Green Chemistry Education Webinar Series

Toxicology and Why You Should Care

January 21, 2014

GC3 GREEN CHEMISTRY & COMMERCE COUNCIL
Business Mainstreaming Green Chemistry

Today's Speakers

Steven G. Gilbert

Institute of Neurotoxicology & Neurological Disorders

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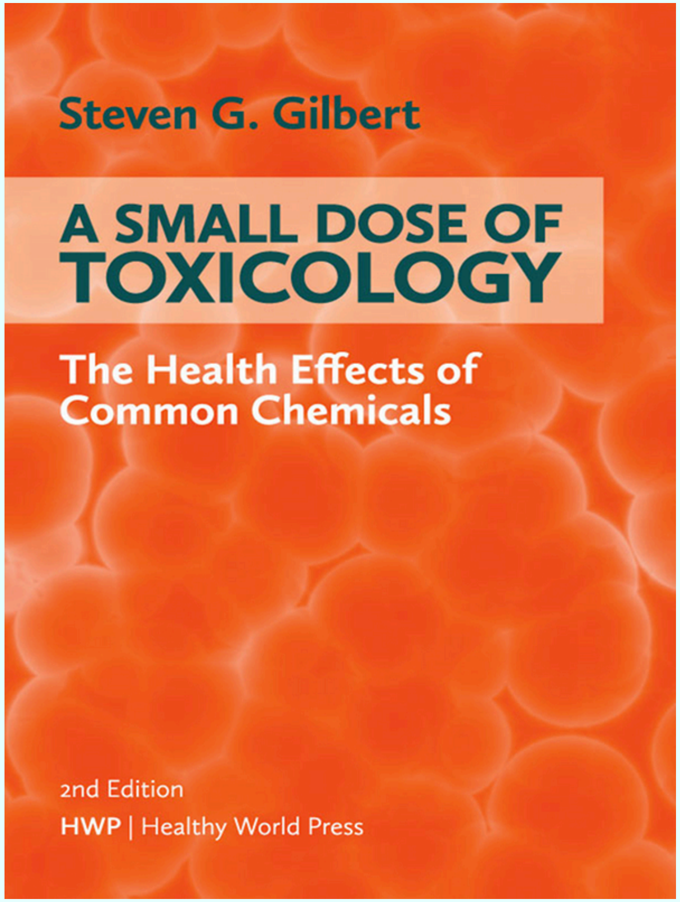
An Very Brief Introduction to the Principles of Toxicology

“Toxicology and Why You Should Care”
GC3 Green Chemistry Education Webinar Series
The Green Chemistry and Commerce Council (GC3)
January 21, 2014

Steven G. Gilbert, PhD, DABT
www.asmalldoseof.org
www.toxipedia.org

A Small Dose of Toxicology 2nd Edition

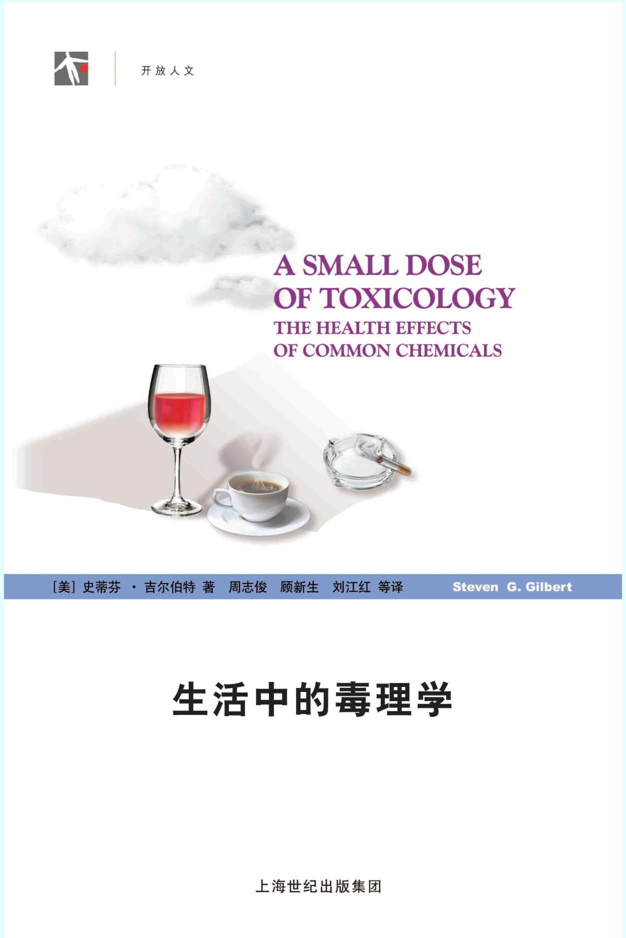


Free e-book Healthy World Press

PowerPoint slides for each chapter

See: www.asmalldoseof.org -- smdose

Chinese Edition - A Small Dose of Toxicology

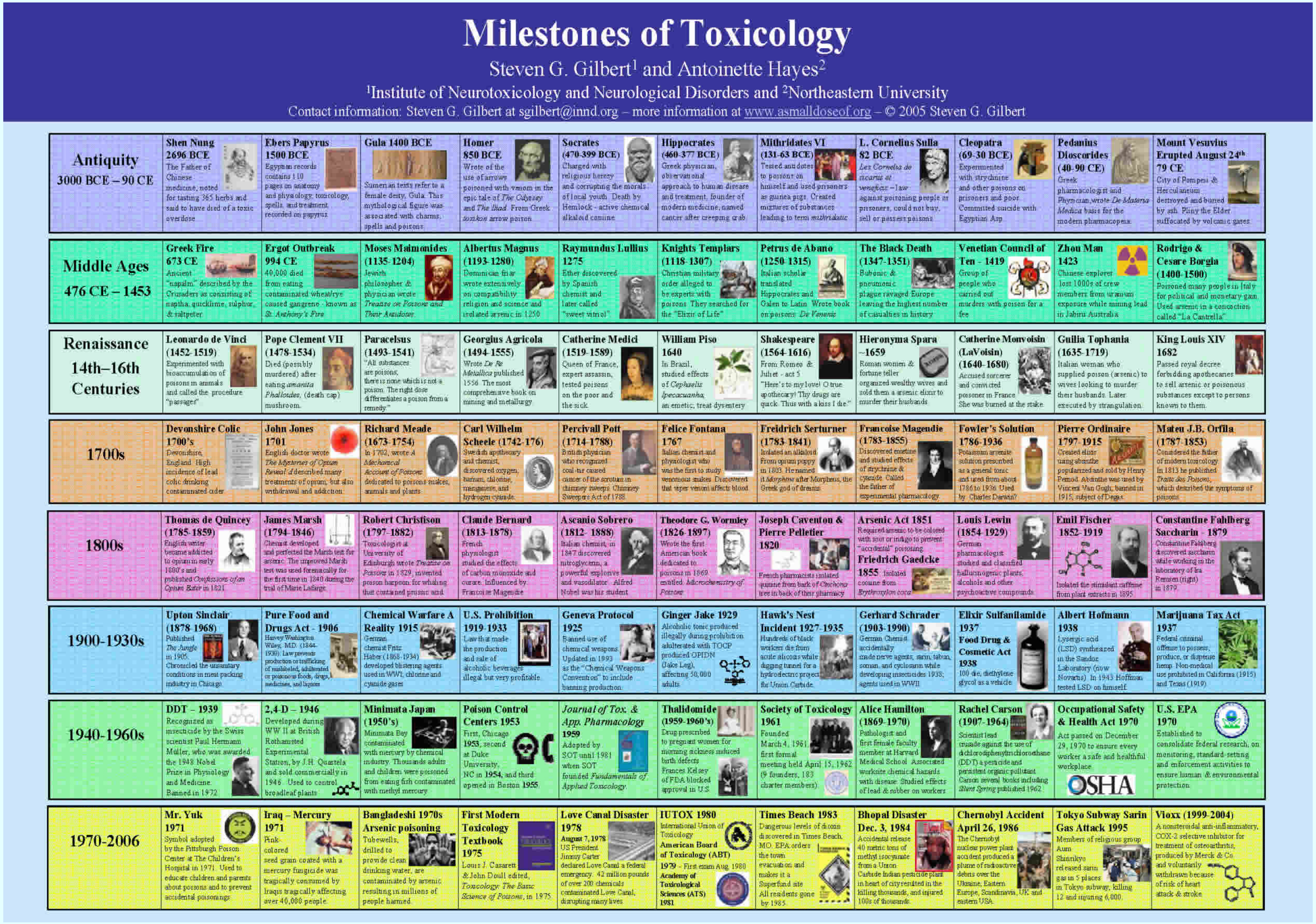


Published by Shanghai Scientific and Technical Publishers in December, 2013.

Translated by a team of Chinese toxicologists led by Drs. Zhijun Zhou, Xinsheng Gu, Jianghong Liu, et al

See: www.chinesesmalldose.org

Milestones of Toxicology



Milestones of Toxicology

Steven G. Gilbert[1] and Antoinette Hayes[2]

[1]Institute of Neurotoxicology and Neurological Disorders and [2]Northeastern University

Contact information: Steven G. Gilbert at sgilbert@innd.org – more information at www.asmalldoseof.org – © 2005 Steven G. Gilbert

