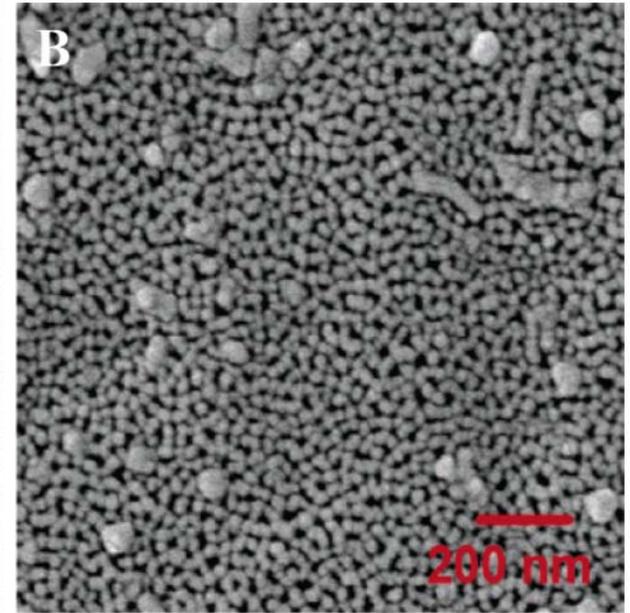
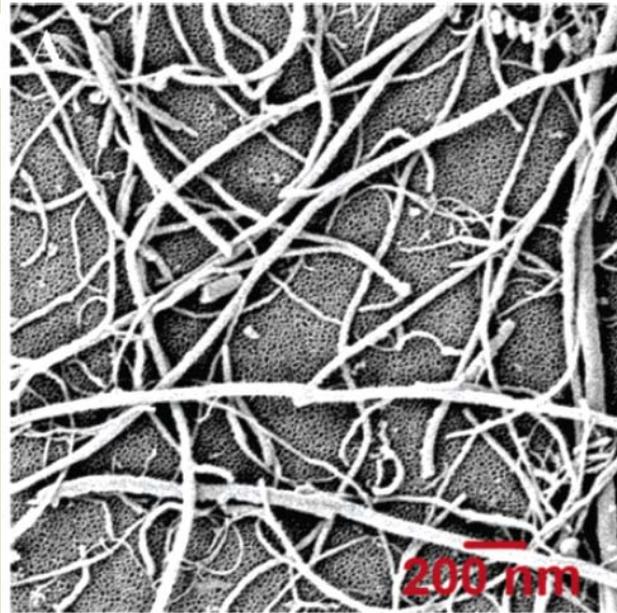
(even without regulation)

- **Consumers avoiding some PC products**
 - Stainless steel water bottles now common
- **Changing products to avoid liability**
 - Baby products labeled “PBA-free”
 - PC baby bottles are gone
- **Looking for alternatives to PC and epoxy**
 - Companies replacing can liners (Hunts, ConAgra)
 - Reformulating cash register paper
 - Eastman marketing Tritan™ copolyester

Chemicals that will Increase in
Importance in the Future

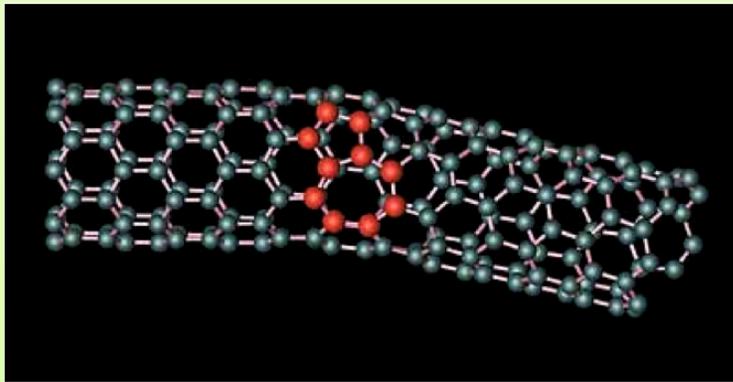
Carbon Nanotubes – what are they?

- Name for Nanotubes comes from their diameter, not their length
- Categorized into single-walled nanotubes & multi-walled nanotubes
- Composed entirely of sp^2 bonds, stronger than the sp^3 bonds in diamonds, made only of carbon
- SWCNT = A & C
- MWCNO = B & D



Carbon Nanotubes – Applications

- Nanotechnology promises medical advances
 - Bio-imaging of Tumors
 - Detecting bacteria like Salmonella at low concentrations
 - Deliver insulin
 - Nicotine Patch
 - Cancer Treatment
- Smarter and lighter materials
- Faster and more efficient electronics
- Better ways to detect, prevent and treat pollution



Carbon Nanotubes

- Engineered nanoscale materials pose particular challenges because they may be comprised of chemicals that are included in the TSCA inventory, but behave very differently than those chemicals
- Accordingly, one of the key issues the EPA wanted to address in 2010 under TSCA is when an engineered nanoscale material should be considered to be a new chemical for purposes of TSCA
- SNURs have been issued that cover nanotubes

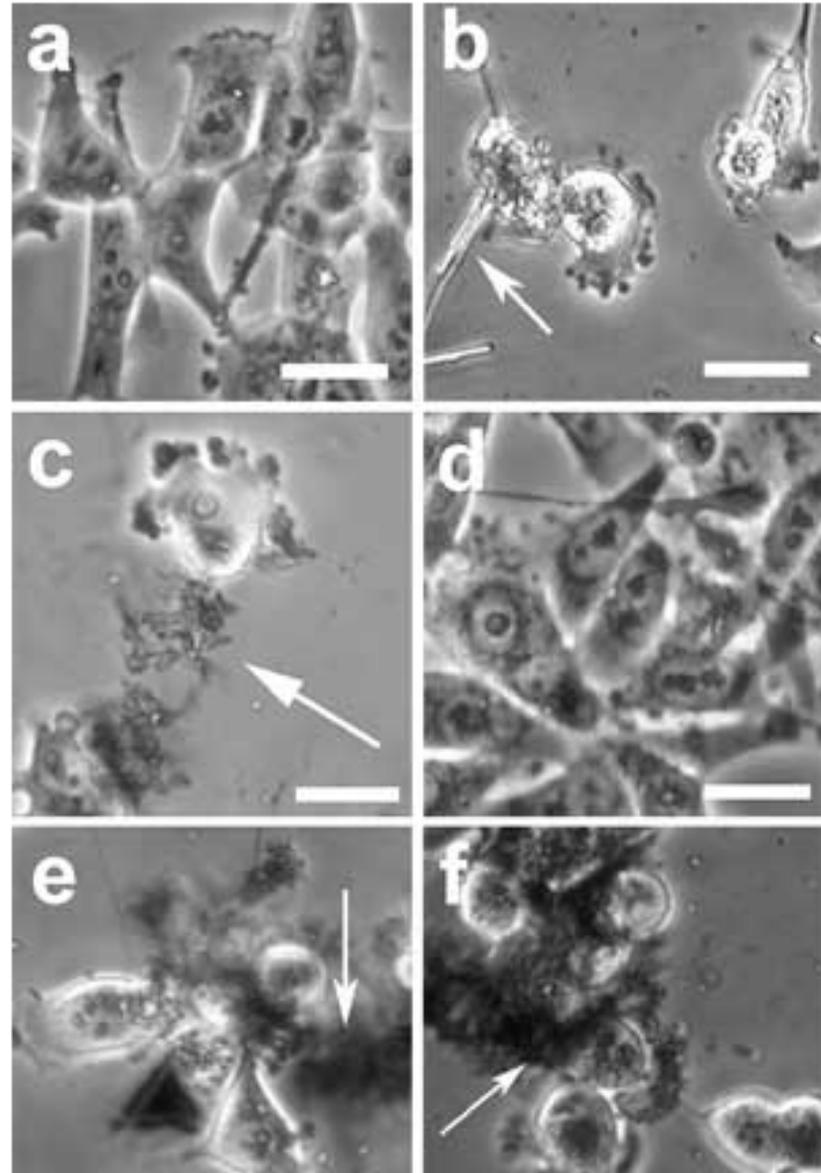
Toxicity of Carbon Nanotubes

- Comparative toxicity studies in which mice were given equal weights of test materials showed that SWCNTs were more toxic than quartz, which is considered a serious occupational health hazard if it is chronically inhaled
- Ultrafine carbon black was shown to produce minimal lung responses
- Concentrations in the environment are currently occupational, future?

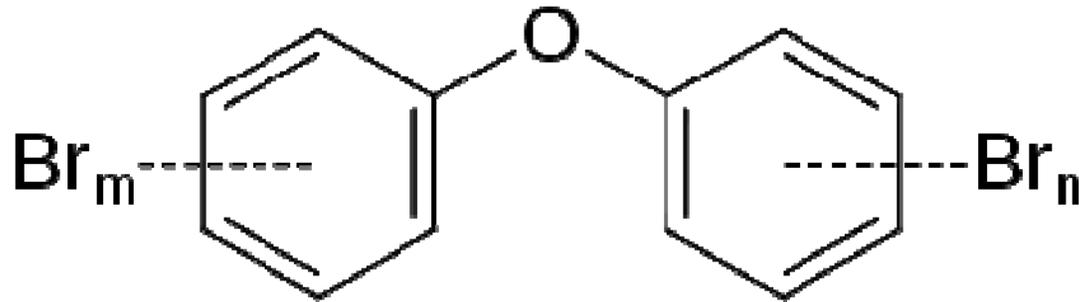
Carbon Nanotubes – Toxicity

Compared to Asbestos Fibers

- Toxicity based on preparation of Carbon Nanotubes
- A. Normal Cells
- B. Cells exposed to Asbestos Fibers
- C. Cells exposed to rope-like CNT
- D. Cells exposed to well-dispersed CNT bundles
- E. Cells exposed to CNT pellets
- F. Cells exposed to raw CNTs



Polybrominated diphenyl ether



Also known as Polybrominated Biphenylethers (PBBEs)

Deca* Mixture			Octa* Mixture			Penta* Mixture		
Component Congeners	Number of Bromines	Percent of Total	Component Congeners	Number of Bromines	Percent of Total	Component Congeners	Number of Bromines	Percent of Total
PBDE-209	10	97%	PBDE-153	6	85%	PBDE-47	4	31%
			PBDE-154	6	14%	PBDE-99	5	48%
						PBDE-100	5	8.8%
						PBDE-153	6	6.6%
						PBDE-154	6	4.4%

*The names of the commercial PBDE mixtures (Deca, Octa, Penta) often do not reflect their actual congener make-up. For example, the "Penta" product actually contains a mixture of tetra-, penta-, and hexa-BDEs with four, five and six bromines, respectively.



PBDEs



- Scientists have found that many bird and marine mammals are highly contaminated with emergent forms of toxic chemicals
- Of particular concern are Polybrominated Diphenyl Ethers, or PBDEs
- Used as flame retardants in many consumer and industrial applications



PBDEs

- In North America, PBDEs remain largely unregulated
- Canada has announced its intention to ban penta and octa PBDEs, and a growing number of states in the U.S. are seeking bans as well
- EU has banned both
- The US Environmental Protection Agency has worked with industry to voluntarily withdraw penta and octa PBDEs from the market
- A number of product manufacturers such as Ikea, Sony and Volvo have dropped these two members of the PBDE family for alternative chemicals
- Consequently consumers can make the choice to avoid PBDEs by buying products such as furniture and electronics from PBDE-free manufacturers, thus encouraging the use of alternative flame retardants
- There is currently considerable disagreement over whether a third form of PBDE known as “deca” poses a health hazard and should be restricted
- According to industry, deca PBDE is stable, does not break down or disperse, and is not taken up by animals in the environment
- New studies suggest that deca PBDE can break down into other forms of PBDEs (octa and penta) that are more harmful and readily absorbed
- Could remain around for the rest of the 21st century

Chemical Control Regulations

TSCA- Going to be Reauthorized?

- Original TSCA legislation passed in 1976
- EPA has never been made the big jump into a department, as it has always been an agency
- There was one weak attempt to re-authorized in the late 1980
- In April, 2010, Frank Lautenberg (D-NJ), chair of the Senate Subcommittee on Superfund, Toxics and Environmental Health, introduced the legislation S. 3209
- A Bill was introduced into the House on July 22, 2010
- In August, 2010, the bill, HR 5820, appears to be bogging down- unlikely to be pass until 2011 or longer
- TSCA Reform, which seemed within reach just a few short months ago, is once again an amorphous concept on Capitol Hill, lacking any definite form, shape, or organization
- Many feel the EPA does not have the tools to act in a modern 21st century approach appropriate for dangerous chemicals
- The chemical industry has asked for stronger law's so that their customers are assured their products are safe

Amended TCSA

- Chemicals should be safe for their intended use
- EPA should prioritize chemicals for safe use determinations to focus on chemicals of highest concern
- The chemical industry, and their downstream business partners, should continue to provide robust information in a transparent manner on chemicals it produces
- Potential risks faced by children should be an important factor in safe use determinations
- Companies and the EPA should work together to enhance public access to chemical health and safety information
- EPA should rely on scientifically valid data and information and should have the resources it needs to ensure the safety of chemicals
- A modernized TSCA should encourage technological innovation

REACH in a Nutshell

- Registration: Manufacturers and importers of chemicals > 1 tpa are required to register their substances to demonstrate they can be used safely (~ 80 000 existing substances + all new substances to be put on the EU market)
- Evaluation of some substances by Member States/European Chemicals Agency
- Authorization only for substances of very high concern
- Restrictions when risks are unacceptable

REACH



REACH- Basic Principles

- Shifting the burden of proof: Manufacturers of chemicals will have to prove that their substances can be used safely
- No data = No market
Manufacturers will have to register their substances and provide data if they want them to stay/be on the market