Antiquity 3000 BCE – 90 CE	**Shen Nung 2696 BCE** The Father of Chinese medicine, noted for tasting 365 herbs and said to have died of a toxic overdose	**Ebers Papyrus 1500 BCE** Egyptian records contains 110 pages on anatomy and physiology, toxicology, spells, and treatment recorded on papyrus	**Gula 1400 BCE** Sumerian texts refer to a female deity, Gula. This mythological figure was associated with charms, spells and poisons	**Homer 850 BCE** Wrote of the use of arrows poisoned with venom in the epic tale of *The Odyssey* and *The Iliad*. From Greek *toxikon* arrow poison	**Socrates (470-399 BCE)** Charged with religious heresy and corrupting the morals of local youth. Death by Hemlock - active chemical alkaloid coniine	**Hippocrates (460-377 BCE)** Greek physician, observational approach to human disease and treatment, founder of modern medicine, named cancer after creeping crab	**Mithridates VI (131-63 BCE)** Tested antidotes to poisons on himself and used prisoners as guinea pigs. Created mixtures of substances leading to term *mithridatic*	**L. Cornelius Sulla 82 BCE** *Lex Cornelia de sicariis et veneficis* – law against poisoning people or prisoners, could not buy, sell or possess poisons	**Cleopatra (69-30 BCE)** Experimented with strychnine and other poisons on prisoners and poor. Committed suicide with Egyptian Asp	**Pedanius Dioscorides (40-90 CE)** Greek pharmacologist and Physician, wrote *De Materia Medica* basis for the modern pharmacopeia	**Mount Vesuvius Erupted August 24th 79 CE** City of Pompeii & Herculaneum destroyed and buried by ash. Pliny the Elder suffocated by volcanic gases
Middle Ages 476 CE – 1453	**Greek Fire 673 CE** Ancient "napalm" described by the Crusaders as consisting of naptha, quicklime, sulphur, & saltpeter	**Ergot Outbreak 994 CE** 40,000 died from eating contaminated wheat/rye caused gangrene - known as *St. Anthony's Fire*	**Moses Maimonides (1135-1204)** Jewish philosopher & physician wrote *Treatise on Poisons and Their Antidotes*	**Albertus Magnus (1193-1280)** Dominican friar wrote extensively on compatibility religion and science and isolated arsenic in 1250	**Raymundus Lullius 1275** Ether discovered by Spanish chemist and later called "sweet vitriol"	**Knights Templars (1118-1307)** Christian military order alleged to be experts with poisons. They searched for the "Elixir of Life"	**Petrus de Abano (1250-1315)** Italian scholar translated Hippocrates and Galen to Latin. Wrote book on poisons *De Venenis*	**The Black Death (1347-1351)** Bubonic & pneumonic plague ravaged Europe leaving the highest number of casualties in history	**Venetian Council of Ten - 1419** Group of people who carried out murders with poison for a fee	**Zhou Man 1423** Chinese explorer lost 1000s of crew members from uranium exposure while mining lead in Jabiru Australia	**Rodrigo & Cesare Borgia (1400-1500)** Poisoned many people in Italy for political and monetary gain. Used arsenic in a concoction called "La Cantrella"
Renaissance 14th–16th Centuries	**Leonardo de Vinci (1452-1519)** Experimented with bioaccumulation of poisons in animals and called the procedure "passages"	**Pope Clement VII (1478-1534)** Died (possibly murdered) after eating *amanita Phalloides*, (death cap) mushroom.	**Paracelsus (1493-1541)** "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."	**Georgius Agricola (1494-1555)** Wrote *De Re Metallica* published 1556. The most comprehensive book on mining and metallurgy.	**Catherine Medici (1519-1589)** Queen of France, expert assassin, tested poisons on the poor and the sick.	**William Piso 1640** In Brazil, studied effects of *Cephaelis Ipecacuanha*, an emetic; treat dysentery	**Shakespeare (1564-1616)** From Romeo & Juliet - act 5 "Here's to my love! O true apothecary! Thy drugs are quick. Thus with a kiss I die."	**Hieronyma Spara ~1659** Roman women & fortune teller organized wealthy wives and sold them a arsenic elixir to murder their husbands	**Catherine Monvoisin (LaVoisin) (1640-1680)** Accused sorcerer and convicted poisoner in France. She was burned at the stake.	**Guilia Tophania (1635-1719)** Italian woman who supplied poison (arsenic) to wives looking to murder their husbands. Later executed by strangulation.	**King Louis XIV 1682** Passed royal decree forbidding apothecaries to sell arsenic or poisonous substances except to persons known to them.
1700s	**Devonshire Colic 1700's** Devonshire, England. High incidence of lead colic drinking contaminated cider	**John Jones 1701** English doctor wrote *The Mysteries of Opium Reveal'd* described many treatments of opium, but also withdrawal and addiction	**Richard Meade (1673-1754)** In 1702, wrote *A Mechanical Account of Poisons* dedicated to poisons snakes, animals and plants	**Carl Wilhelm Scheele (1742-176)** Swedish apothecary and chemist, discovered oxygen, barium, chlorine, manganese, and hydrogen cyanide.	**Percivall Pott (1714-1788)** British physician who recognized coal-tar caused cancer of the scrotum in chimney sweeps. Chimney Sweepers Act of 1788	**Felice Fontana 1767** Italian chemist and physiologist who was the first to study venomous snakes. Discovered that viper venom affects blood	**Freidrich Serturner (1783-1841)** Isolated an alkaloid from opium poppy in 1803. He named it *Morphine* after Morpheus, the Greek god of dreams	**Francoise Magendie (1783-1855)** Discovered emetine and studied effects of strychnine & cyanide. Called the father of experimental pharmacology	**Fowler's Solution 1786-1936** Potassium arsenite solution prescribed as a general tonic and used from about 1786 to 1936. Used by Charles Darwin?	**Pierre Ordinaire 1797-1915** Created elixir using absinthe popularized and sold by Henry Pernod. Absinthe was used by Vincent Van Gogh, banned in 1915; subject of Degas	**Mateu J.B. Orfila (1787-1853)** Considered the father of modern toxicology. In 1813 he published *Traité des Poisons*, which described the symptoms of poisons
1800s	**Thomas de Quincey (1785-1859)** English writer became addicted to opium in early 1800's and published *Confessions of an Opium Eater* in 1821	**James Marsh (1794-1846)** Chemist developed and perfected the Marsh test for arsenic. The improved Marsh test was used forensically for the first time in 1840 during the trial of Marie Lafarge.	**Robert Christison (1797-1882)** Toxicologist at University of Edinburgh wrote *Treatise on Poisons* in 1829, invented poison harpoon for whaling that contained prussic acid.	**Claude Bernard (1813-1878)** French physiologist studied the effects of carbon monoxide and curare. Influenced by Francoise Magendie	**Ascanio Sobrero (1812-1888)** Italian chemist, in 1847 discovered nitroglycerin, a powerful explosive and vasodilator. Alfred Nobel was his student	**Theodore G. Wormley (1826-1897)** Wrote the first American book dedicated to poisons in 1869 entitled *Microchemistry of Poisons*	**Joseph Caventou & Pierre Pelletier 1820** French pharmacists isolated quinine from bark of *Cinchona* tree in back of their pharmacy	**Arsenic Act 1851** Required arsenic to be colored with soot or indigo to prevent "accidental" poisoning **Friedrich Gaedcke 1855** Isolated cocaine from *Erythroxylon coca*	**Louis Lewin (1854-1929)** German pharmacologist studied and classified hallucinogenic plants, alcohols and other psychoactive compounds	**Emil Fischer 1852-1919** Isolated the stimulant caffeine from plant extracts in 1895	**Constantine Fahlberg Saccharin - 1879** Constantine Fahlberg discovered saccharin while working in the laboratory of Ira Remsen (right) in 1879
1900-1930s	**Upton Sinclair (1878-1968)** Published *The Jungle* in 1905. Chronicled the unsanitary conditions in meat packing industry in Chicago	**Pure Food and Drugs Act - 1906** Harvey Washington Wiley, MD (1844-1930). Law prevents production or trafficking of mislabeled, adulterated or poisonous foods, drugs, medicines, and liquors	**Chemical Warfare A Reality 1915** German chemist Fritz Haber (1868-1934) developed blistering agents used in WWI; chlorine and cyanide gases	**U.S. Prohibition 1919-1933** Law that made the production and sale of alcoholic beverages illegal but very profitable	**Geneva Protocol 1925** Banned use of chemical weapons. Updated in 1993 as the "Chemical Weapons Convention" to include banning production.	**Ginger Jake 1929** Alcoholic tonic produced illegally during prohibition adulterated with TOCP produced OPIDN (Jake Leg), affecting 50,000 adults	**Hawk's Nest Incident 1927-1935** Hundreds of black workers die from acute silicosis while digging tunnel for a hydroelectric project for Union Carbide	**Gerhard Schrader (1903-1990)** German Chemist accidentally made nerve agents, sarin, tabun, soman, and cyclosarin while developing insecticides 1938; agents used in WWII	**Elixir Sulfanilamide 1937** **Food Drug & Cosmetic Act 1938** 100 die, diethylene glycol as a vehicle	**Albert Hofmann 1938** Lysergic acid (LSD) synthesized in the Sandoz Laboratory (now Novartis). In 1943 Hoffman tested LSD on himself.	**Marijuana Tax Act 1937** Federal criminal offense to possess, produce, or dispense hemp. Non-medical use prohibited in California (1915) and Texas (1919)
1940-1960s	**DDT – 1939** Recognized as insecticide by the Swiss scientist Paul Hermann Muller, who was awarded the 1948 Nobel Prize in Physiology and Medicine. Banned in 1972	**2,4-D – 1946** Developed during WW II at British Rothamsted Experimental Station, by J.H. Quastela and sold commercially in 1946. Used to control broadleaf plants	**Minimata Japan (1950's)** Minimata Bay contaminated with mercury by chemical industry. Thousands adults and children were poisoned from eating fish contaminated with methyl mercury	**Poison Control Centers 1953** First, Chicago **1953**, second at Duke University, NC in **1954**, and third opened in Boston **1955**	***Journal of Tox. & App. Pharmacology* 1959** Adopted by SOT until 1981 when SOT founded *Fundamentals of Applied Toxicology*.	**Thalidomide (1959-1960's)** Drug prescribed to pregnant women for morning sickness induced birth defects. Frances Kelsey of FDA blocked approval in U.S.	**Society of Toxicology 1961** Founded March 4, 1961 first formal meeting held April 15, 1962 (9 founders, 183 charter members)	**Alice Hamilton (1869-1970)** Pathologist and first female faculty member at Harvard Medical School. Associated worksite chemical hazards with disease. Studied effects of lead & rubber on workers	**Rachel Carson (1907-1964)** Scientist lead crusade against the use of dichlorodiphenyltrichloroethane (DDT) a pesticide and persistent organic pollutant. Carson several books including *Silent Spring* published 1962	**Occupational Safety & Health Act 1970** Act passed on December 29, 1970 to ensure every worker a safe and healthful workplace. OSHA	**U.S. EPA 1970** Established to consolidate federal research, on monitoring, standard-setting and enforcement activities to ensure human & environmental protection
1970-2006	**Mr. Yuk 1971** Symbol adopted by the Pittsburgh Poison Center at The Children's Hospital in 1971. Used to educate children and parents about poisons and to prevent accidental poisonings	**Iraq – Mercury 1971** Pink-colored seed grain coated with a mercury fungicide was tragically consumed by Iraqis tragically affecting over 40,000 people.	**Bangladeshi 1970s Arsenic poisoning** Tubewells, drilled to provide clean drinking water, are contaminated by arsenic resulting in millions of people harmed	**First Modern Toxicology Textbook 1975** Louis J. Casarett & John Doull edited, *Toxicology: The Basic Science of Poisons*, in 1975	**Love Canal Disaster 1978** August 7, 1978 US President Jimmy Carter declared Love Canal a federal emergency. 42 million pounds of over 200 chemicals contaminated Love Canal, disrupting many lives	**IUTOX 1980** International Union of Toxicology **American Board of Toxicology (ABT) 1979** – First exam Aug. 1980 **Academy of Toxicological Sciences (ATS) 1981**	**Times Beach 1983** Dangerous levels of dioxin discovered in Times Beach, MO. EPA orders the town evacuation and makes it a Superfund site. All residents gone by 1985	**Bhopal Disaster Dec. 3, 1984** Accidental release 40 metric tons of methyl isocyanate from a Union Carbide Indian pesticide plant in heart of city resulted in the killing thousands, and injured 100s of thousands	**Chernobyl Accident April 26, 1986** The Chernobyl nuclear power plant accident produced a plume of radioactive debris over the Ukraine, Eastern Europe, Scandinavia, UK and eastern USA	**Tokyo Subway Sarin Gas Attack 1995** Members of religious group Aum Shinrikyo released sarin gas in 5 places in Tokyo subway, killing 12 and injuring 6,000	**Vioxx (1999-2004)** A nonsteroidal anti-inflammatory, COX-2 selective inhibitor for treatment of osteoarthritis, produced by Merck & Co. and voluntarily withdrawn because of risk of heart attack & stroke

www.toxipedia.org

A free toxicology encyclopedia and resource center.

Toxipedia – scientific information in the context of history society and culture.

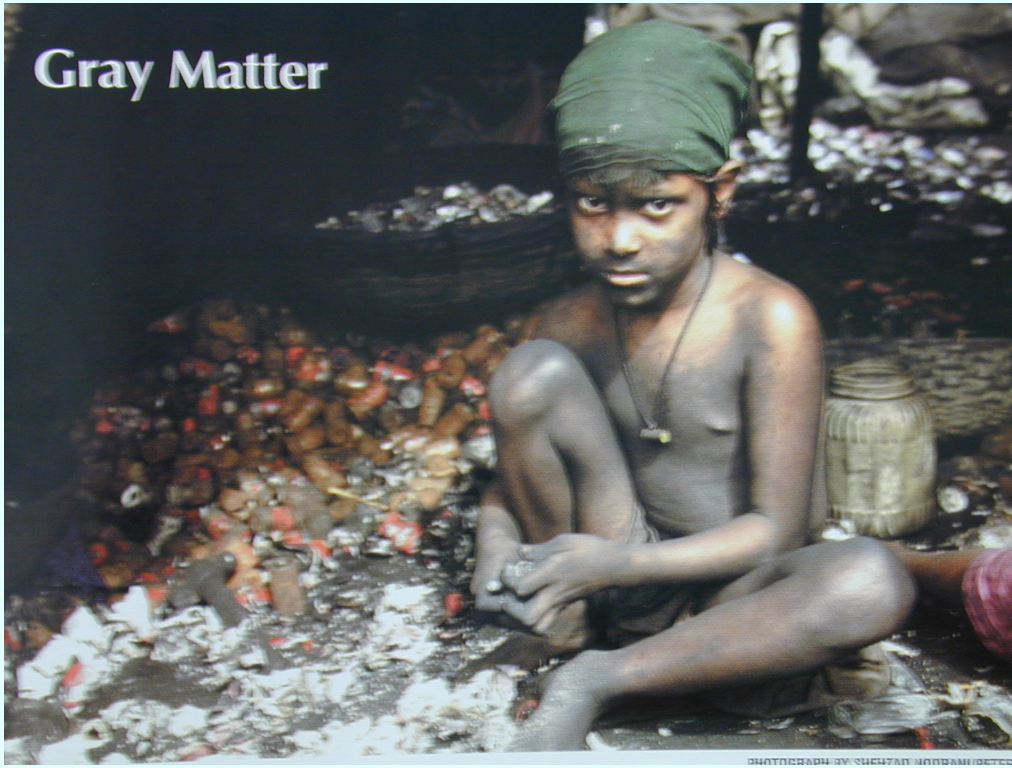
Teaching resources section.

toxipedia
connecting science and people

Inheriting The Future

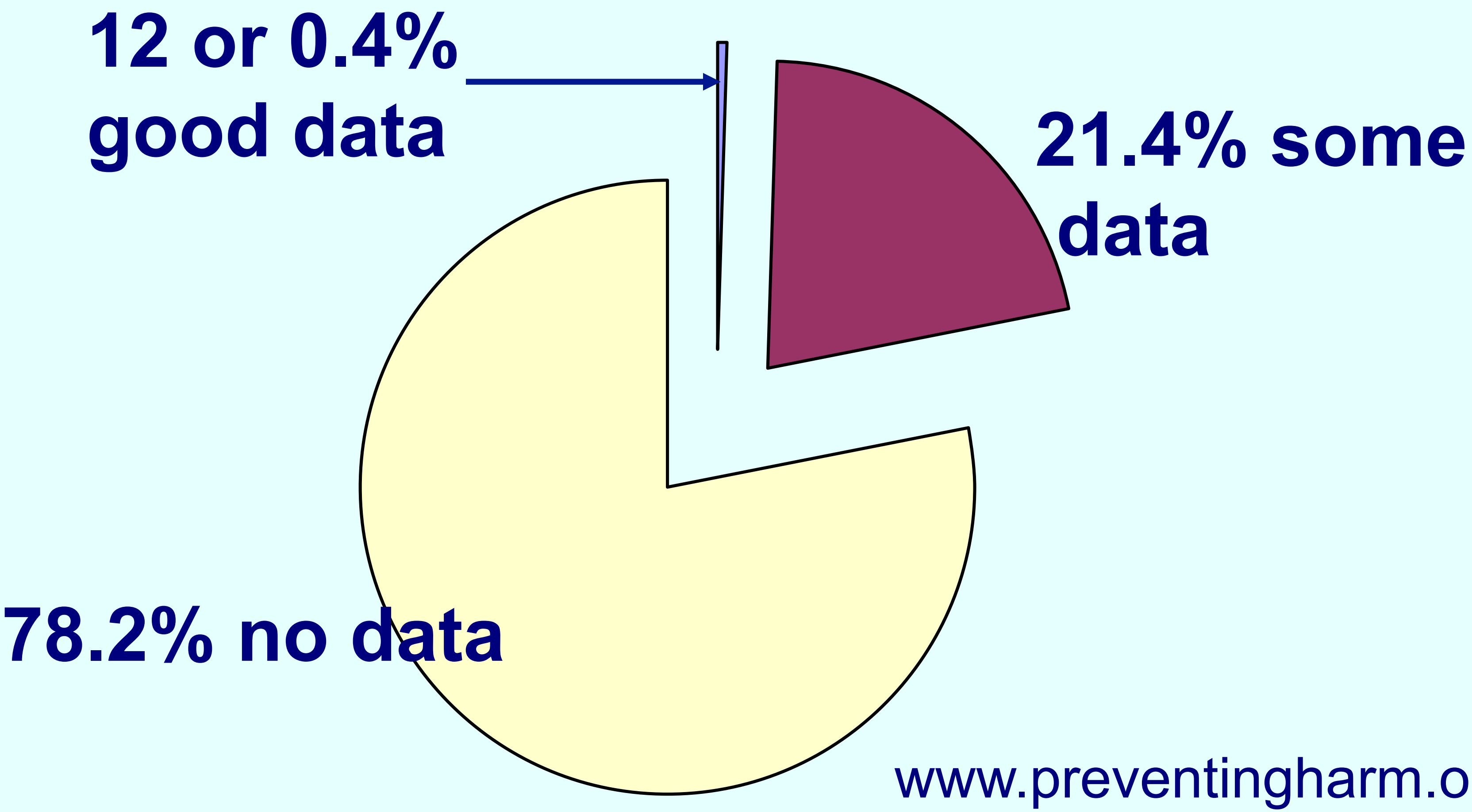
- Global Warming
- Burning Coal
- Coal Waste
- Mercury from Coal to Fish
- Nuclear waste
- Chemical body burden
- Chemical use
- Sustainability

Child Health



So Many Chemicals so Little Data

2863 above 1 Million pounds



www.preventingharm.org

The Consequences

- Nearly 12 million children (17%) under age 18 in the US suffer from one or more developmental disabilities
- Learning disabilities – 5-10% of kids in public school
- ADHD – 3-6% of all school kids, maybe higher

Toxicology Definitions

The study of poisons
or
the adverse effects of chemical and physical agents on living organisms.

Human & Environmental Health

"Conditions that ensure that all living things have the best opportunity to reach and maintain their full genetic potential."

Steven G. Gilbert, 1999

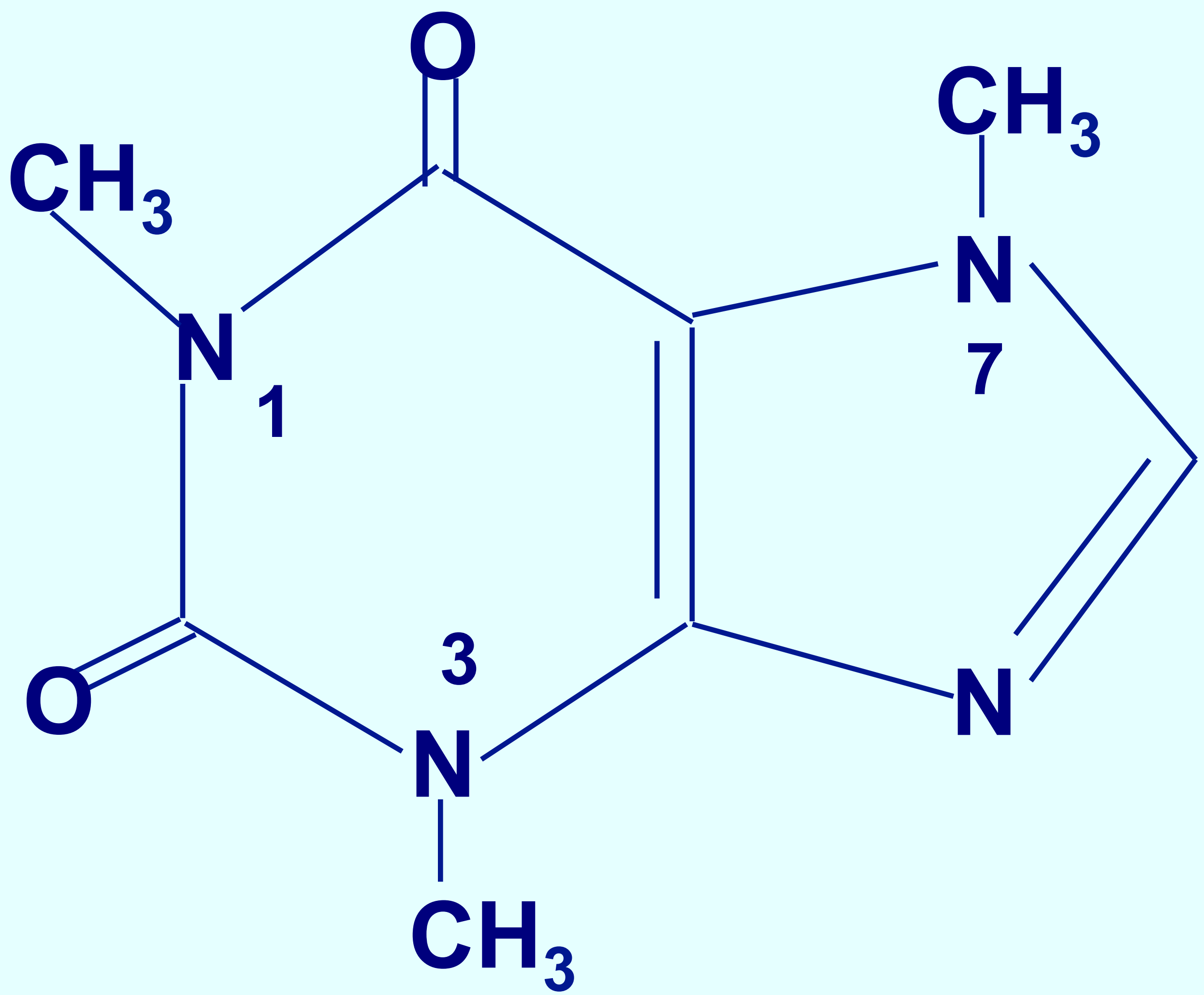
Gilbert SG. Ethical, legal, and social issues: our children's future. Neurotoxicology. 2005;26:521-30.