Registration – By Tonnage

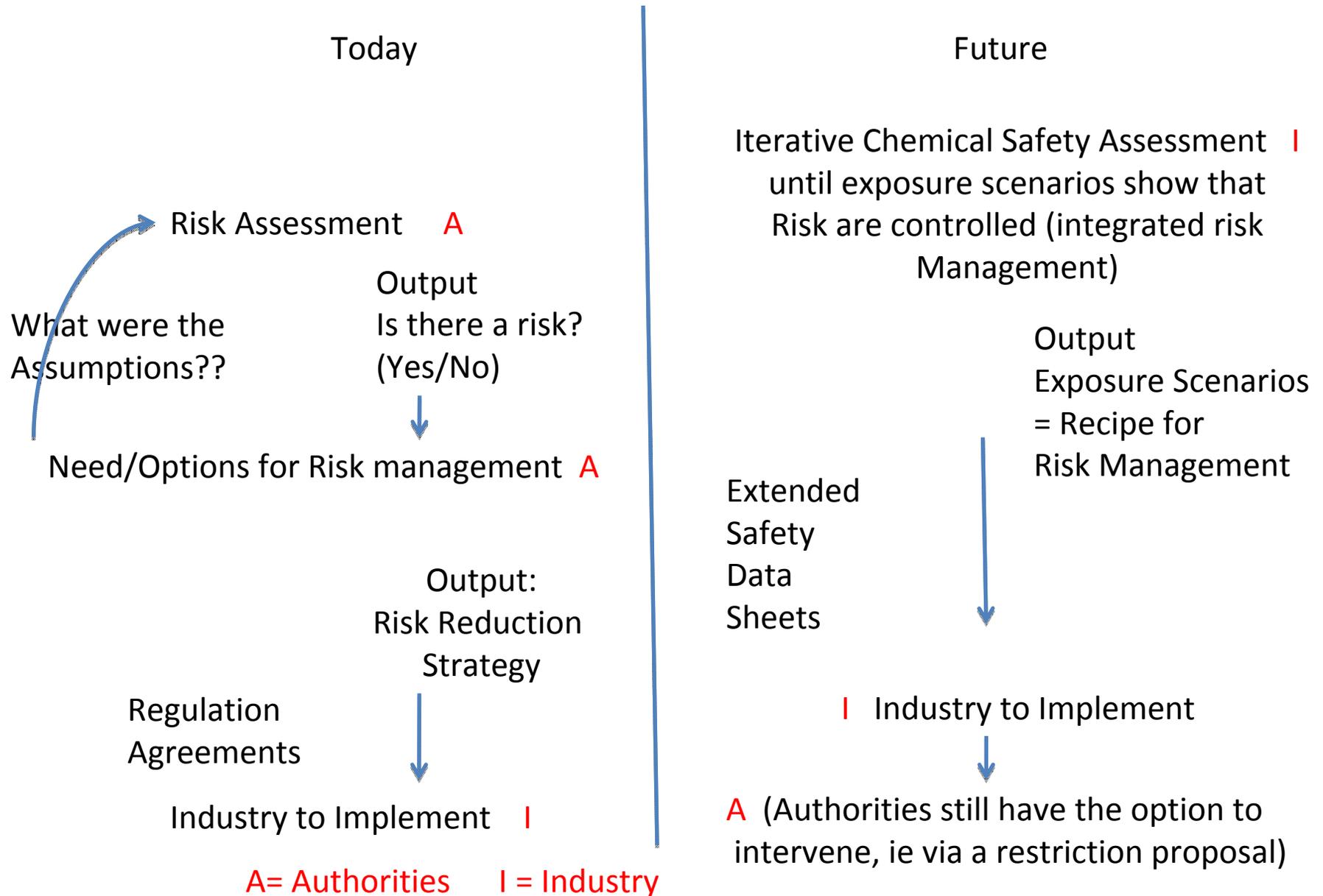
- **Non-Phase-In Substances:**

1 year after enforcement

- **Phase-In Substances (PIS's)(~100,000):**

CMR's	≥ 1 t/y	by Dec 1, 2010
R 50 / 53	≥ 100 t/y	
all PIS's	≥ 1000 t/y	
all PIS's	≥ 100 t/y	By June 1st, 2013
all PIS's	≥ 1 t/y	by June 1st, 2018

Risk Assessment Under REACH



Core Tools for Industry under REACH

- The Chemical Safety Assessment (CSA) is the tool used to **determine**
- The Chemicals Safety Report (CSR) is the tool used to **record/document**
- The Safety Data Sheet (SDS) is the tool used to **communicate**

Conditions for use (for sufficiently protecting human health and the environment):

- Risk management measures
- Operational conditions



Exposure
Scenarios

Discussions around Toxicology Issues Driven by Governmental Regulators

Toxicology Testing

- Good Laboratory Practices (GLP)
- Organization of Co-operation and development (OECD) develop the testing protocols- (30 countries)
- Need strong analytical measurement capability

Toxicology Testing

- Acutes
 - Skin and Eye irritation
 - Dermal and Oral LD50
 - Skin and inhalation sensitization
 - Inhalation is required only if compound has a vapor pressure

Toxicology Testing

- Skin and Inhalation sensitization
- Tests that are used
 - Buehler Guinea Pig test
 - Guinea pig Maximization Test (GPMT)
 - Human Repeat Insult Patch Test (HRITP)
 - Local Lymph Node Assay (LLNA)
 - Uses 3H labeled thymidine
 - Looks at proliferation of lymphocytes
 - In Mice
 - 1% threshold vs. higher

Toxicology Testing

- Chronic- feeding studies
 - Reproductive
 - Developmental
 - Cancer
- Chronic study methods
 - 1-generation; 2-generation; pubertal assay
 - Sometimes an issue with impurities
 - <1%, >1%
 - Generally can not test out of the problem (CMR)
 - Additive; synergistic; antagonistic

Toxicology Testing

- Mutagenicity Testing
 - Ames
 - Mouse lymphoma gene mutation
 - Chinese hamster ovary
 - DNA strand breaks

Toxicology Testing

- Bioaccumulation
 - Usually done in fish
 - ^{14}C
 - Cold study- need very powerful analytical
 - Semi-Permanable Membrane Devices (SPMD)

How is Human Health Measured

- Toxicity tests
- Epidemiological studies
- Dose-effect relationships

Toxicology Testing

- Aquatic testing
 - Thresholds- <0.1, <1, <10, <100, >100mg/L
 - Fish, daphnia, algae, (sometimes sewer sludge)
 - Sometimes chronic studies in the same species
 - Earthworms
 - Persistency
 - Biodegradation- Environmental fate; toxicity of decay daughters
 - PBT, vPvB

The Precautionary Principle

- Used by Governments and Industry
 - A scientific assessment of risk (what's safe!)
 - An analysis of the policy implications of taking measures to prevent harm
 - An analysis of the potential effectiveness of measures
 - A prediction of the state of future scientific knowledge
 - A perception that there is a significant risk of harm
- Scientific Uncertainty

Do you see problems with this new emphasis
on Safety?

- So how do you define safe?
- Is safe the same for all things, or difference depending on use?
- What part does exposure take?

Remember $\text{Hazards} \times \text{Exposure} = \text{Risk}$

Toxicology Testing Costs

- Base Set:
 - Acute Skin Irritation: ~\$1,880
 - Acute Eye Irritation: ~\$1,880
 - Acute Oral Tox: ~\$1,840
 - Acute Dermal Tox: ~\$3,090-4,650
 - 28-day repeat dose: ~\$110,000
 - Ames Assay: ~\$4,410
 - Chrom ab.: ~\$31,800
 - Mouse Micronucleus: ~\$16,670 – 24,970
 - Local Lymph Node Assay: ~\$4,140 – 6,200
 - Buehler Method: ~\$36,000
 - Acute toxicity to Daphnia magna: ~\$3,860
 - Acute toxicity to fish: ~\$5,290
 - Algal Growth Inhibition: ~\$4,830
 - Activated sludge Respiration: ~\$4,220
 - Analytical support for ecotox: ~\$9,640 - \$20,810
 - Ready biodegradation: ~\$5,460-9,680
- P&Cs- ~\$66,000
- 90-DAY: ~ \$250,000
- 2-Gen: ~ \$575,000

EU REACH estimate (~2006)
of testing costs- \$112--170,000

Total \$338,000 plus monitoring +10-15%
2X beyond REACH estimates

If you throw in some additional feeding
studies for CMRs, you can approach or
exceed \$1M pretty quickly

P&Cs Costs

Determination of Physico-Chemical Properties

1g/50ml	A1	Melting/Freezing Temperature		1,230
1g/50ml	A2	Boiling Temperature		1,230
50g/50ml	A3	Relative Density		1,370
10g/30ml	A4	Vapour Pressure (Calculation or Study)	1,490 or	5,460
2g/2ml	A5	Surface Tension (Soluble or Insoluble)	1,430 or	2,750
25g/25ml	A6	Water Solubility		7,130
	A8	Partition Coefficient (Calculation)		1,490
5g/5ml	A8	Partition Coefficient (HPLC or Flask Shake)	5,620 or	7,940
50ml	A9	Flash Point (Liquids or Low Melting Solids) (1)		(1230)
35g or 150g	A10	Flammability (Solids)		1,720
350g/350ml	A14	Explosive Properties (2)	1,170 or	6,910
50g/50ml	A15	Auto-Ignition Temperature (Low Melting Solids or Liquids) (3)		(4,100)
10g	A16	Relative Self-Ignition Temperature for Solids		2,340
300g	A17	Oxidising Properties (Solids) (2)	1,170 or	6,690
50ml	A21	Oxidising Properties (Liquids) (2)	(1,170 or	9,640)
150g	OECD 110	Particle Size Distribution (Screening or Full Study)	1,430 or	5,030

Status of alternative non-animal tests

In vitro tests available

Eye corrosion

Skin corrosion/irritation

Phototoxicity

Genotoxicity

No in vitro tests

Eye irritation

Skin sensitization

Acute toxicity

Repeated dose-toxicity (sub chronic/chronic)

Reproduction toxicity

Carcinogenicity

Mutagenicity

Neurotoxicity

Risk Assessment

- Costs
- Technical feasibility
- Public Perception
- Tolerability of risks
 - 1 in 1000
 - 1 in 10,000
 - 1 in 100,000
 - 1 in 1,000,000

Risk Management

- Risk = Hazard x Exposure
 - Risk
 - Likelihood that material will cause harm
 - Hazard
 - Inherent harmful property of a material
 - Exposure
 - Contact of the material with humans or environment

Risk Management

- Examples of Risk

- Highly

- Toxic x No Exposure = No Risk

- Substance

-

- Highly

- Toxic x Low Exposure = Moderate Risk

- Substance

-

- Highly

- Toxic x Moderate Exposure = High Risk

- Substance

Risk Management

- Examples of Risk

- Highly

- Toxic x No Exposure = No Risk

- Substance

- Highly

- Toxic x Low Exposure = Moderate Risk

- Substance

- Highly

- Toxic x Moderate Exposure = High Risk

- Substance

- The high exposure corollaries with low, moderate or high toxicity substances also apply in the same way

Risk Management

- Elements of the Risk Management Process



Establishing a Risk Management Program

– How Risk Management is Implemented?