Precautionary Principle

"When an activity raises threats of harm to human health or the environment, precautionary measures should be take even if some cause and effect relationships are not fully established scientifically."

Wingspread Conference, 1998.

What Is This?



Key Words

Dose / Response

Risk =

Hazard X Exposure

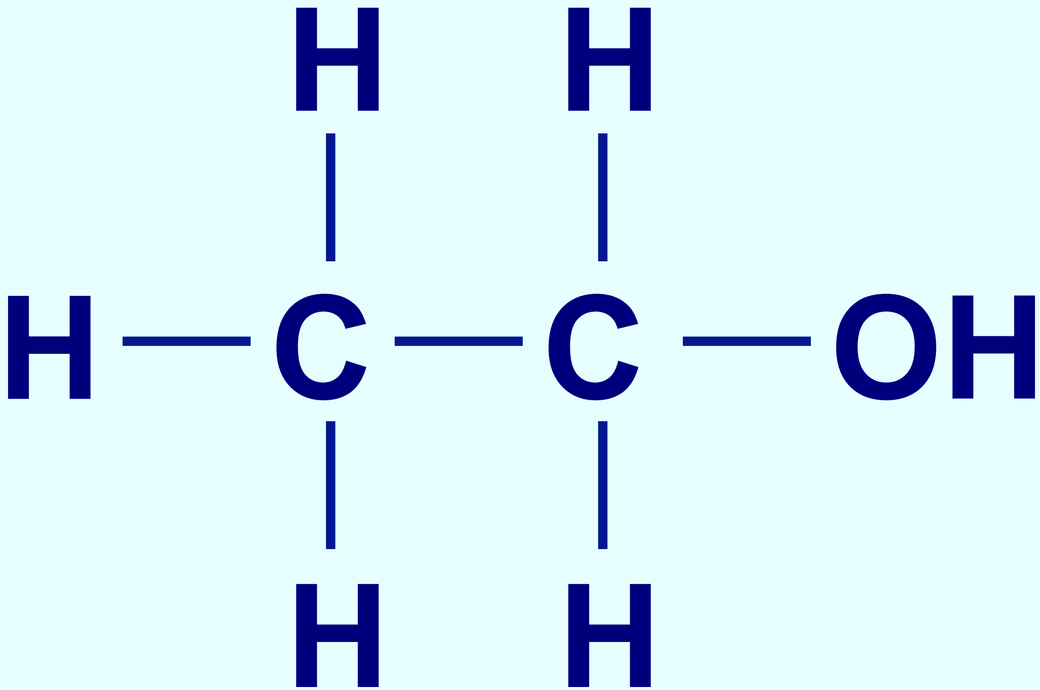
Individual Sensitivity

Thalidomide

- Introduced in 1956 as sedative (sleeping pill) and to reduce nausea and vomiting during pregnancy
- Withdrawn in 1961

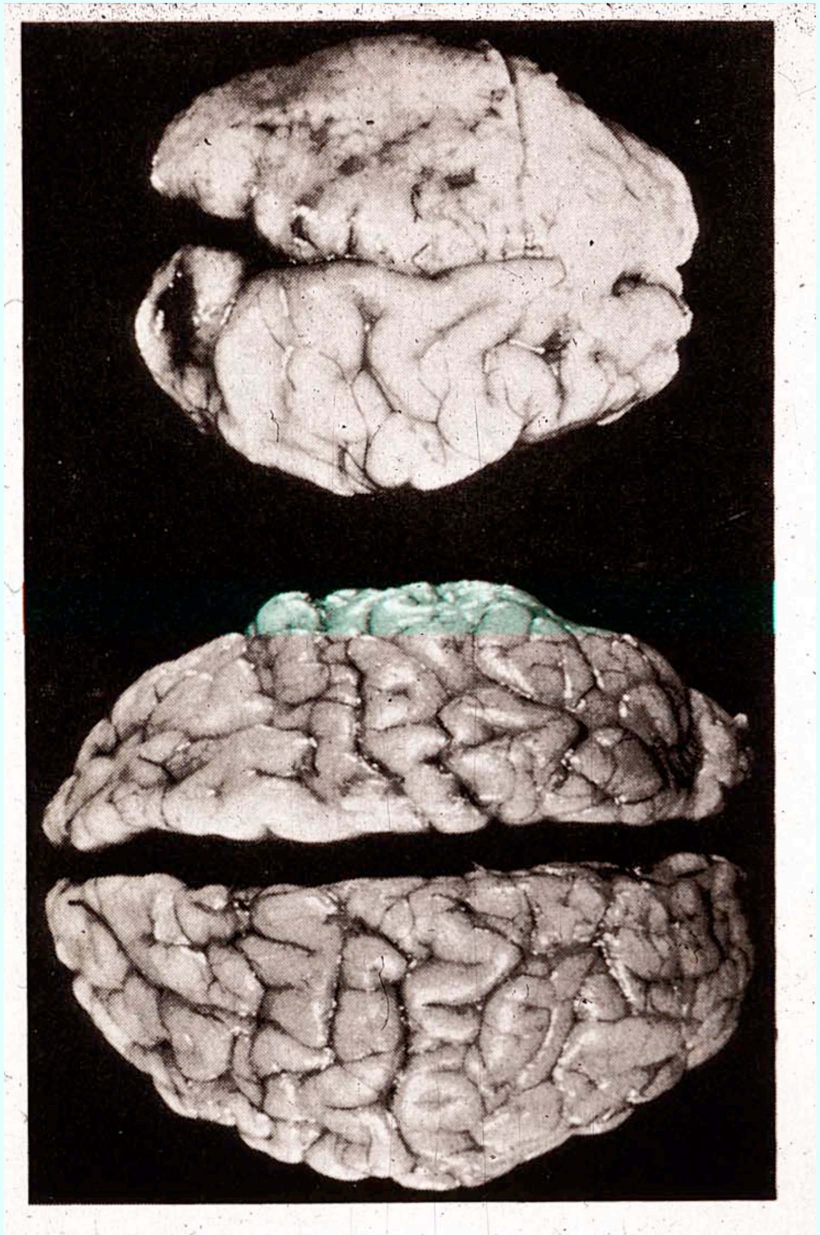
- Discovered to be a human teratogen causing absence of limbs or limb malformations in newborns
- 5000 to 7000 infants effected
- Resulted in new drug testing rules

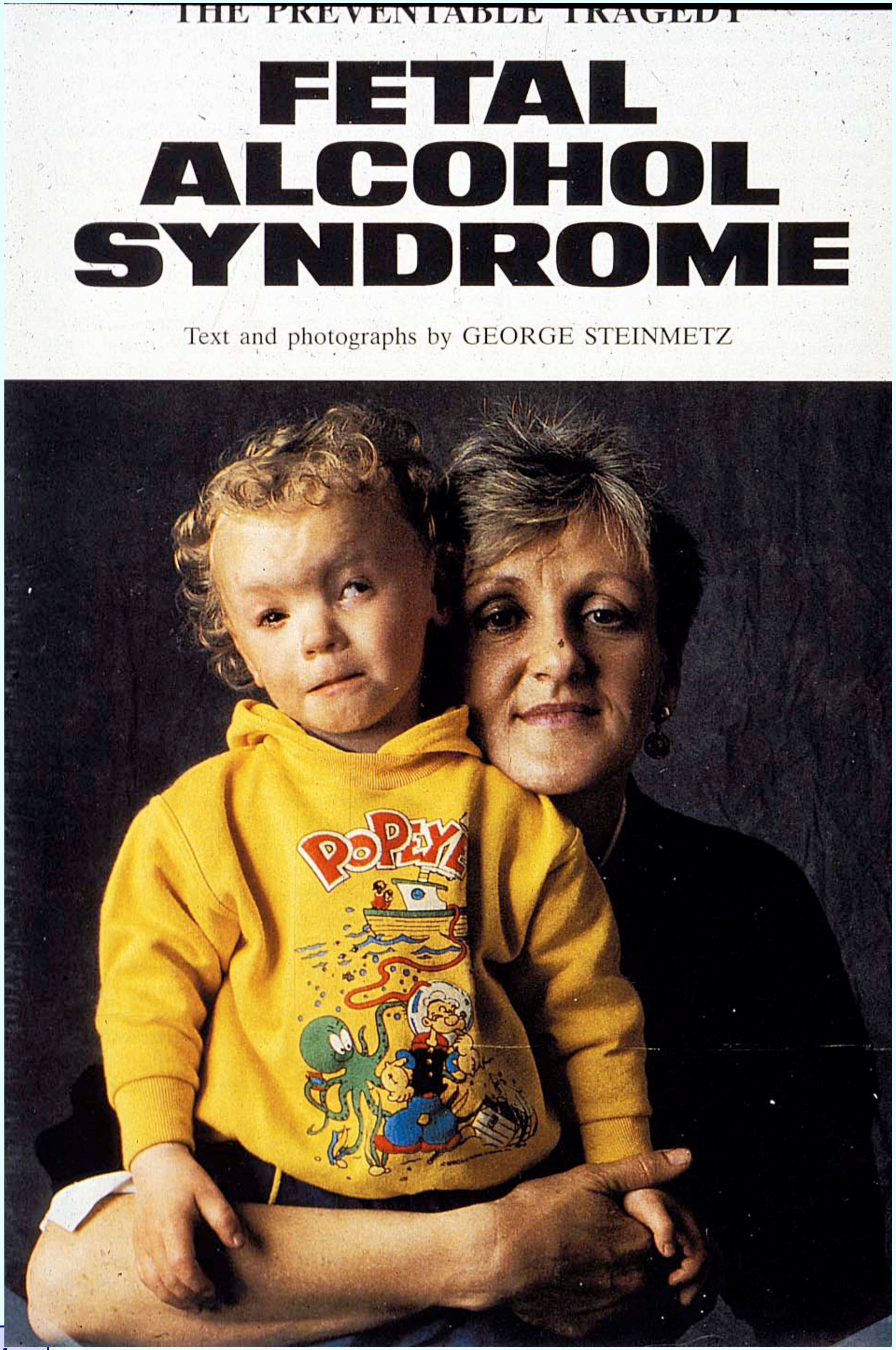
What Is This?



$(CH_3\text{-}CH_2\text{-}OH)$

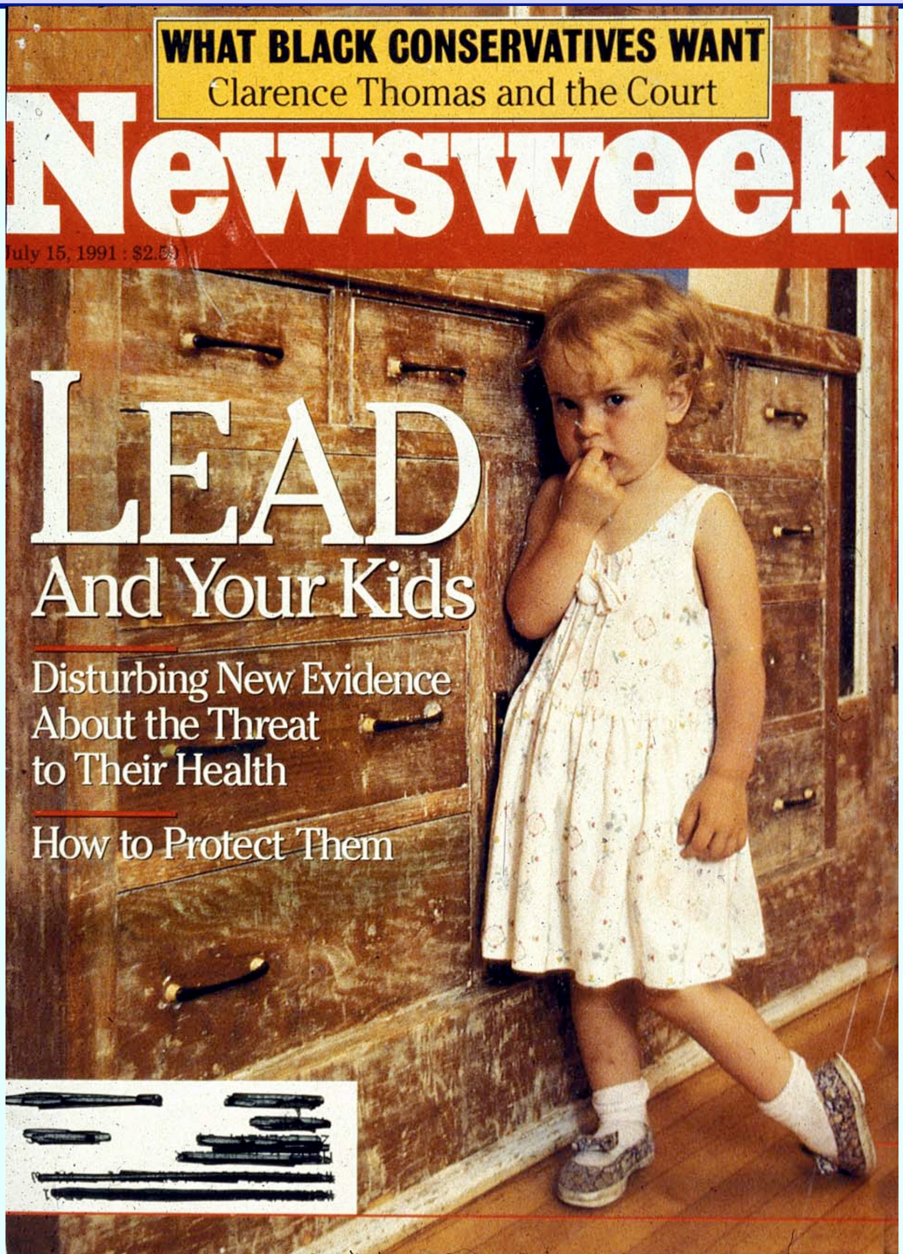
Effects of Prenatal Alcohol




THE PREVENTABLE TRAGEDY
FETAL ALCOHOL SYNDROME
Text and photographs by GEORGE STEINMETZ