- A risk management plan is written
- Identify the consequences if a plan does not exist and assess the adequacy of existing safeguards
- Use a qualitative risk prioritization matrix
- Information put into MSDS
- Wearing proper PPE

Risk Management Program

– When is an Risk Assessment required?

- New product
- New process for producing the product
- Any capital project
- Equipment or process changes
- New HES information
- New markets
- Regulatory changes
- Increased public concern or scrutiny
- Changes in distribution or transportation

How is green chemistry going to lead the way
in the 21st century?

THE TWELVE PRINCIPLES OF GREEN CHEMISTRY

- 1 It is better to **prevent waste** than to treat or clean up waste after it is formed.
- 2 Synthetic methods should be designed to **maximize the incorporation of all materials** used in the process into the final product.
- 3 Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or **no toxicity** to human health and the environment.
- 4 Chemical products should be designed to **preserve efficacy of function** while reducing toxicity.
- 5 The use of **auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary** whenever possible and, innocuous when used.
- 6 **Energy requirements should be recognized for their environmental and economic impacts and should be minimized.** Synthetic methods should be conducted at ambient temperature and pressure.
- 7 A raw material **feedstock should be renewable** rather than depleting whenever technically and economically practical.
- 8 **Unnecessary derivatization** (blocking group, protection/ deprotection, temporary modification of physical/ chemical processes) **should be avoided** whenever possible.
- 9 **Catalytic reagents (as selective as possible) are superior** to stoichiometric reagents.
- 10 Chemical products should be designed so that at the **end of their function they do not persist** in the environment and break down into innocuous degradation products.
- 11 Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances.
- 12 Substances and the form of a substance used in a chemical process should be chosen so as to **minimize the potential for chemical accidents**, including releases, explosions, and fires.

Green Chemistry

Business requirements

- Screen new substances before sale
- Be transparent about substances with compromises vs Intellectual properties
- Must be economically viable over the long haul
- Ask yourself- would I be comfortable using and making this product?
 - Protecting company assets

Further Business Requirements

- Take a life-cycle look
 - Societal implications
 - No waste
 - Use raw materials efficiency
 - Use less energy
 - Avoid use of tox substances
 - Use re-newables
 - Understand trade-offs
 - Minimize accidents

Green vs. Sustainable Chemistry

Green = Environmental & Socially Improved

Sustainable = Financially Viable

= Socially Considerate

= Environmentally Sound

What is Sustainability?

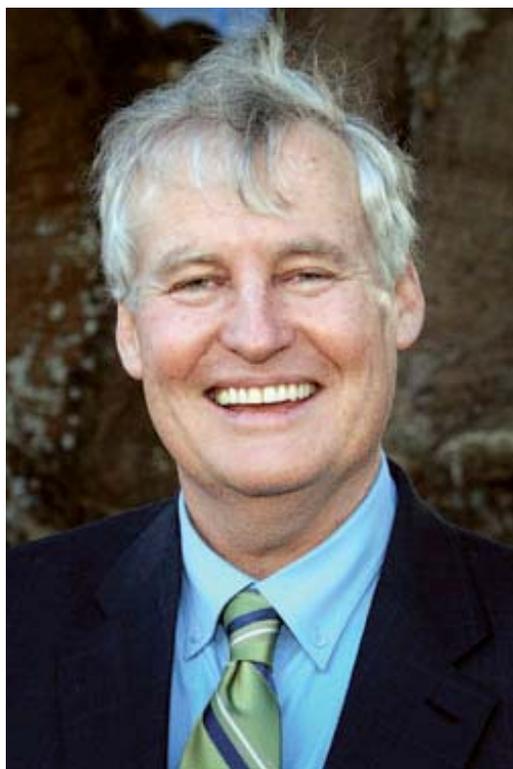
Sustainability has many definitions but the basic principles and concepts remain constant: balancing a growing economy, protection for the environment, and social responsibility, so they together lead to an improved quality of life for ourselves and future generations.

President George W. Bush
January 24, 2007
(Executive Order #13423)

Sustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs.

UN World Commission on Environment and Development (WCED)
"Our Common Future"
(The Brundtland Report)

Academics



Terry Collins-Thomas Lord Professor of
Chemistry
Carnegie Mellon University

Director of the Institute for Green
Chemistry at CMU

1998 Presidential Green Chemistry
Challenge Award

Reknown educator of green chemists

"Sustainable" means to create and maintain conditions, under which humans and nature can exist in productive harmony, that permit fulfilling the social, economic, and other requirements of present and future generations of Americans..."

Industrial View



Executive-on-loan (Dow Chemical)
Sustainability Products and Solutions Programs
Center for responsible Business
Haas Business School,
UC Berkeley

The vision of the Sustainable Products & Solutions Program is to create a multi-disciplinary learning and research environment where the foundations of sustainability - society, science, engineering, environment, and finance - are all considered simultaneously as new products and solutions are explored. The Program's working definitions of sustainable products & solutions involve a business model that is financially sustainable after valuing its social, health, and environmental costs and benefits. This valuation is grounded in scientific evidence and involves the entire supply chain and life-cycle of the product or solution.

What Controls Sustainability

- Knowledge
- Technology
- Need to control human determinants
 - Education
 - Innovation
 - Investment
 - Business
 - Advocacy
 - Research
 - Globalization
- Safe Energy
- Use Renewable feedstocks
- Get rid of hazardous substances

How is Industry Responding?

- Responsible Care
- Product Stewardship
- Marketing advantages around being “green”
- Going to be increasing legislation action facing industry on key issues
- Most large Corporation have green or sustainability chemistry positions in their R&D organizations