A Small Dose of Lead

Lead In Homes

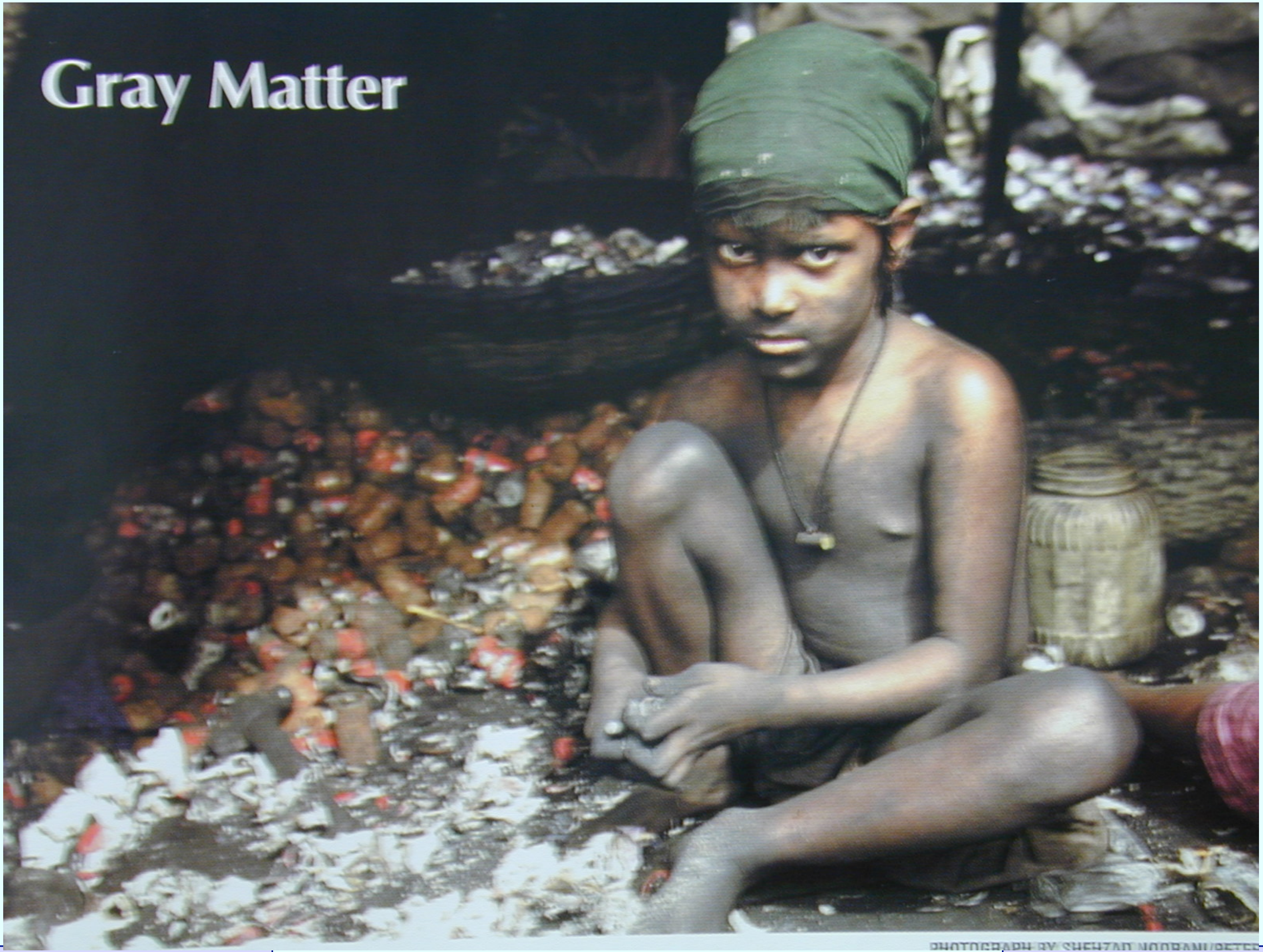


Lead History

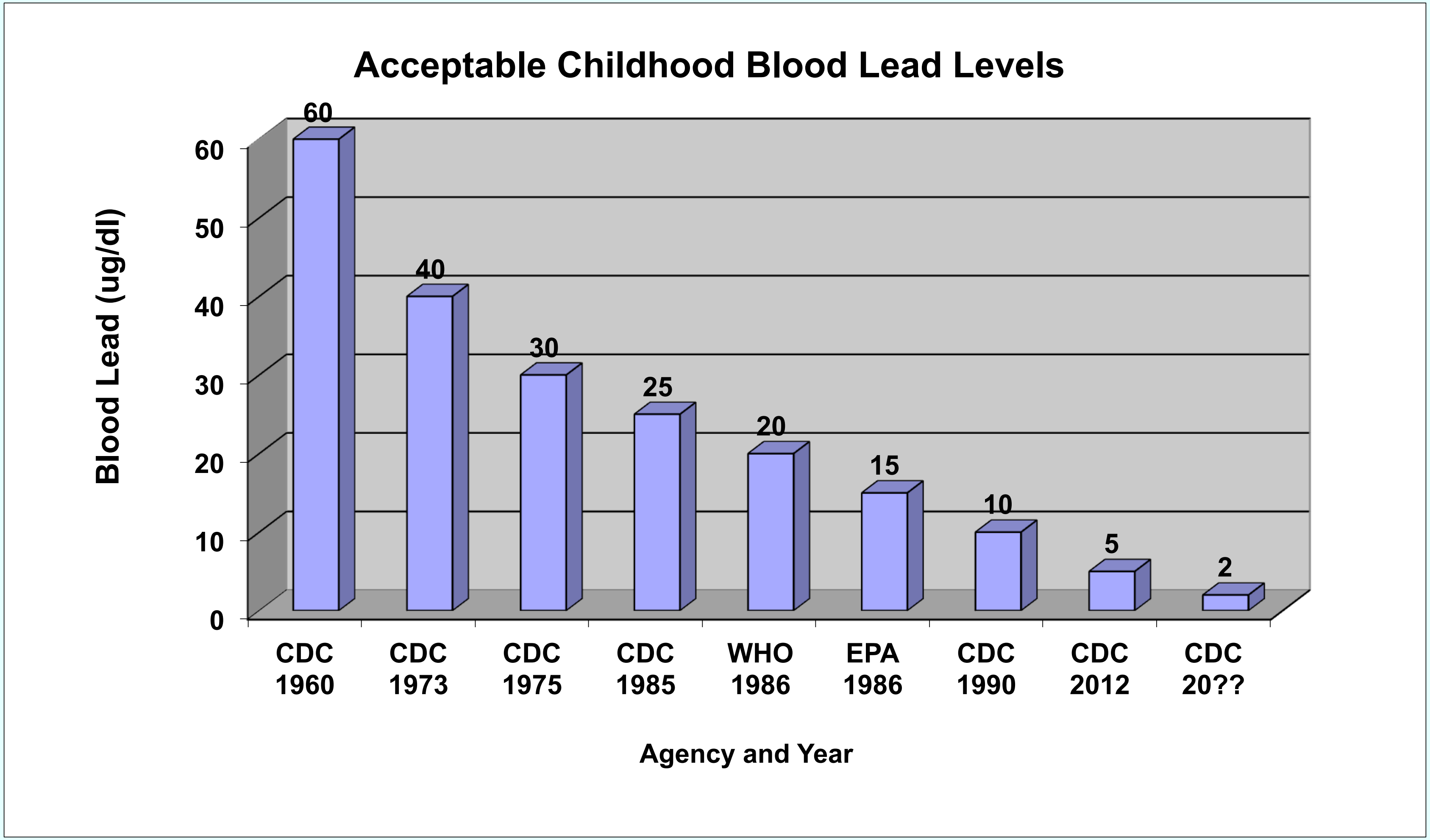
Lead Makes the Mind Give Way

Greek 2^{nd} BC

Recycling Lead

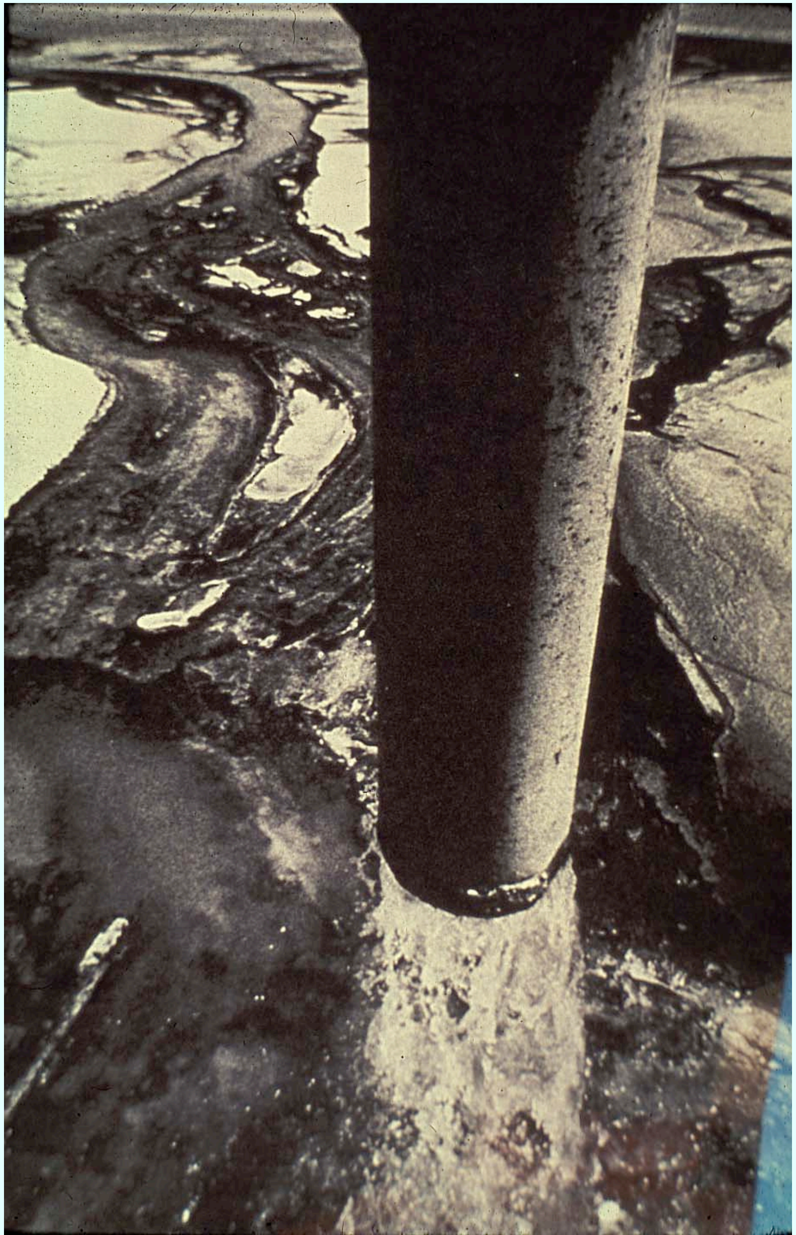


Agency Blood Lead Levels

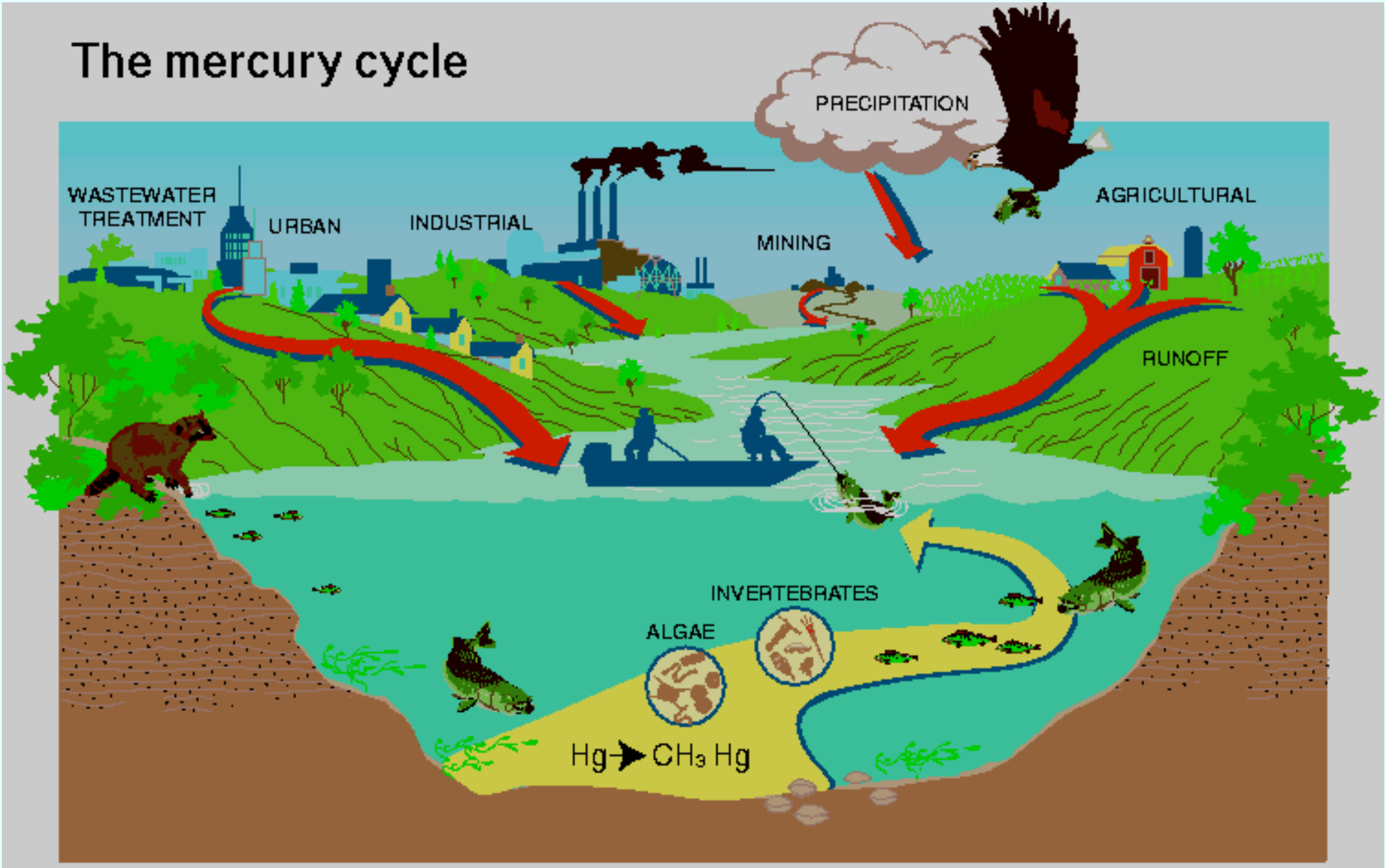


Hg – Solid Enough to Sit On

Discharge in Minamata Bay



The Mercury Cycle

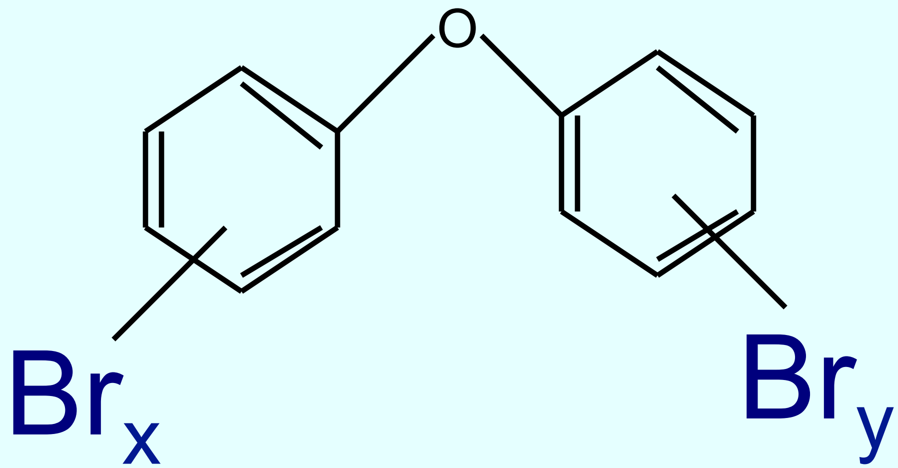


(Illustration by Connie J. Dean, U.S. Geological Survey)