The 12 Principles of Green Chemistry-

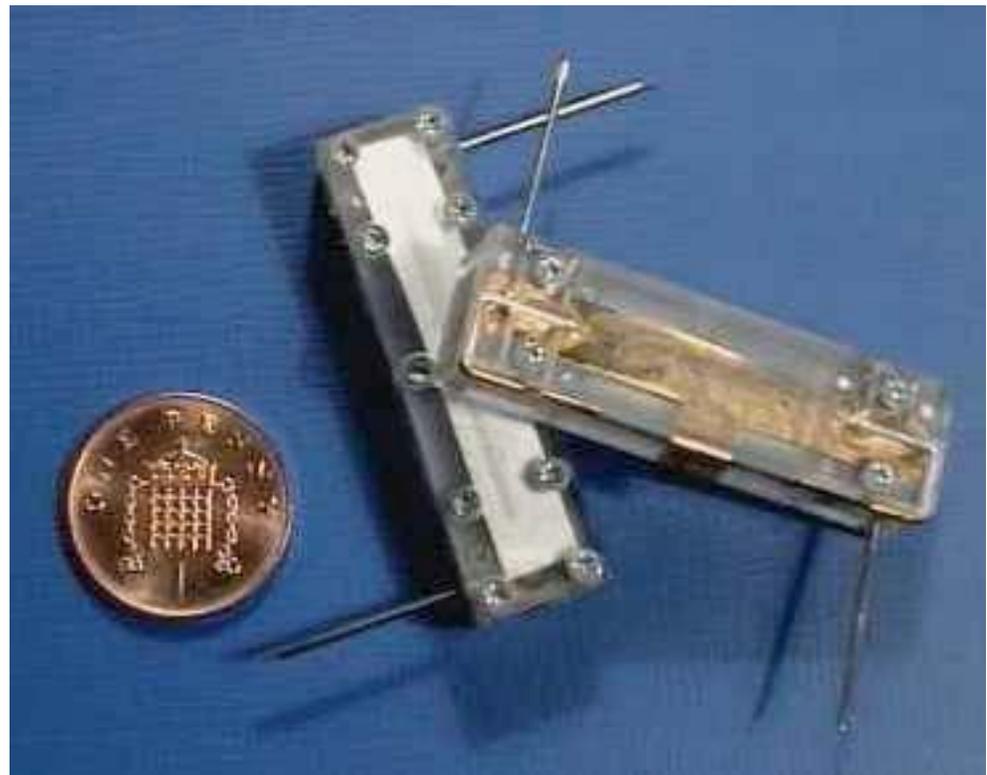
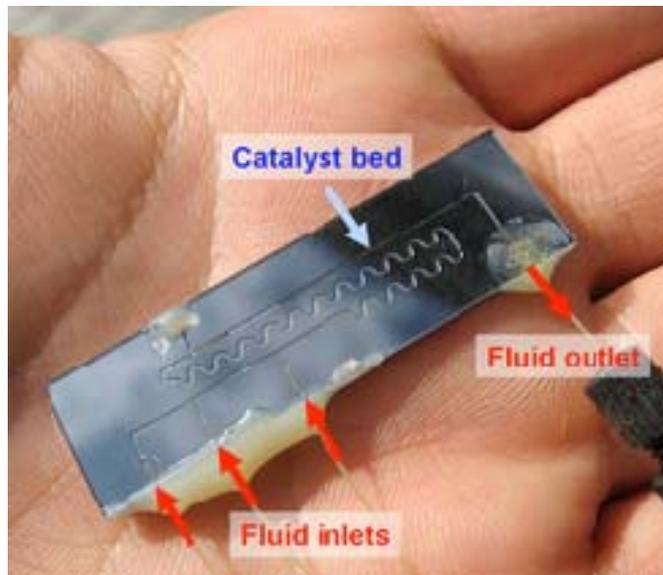
Colors indicate Dr. Berkeley Cues' view of
Pharma's performance- 2010

1. **Prevention**
2. **Atom Economy**
3. **Less Hazardous Chemical Syntheses**
4. **Designing Safer Chemicals**
5. **Safer Solvents and Auxiliaries**
6. **Design for Energy Efficiency**
7. **Use of Renewable Feed Stocks**
8. **Reduce Derivatives**
9. **Catalysis**
10. **Design for Degradation**
11. **Real-time Analysis for Pollution Prevention**
12. **Inherently Safer Chemistry for Accident Prevention**

Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998). ISBN 0 19 850698 8 as found on www.epa.gov/greenchemistry

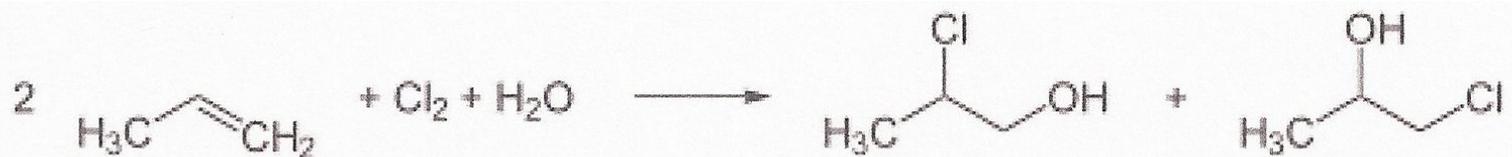
Green Chemistry Successes

Microreactors



Traditional Route to Making Propylene Oxide

Hydrochlorination



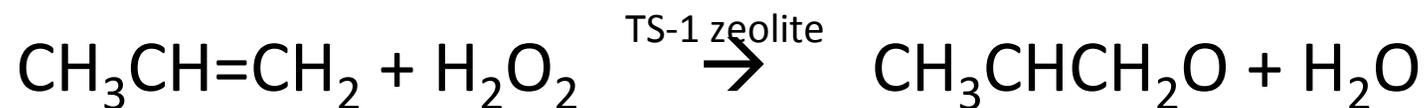
Chloropropanol



Now if you don't have a big integrated chlorine plant, how would you make PO?