Fetal Effects of MeHg

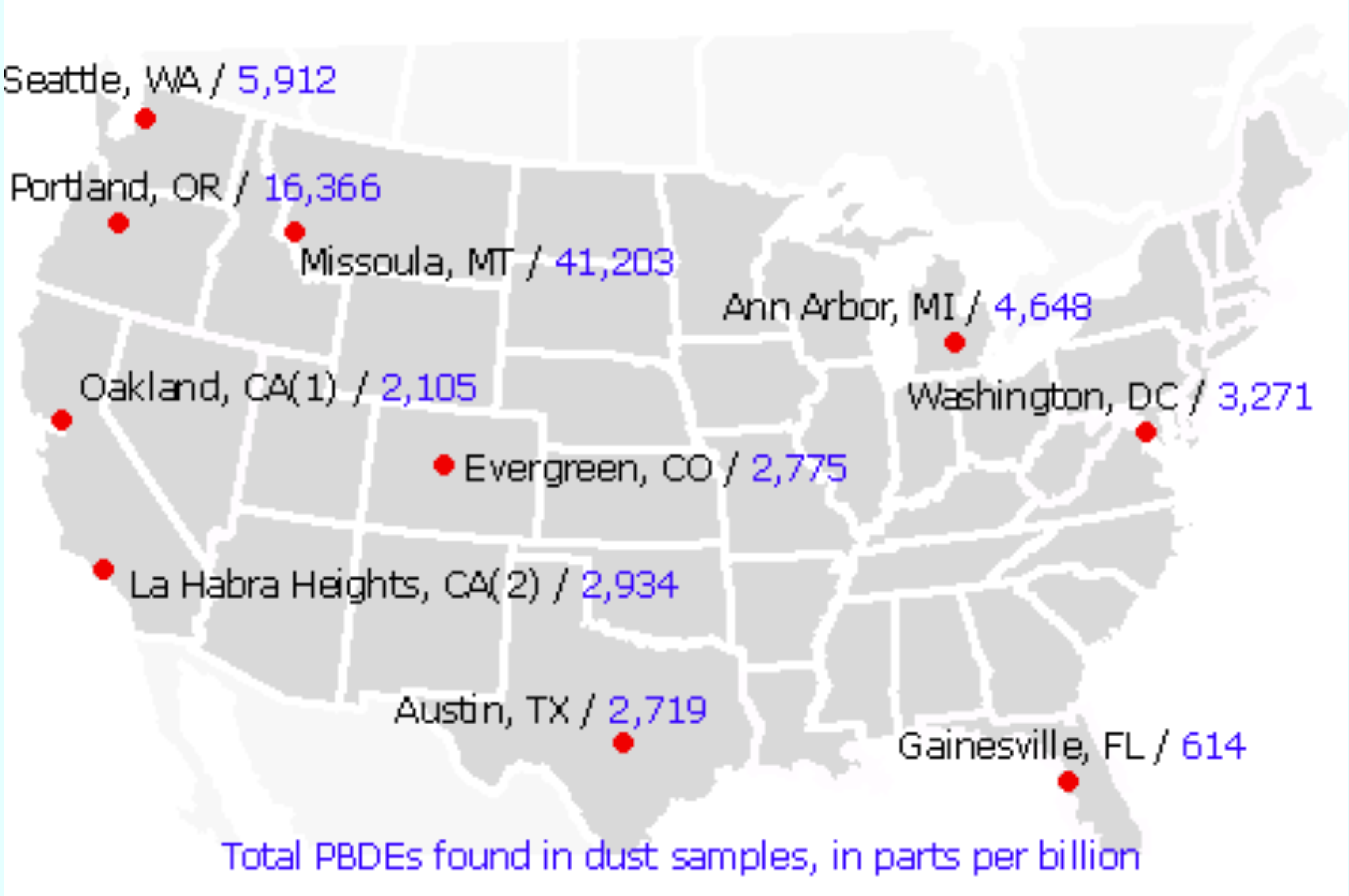
Structure of PBDEs

PolyBrominated Diphenyl Ether



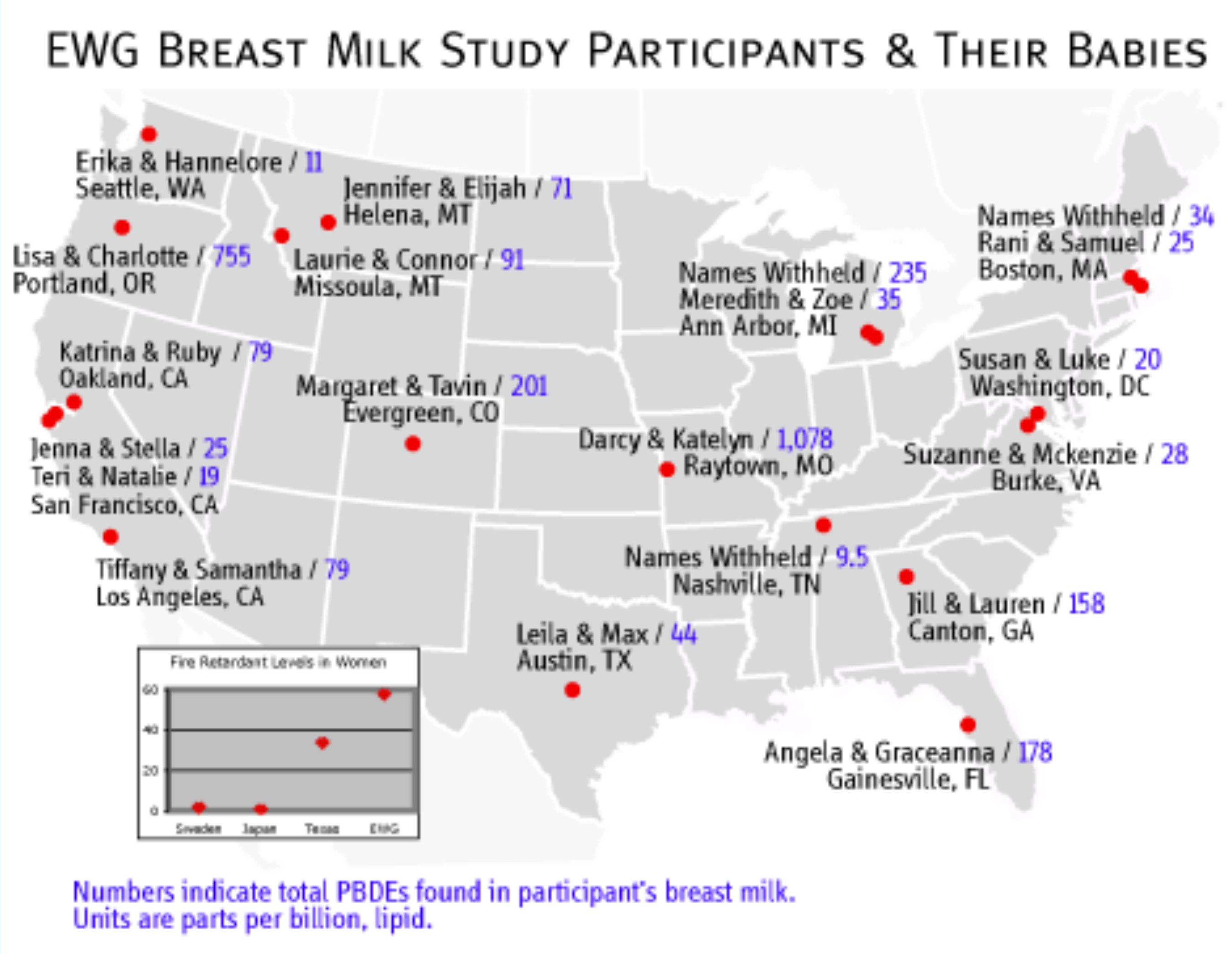
X & Y are number of Bromine atoms
Common Penta, Octa, and Deca

PBDEs in House Dust (ppb)



From EWG - Toxic Fire Retardants Contaminate American Homes - http://www.ewg.org/reports/inthedust/summary.php

PBDEs in Breast Milk (ppb)



From EWG - Toxic Fire Retardants in Breast Milk from American Mothers - http://www.ewg.org/reports/mothersmilk/es.php

Susceptibility & Variability

- Young or Old
- Male or Female
- Individual Variability
- Genetics Differences
- Species Differences

Precautionary Principle

"When an activity raises threats of harm to human health or the environment, precautionary measures should be take even if some cause and effect relationships are not fully established scientifically."

Wingspread Conference, 1998.

Central components

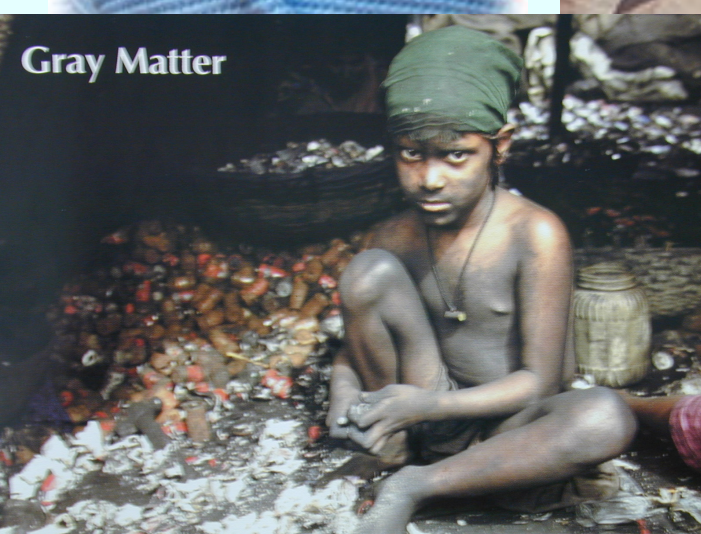
- Taking preventive action in the face of uncertainty
- Shifting the burden of proof/responsibility to the proponents of an activity
- Exploring a wide range of alternatives to possibly harmful actions
- Increasing public participation in decision making

Wingspread Conference, 1998.

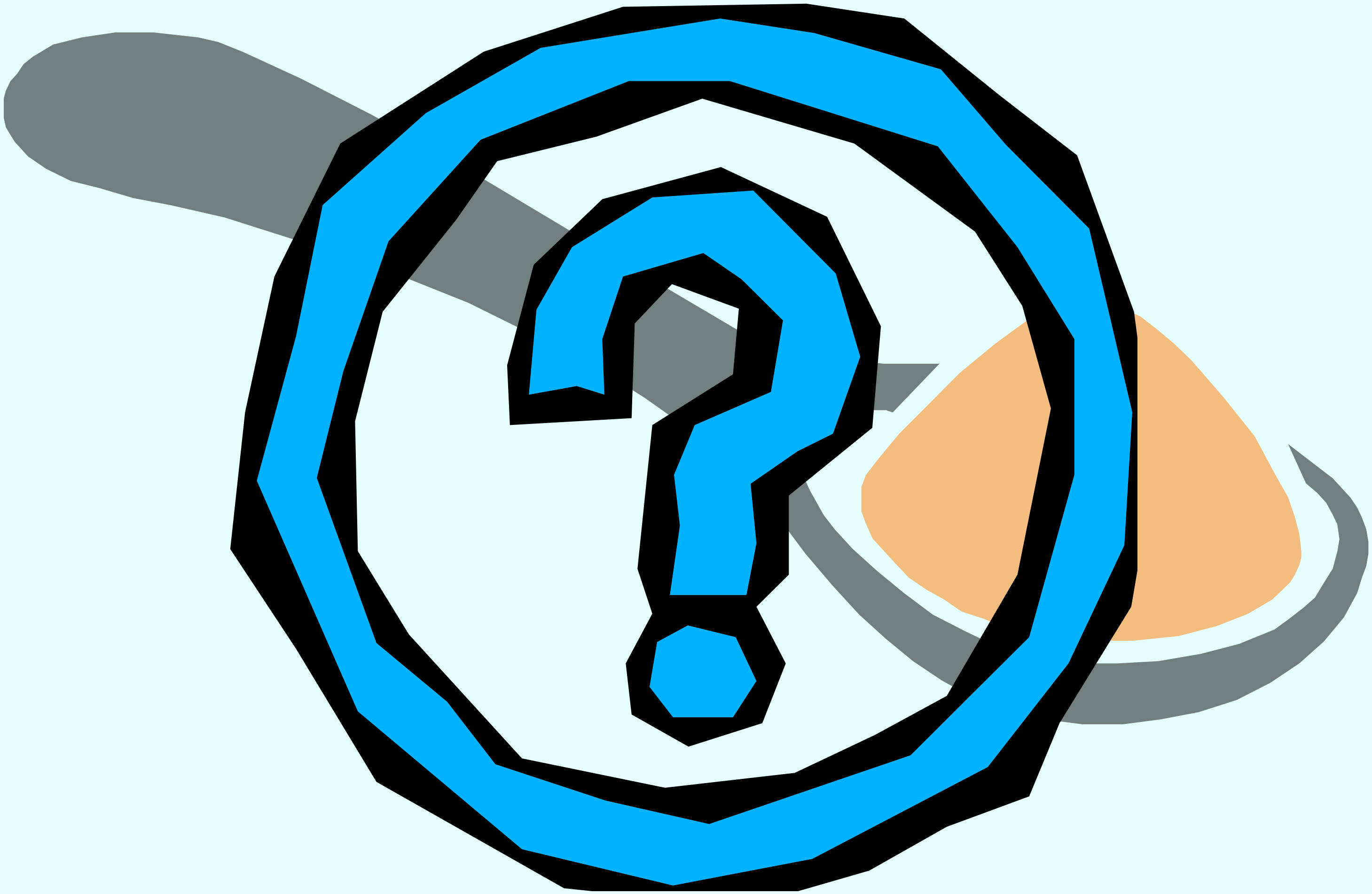
Knowledge - Responsibility

- Children have a right to a safe, fair and healthy environment
- Ethical Responsibility to share and use of knowledge
- Duty to promote health and well being of children
- Thoughtful public health advocate