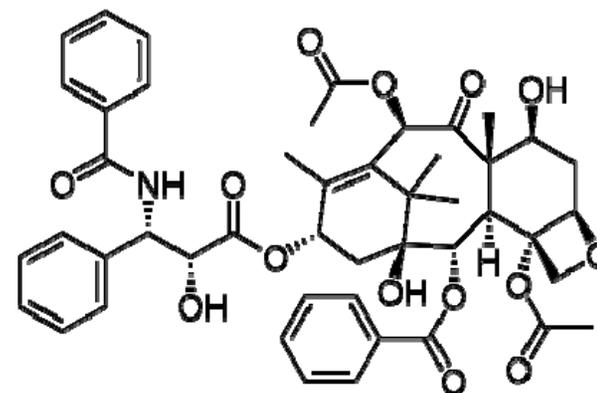
“Greener” Route to PO

Propylene / Hydrogen Peroxide Route

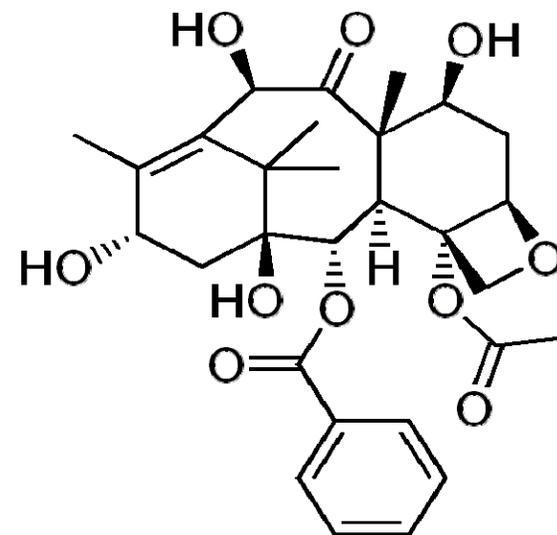


Propylene + Hydrogen Peroxide → PO + Water

Taxol Synthesis

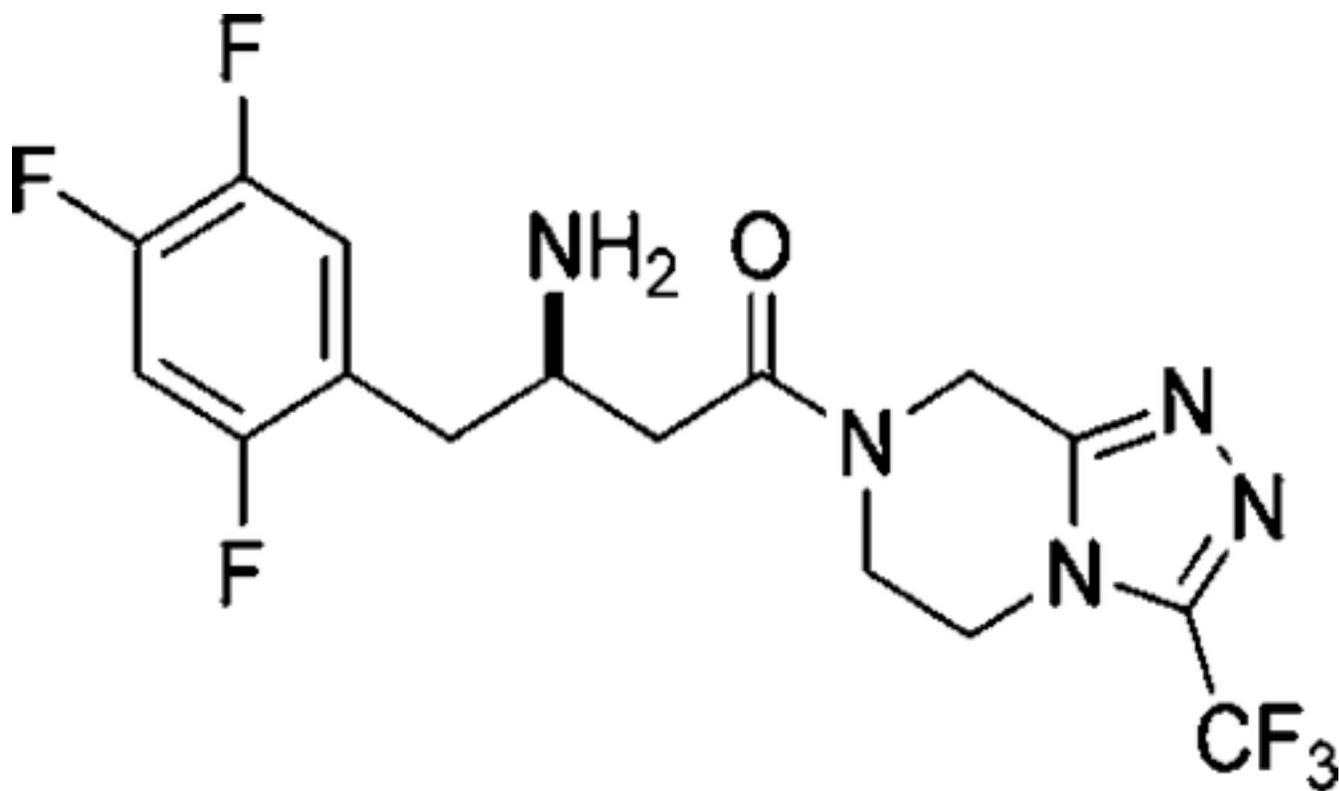


- Isolation from bark of *Taxus Brevifolia* is not a viable long-term option for large scale production.
- Semi-synthesis from 10-deacetylbacctin III has proved commercially viable.
 - Isolated from needles and leaves of *Taxus* species
 - Patented Process: 80% yield
- Biosynthetic route in cells cultured from needles of the Chinese yew tree using aqueous-based plant cell fermentation is currently the route used (2004 Presidential Green Chemistry Challenge Award)



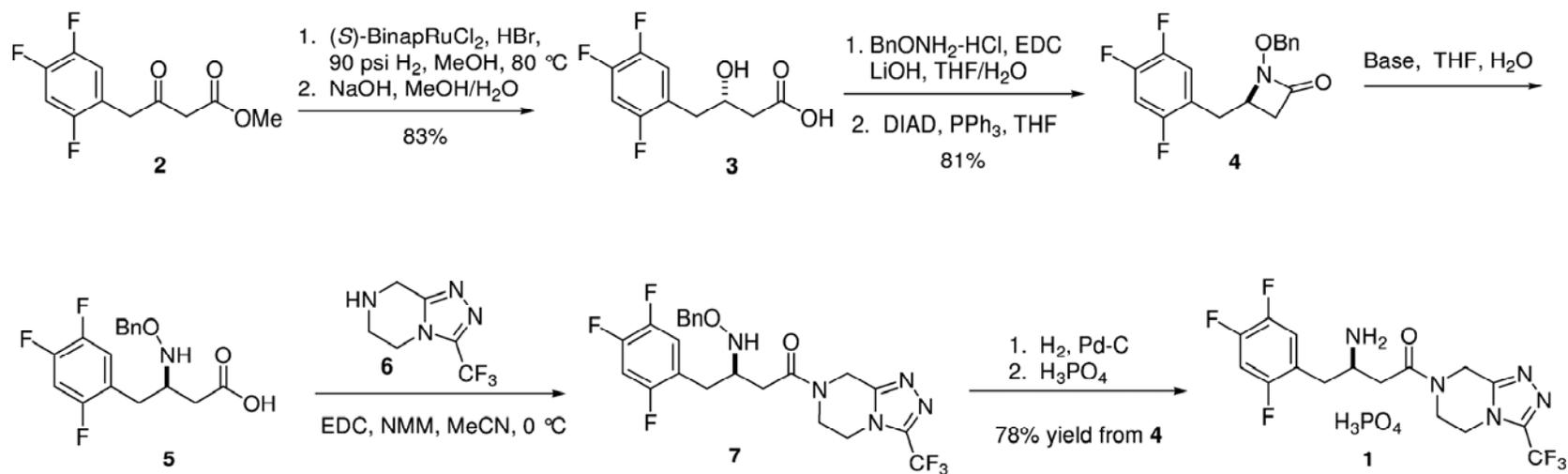
10-deacetylbacctin III

Highly Efficient Asymmetric Synthesis of Sitagliptin



Sitagliptin

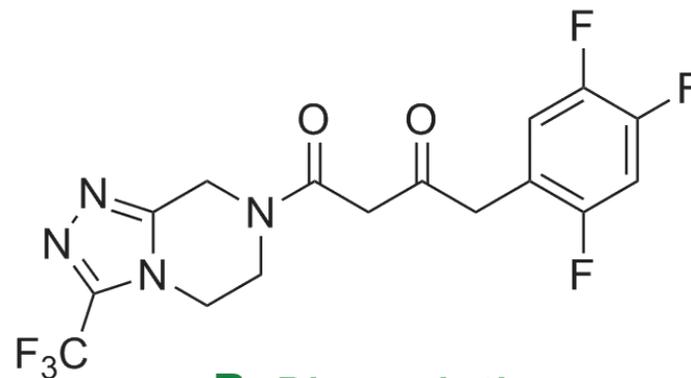
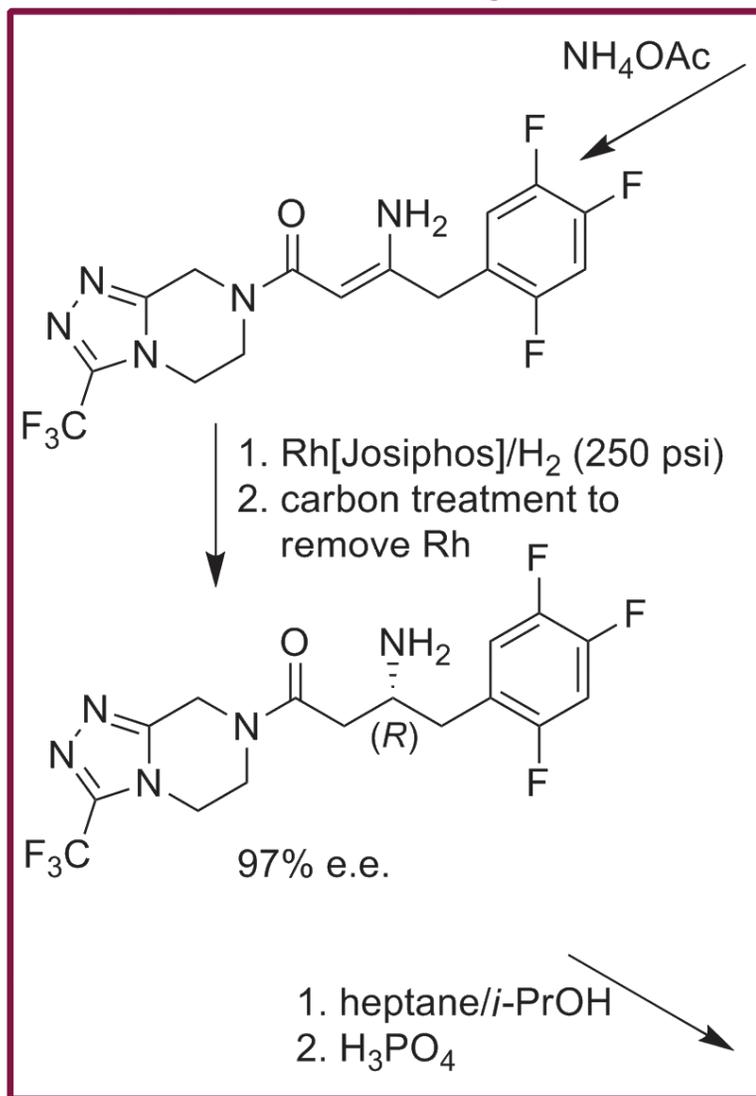
First-generation Sitagliptin Chemical Synthesis



First generation process- 52% yield
A large amounts of waste generated

Chemocatalytic Sitagliptin

A Chemocatalytic

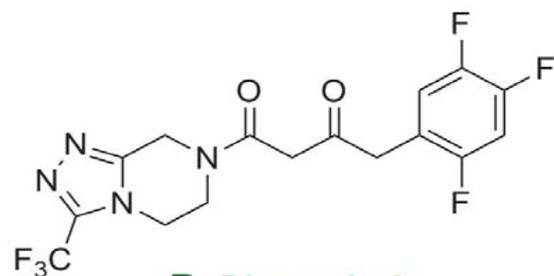


i-Pr = isopropyl

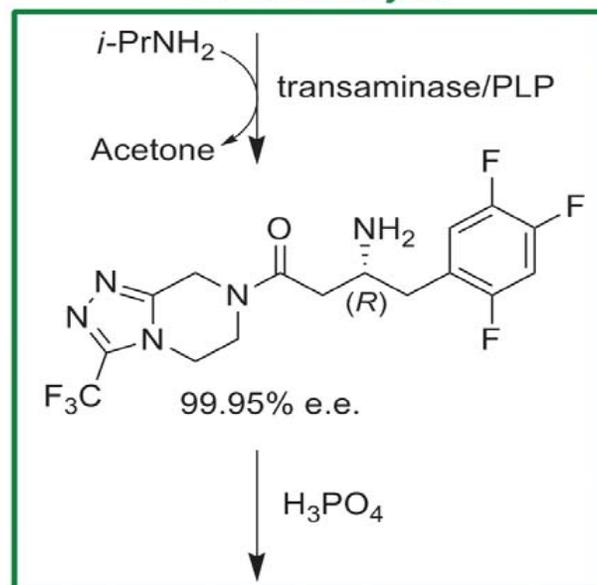
Revisited Sitagliptin

- A highly efficient, asymmetric synthesis of Sitagliptin, which has been implemented by Merck on manufacturing scale
- The entire synthesis is carried out with a minimum number of operations: a one-pot process affords the crystalline dehydrositigliptin in >99.6 wt %
- The highly enantioselective hydrogenation of dehydrositigliptin in the presence of as low as 0.15 mol % ^tBu JOSIPHOS-Rh(I) gives Sitagliptin in high yield and >95% ee
- After all of the precious metal catalyst is selectively recovered/removed from the process stream, Sitagliptin is isolated as its free base, which was then converted to its final desired pharmaceutical form, its monohydrate phosphate salt, in >99.9 A% purity and >99.9% ee
- Synthesis wins the 2006 Presidential Green Chemistry Challenge Award for Merck
- Increased yield by 50% over old first generation process
- Reduced waste; 220 pounds per one pound of product produced and completely eliminated water waste

Sitagliptin Re-Revisited Again



B Biocatalytic



Sitagliptin from Enzymes

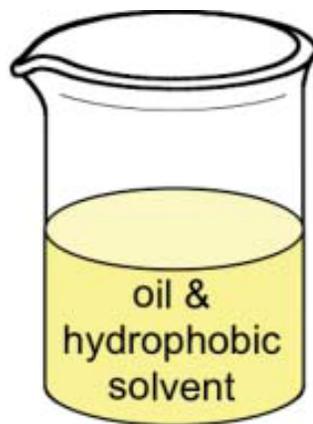
- Merck and Codexis reported an efficient bio-catalytic process to replace a recently implemented rhodium-catalyzed asymmetric enamine hydrogenation
- The streamlined, enzymatic process eliminated the high pressure hydrogenation, all metals (rhodium and iron) and the wasteful chiral purification step
- Starting from an enzyme that had the catalytic machinery to perform the desired chemistry but lacked any activity toward the pro-sitagliptin ketone
- Merck and Codexis applied a substrate walking, modeling, and mutation approach to create a transaminase with marginal activity for the synthesis of the chiral amine- <0.5%
- This variant was then further engineered via directed evolution for practical application in a manufacturing setting (11 rounds of evolution) with biocatalytic activity of over 25,000 fold with no detectable amounts of the undesired S-enantiomer
- The resultant biocatalysts showed broad applicability toward the synthesis of chiral amines that previously were accessible only via resolution
- This work underscores the maturation of biocatalysis to enable efficient, economical and environmentally benign processes for the manufacture of pharmaceuticals
- 56% improvement in productivity with existing equipment
- 10-13 % overall increase in yield and a 19% reduction in overall waste generation
- Wins the 2010 Presidential Green Chemistry Challenge Award

Switchable Hydrophilicity solvents

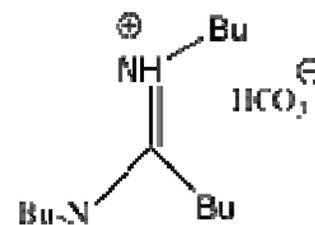
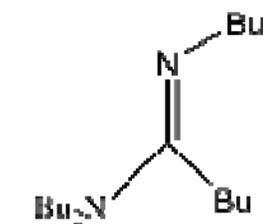
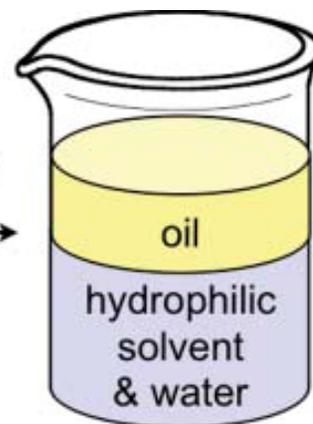
Flakes of soy beans



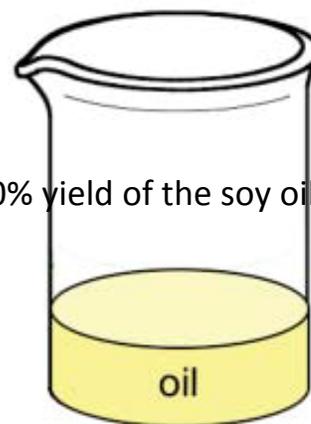
Extract with solvent



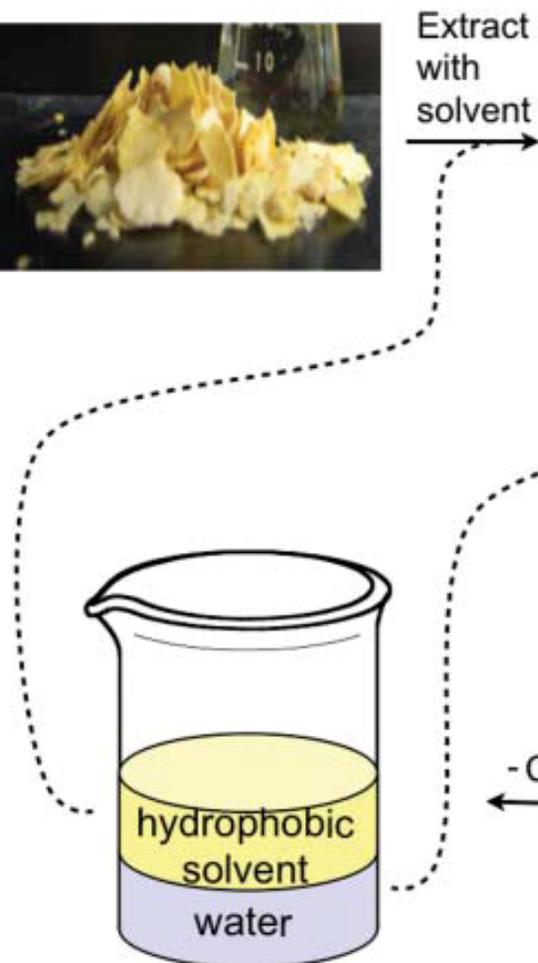
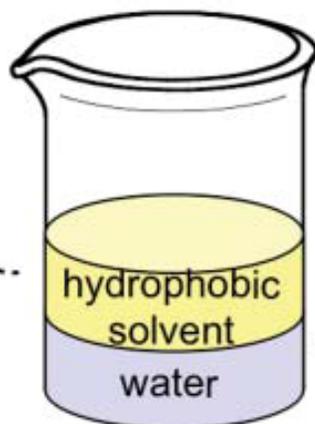
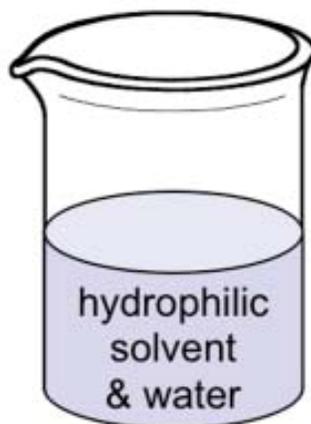
Add water & CO₂



10% yield of the soy oil



-CO₂



Switchable Solvents

- A switchable-hydrophilicity solvent, is hydrophobic and has very low miscibility with water when in air but is hydrophilic and has complete miscibility with water when under an atmosphere of CO₂
- Philip Jessop has reported the first example of such a solvent, *N,N,N-tributylpentanamide*
- Solvents such as these could be used for the extraction of low-polarity organic products, such as vegetable oils, followed by the removal of the solvent from the product by carbonated water
- Carbonated water is able to extract the solvent from the product because the CO₂ converts the solvent to its hydrophilic form
- The solvent can then be separated from the carbonated water upon removal of the CO₂, because this removal triggers the conversion of the solvent back to its hydrophobic, water-immiscible form
- Importantly, distillation is not required for removal of the solvent from the product

References

- “Green Chemistry- Theory and Practice,” P. T. Anastas, J. C. Warner, Oxford Univ. Press, 1999
- “Green Chemistry, an introductory text,” M. Lancaster, The Royal Society of Chemistry, Cambridge, UK, 2002
- “Current Topics in Green Chemistry,” UC Berkeley, Extension, Course, X414, Peter M. Stonebraker, Spring 2011
- “TSCA Handbook,” 3rd edition, McKenna and Cuneo, LLP, Government Institutes, 1997
- Toxic Substances and Pesticides Regulation Deskbook, Latham and Watkins, Environmental Law reporter, 1995
- “Cost of REACH Underestimated,” C&E News, 8/31/2009, p. 7
- “Mixed Reception for Chemicals Bill,” Cheryl Hogue, C&E News, August 2, 2010, p. 11
- Cassarett and Doull’s Toxicology, The Basic Science of Poisons, 6th edition, C. Klaassan, McGraw Hill, 2001
- The textbook of Modern Toxicology, 3rd edition, E. Hodgson, Wiley-Interscience, 2004
- Regulatory Toxicology, 2 edition, S. C. Gad, Taylor and Francis, 2001
- Environmental Toxicology, 2nd edition, Ming-Ho Yo, CRC Press, 2005
- “Orcas on the Edge,” 10-01-2006, Ken Olsen
- “Poisoned Killer Whales? Blame Salmon, Maria Cone, 1/20/2009.
- “Fireproof killer whales: flame-retardant chemicals and the conservation imperative in the charismatic icon of British Columbia, Canada, Peter Ross, Can. J. Fish and Aquatic Science, 63, 224-243, 2006
- WSJ, June 24, 2010
- “More Dioxin Delays,” C&E News, Cheryl Hogue, Nov. 15, 2010, p. 30-32
- “Bisphenol A,” “Debating BPA’s Toxicity,” “Exposure Routes Confound BPA Debate,” C&E News, June 6, 2011, p. 13-22
- “Carbon Nanotubes,” Jessica Coulter, ppt presentation, April 7, 2010, UC Berkeley Extension Chem 3BL, by permission
- “CycloShield™ Copolyesters, Greener, BPA-free, Super Tough Alternative to Polycarbonate,” Donald R. Kelsey (retired), Betty M. Scardino, Janusz, S. Grebowicz and Hoe H. Chu, *Macromolecules*, **2000**, 33, 5810 by permission
- “Green Chemistry,” Green Chemistry and Sustainable Design Lecture- UC Berkeley College of Chemistry, September 15, 2010, Terry Collins, Teresa Heinz Prof. of green Chemistry, Carnegie Mellon Univ., by permission
- “Green/Sustainable Chemistry: How do we know when we get there?,” Green Chemistry and Sustainable Design Lecture- UC Berkeley College of Chemistry, October 5, 2009, Tony Kingsbury, Executive-on-Loan (Dow Chemical) Sustainable Products & Solutions Program, UC Berkeley by permission
- “Green Chemistry Initiative at American Chemical Society,” Green Chemistry and Sustainable Design Lecture- UC Berkeley College of Chemistry, November 9, 2009, Robert Peoples, Director of ACS Green Chemistry Institute, by permission
- “A Love Affair With Sustainability,” Marc Reisch, C&E News, Nov. 1, 2010, p. 12-13.
- Roger Sheldon, *Chem Tech*, 1994, 24, 38

References II

- “Green Chemistry Supports Sustainability in the Pharmaceutical Industry, Green Chemistry and Sustainable Design Lecture- UC Berkeley College of Chemistry, September 20, 2010, Berkeley W. Cue, BWC Pharma Consulting by permission
- “Key green chemistry research areas- a perspective from pharmaceutical manufacturers,” David Constable, et al, ACS 36*GCI Pharmaceutical Roundtable, *J. of Green Chemistry*, April 17, 2007.
- “Green Claims,” *C&E News*, October 25, 2010, p. 42
- *Green Catalysis Volume 3: Biocatalysts*, Edited by Paul T. Anastas, Wiley-VCH, 2009
- “Boosting Taxol Production,” *C&E News*, October 4, 2010, p. 6
- “Sitagliptin.” Karl B. Hansen, Yi Hsiao, Feng Xu, Nelo Rivera, Andrew Clausen, Michele Kubryk, Shane Krska, Thorsten Rosner, Bryon Simmons; Jaume Balsells; Nori Ikemoto; Yongkui Sun; Felix Spindler; Christophe Malan; Edward J. J. Grabowski; Joseph D. Armstrong III., *J. Am. Chem. Soc.* **2009**, 131, 8798-8804
- “Chiral Amines from Ketones Applied to Sitagliptin Manufacture,” Christopher K. Savile, Jacob M. Janey, Emily C. Mundorff, Jeffrey C. Moore, Sarena Tam, William R. Jarvis, Jeffrey C. Colbeck, Anke Krebber, Fred J. Fleitz, Jos Brands, Paul N. Devine, Gjalte W. Huisman, Gregory J. Hughes, *Science*, 2010, 329, 305
- ACS GCI Pharmaceutical Roundtable- Collaboration to Deliver a Solvent Selection Guide for the Pharmaceutical Industry, Sept. 2008
- “Biocatalysts- mechanism and reactions,” Elizabeth Looke-Stewart, ppt presentation, April 7, 2010, UC Berkeley Extension Chem 3BL, by permission
- “Green Solvents for Chemistry,” William M. Nelson, Oxford Press, 2003
- “Clean Solvents for Organic Synthesis,” V.K. Ahluwalia and Rajender S. Varma, Alpha Science International Ltd., Oxford, UK, 2009
- “Alternative Media for Chemical Reactions and Processing,” Martin A. Abraham, American Chemical Society, Washington DC, 2002
- “What is a Green Solvent? A Comprehensive Framework for the Environmental Assessment of Solvents,” Christian Capello, Ulrich Fischer and Konrad Hungerbühler, *Green Chemistry*, March 2007
- “Green Solvents-Progress in Science and Applications,” Walter Leitner, *Green Chemistry*, Nov. 2009
- “Green Reaction Media in Organic Synthesis,” Koichi Mikami, Blackwell Publishing, Oxford, UK, 2005
- “Green Solvents for Sustainable Organic Synthesis: State of the Art,” Roger Sheldon, *Green Chemistry*, March, 2005.
- Jessop- ChemSusChem, DOI: 10.1002/cssc.201000001 and *Green Chem.*, DOI:10.1039/b926885e