The Potential of Children



Principles of Toxicology



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United States Environmental Protection Agency

DfE Methods for Hazard Evaluation in Alternatives Assessment

Cal Baier-Anderson

January 21, 2014

Contents

DfE Approaches to Hazard Evaluation:

- Background on DfE
- What is safer?
- Explanation DfE criteria
- Examples

Background on DfE

- Goals
  - Non-regulatory approach to incentivize development of safer products
  - Identification and selection of safer chemical ingredients
  - Life cycle impacts are considered
- Central Elements
  - EPA technical tools and expertise
  - Multi-stakeholder participation
- Programs
  - Safer Product Labeling Program
  - Alternatives Assessments Program

Alternatives Assessment Program

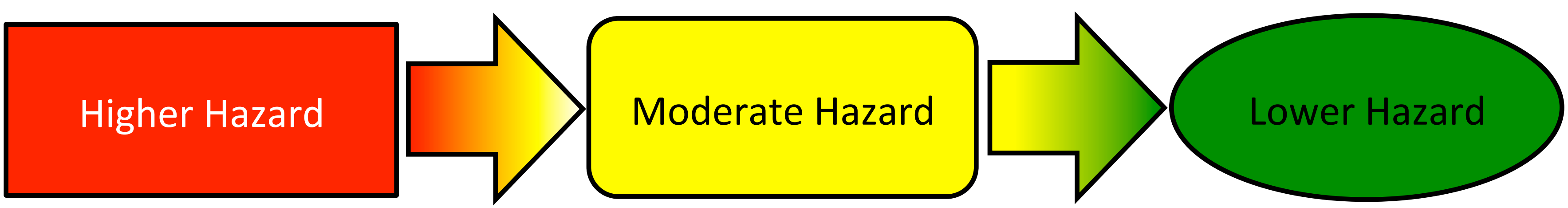
- Chemical alternatives assessments:
  - Identify and evaluate potentially safer alternatives
  - Involve stakeholders from across the spectrum of interested parties
- The outcome of an alternatives assessment:
  - Provides the best information on hazard from literature and models (Based on New Chemicals Program approaches)
  - Helps stakeholders choose safer alternatives
    - Provides information that manufacturers can use to create more sustainable products
    - Helps minimize the potential for unintended consequences by reducing the likelihood of moving to alternatives that could pose a concern

Green Chemistry and Hazard

- Prevent Waste
- Maximize Atom Economy
- Use Less Hazardous Chemical Syntheses
- Design Safer Chemicals
- Use Safer Solvents and Reaction Conditions
- Design for Energy Efficiency
- Use Renewable Feedstocks
- Avoid Chemical Derivatives
- Use Catalysis
- Design for Degradation
- Analyze in Real-time for P2
- Minimize Potential for Accidents

What is Safer?

- Risk is a function of HAZARD and EXPOSURE
  - Safer ≈ less risk
- Conventional approach is to control exposure
  - Exposure controls can and do fail
- Alternatively, substitute with LOWER HAZARD chemicals
  - Predicated on understanding <u>relative</u> continuum of hazard
  - Consider other factors that may alter risk equation



Importance of Functional Use

- The functionality of a chemical is related to structure and p-chem properties
- Criteria can be tailored to functional class to distinguish safer chemicals
- Functional use classes
  - Surfactants
  - Solvents
  - Chelating and sequestering agents
  - Fragrances
  - Colorants
  - Preservatives

Hazard Endpoints

Human Health Toxicity

- Acute mammalian toxicity
- Carcinogenicity
- Mutagenicity/ Genotoxicity
- Reproductive Toxicity
- Developmental Toxicity
- Neurotoxicity
- Repeated Dose Toxicity
- Respiratory Sensitization
- Skin Sensitization
- Eye and Skin Irritation/Corrosivity
- Endocrine Activity

Environmental Fate & Effects

- Aquatic toxicity
- Environmental persistence
- Bioaccumulation

Additional Endpoints

- Physical hazards
- Ecotoxicity (birds, bees)
- And more

EPA Threshold-Based Criteria

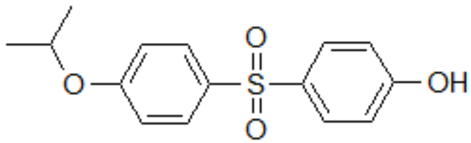
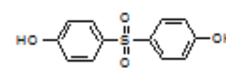
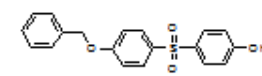
Endpoint (LOAEL, NOAEL)	High	Moderate	Low	Very Low
Oral (mg/kg-bw/d)	<50	50-250	> 250-1000	>1000
Dermal (mg/kg-bw/d)	<100	100-500	>500-2000	>2000
Inhalation (vapor, mg/L/d)	<1	1-2.5	>2.5-20	>20
Inhalation (dust, mg/L/d)	<0.1	0.1-0.5	> 0.5-5	5

- Chemicals with data
- Considers exposure route
- Examples of threshold-based criteria:
  - Acute toxicity
  - Acute aquatic toxicity
  - Bioaccumulation
  - Repeated dose toxicity
  - Reproductive & developmental toxicity

EPA Evidence-Based Criteria

- Strength of evidence linking a chemical to an effect
  - Cancer, Mutagenicity
- Examples
  - HIGH CONCERN
    - Evidence of adverse effects in humans or
    - Conclusive evidence of severe effects in animal studies
  - MODERATE CONCERN
    - Suggestive animal studies for chemical or analogs or
    - Chemical class/SAR known to produce toxicity
  - LOW CONCERN
    - No concern identified

Consider Chemical Properties

	**CASRN:** 95235-30-6 **MW:** 292.35 **MF:** $C_{15}H_{16}O_4S$ **Physical Forms:** **Neat:** Solid **Use:** Developer for thermal paper
SMILES: O=S(=O)(c1ccc(O)cc1)c2ccc(OC(C)C)cc2	
Name: 4-hydroxyphenyl 4-isoprooxyphenylsulfone	
Synonyms: Phenol, 4-[[4-(1-methylethoxy)phenyl]sulfonyl]-; 4-(4-isopropoxyphenylsulfonyl)phenol; Phenol, 4-[[4-(1-methylethoxy)phenyl]sulfonyl]-; 4-Hydroxy-4-isopropoxydiphenylsulfone; D-8; DD-8; ALD-2000	
Polymeric: No **Oligomers:** Not applicable	
Metabolites, Degradates and Transformation Products: None identified	
Analog: Bisphenol S (80-09-1) **Endpoint(s) using analog values:** Reproductive effects, developmental effects, and repeated dose effects **Analog:** BPS-MPE (63134-33-8) **Endpoint(s) using analog values:** Acute mammalian toxicity; eye irritation; dermal irritation; skin sensitization	**Analog Structures:** Structure:   Name: Bisphenol S (80-09-1) BPS-MPE (63134-33-8)
Structural Alerts: Phenols, neurotoxicity (U.S. EPA, 2010)	
Risk Phrases: 51/53 - Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (ESIS, 2011).	
Risk Assessments: None identified	

Summarize Data

Developmental Effects		**MODERATE: Estimated based on analogy to bisphenol S. In a reproduction/developmental toxicity screening test, oral exposure of parental rats to the analog bisphenol S resulted in marked systemic effects and decreased number of live offspring (PND 4) at the highest dose level (300 mg/kg-day with a NOAEL of 60 mg/kg-day. Based on the NOAEL, a Moderate hazard designation is selected.**		
	Reproduction/ Developmental Toxicity Screen	Parental toxicity: NOAEL = 10 mg/kg bw-day LOAEL = 60 mg/kg bw-day Reproductive toxicity: NOAEL = 60 mg/kg bw-day LOAEL = 300 mg/kg bw-day (Estimated by analogy)	ECHA, 2011; Professional judgment	Adequate; using the analog bisphenol S, data are for an adequate guideline study (OECD 421) reported in a secondary source.
		Potential for developmental toxicity (Estimated by analogy)	Professional judgment	Estimated based on reported experimental data for the analog bisphenol S.

Compare Chemicals

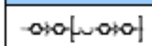
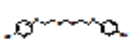
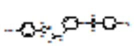
This table only contains information regarding the inherent hazards of the chemicals evaluated. Evaluation of risk considers both the hazard and exposure.
The caveats listed in the legend and footnote sections must be taken into account when interpreting the hazard information in the table below.

VL = Very Low hazard L = Low hazard M = Moderate hazard H = High hazard VH = Very High hazard — Endpoints in colored text (VL, L, M, H, and VH) were assigned based on empirical data. Endpoints in black italics (*VL, L, M, H, and VH*) were assigned using values from estimation software and professional judgment.

◊ The highest hazard designation of a representative component of the oligomeric mixture with MWs <1,000.

‡ The highest hazard designation of any of the oligomers with MW <1,000

§ Based on analogy to experimental data for a structurally similar compound.

Structure	Chemical (for TSCA inventory name and relevant trade names see the individual profiles in Section 4.8)	CASRN	Human Health Effects: Acute Toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Aquatic Toxicity: Acute	Chronic	Environmental Fate: Persistence	Bioaccumulation
Oligomeric and Polymeric Alternatives																	
	D-90 Phenol, 4,4'-sulfonylbis-, polymer with 1,1'-oxybis[2-chloroethane]	191680-83-8	L	*M*	L	*L*	*L*	*M*	L	L		M	VL	*L*‡	*L*‡	*VH*‡	*H*‡
	DD-70 1,7-bis(4-Hydroxyphenylthio)-3,5-dioxaheptane	93589-69-6	*L*	*M*	*L*	*M*	*M*§	*M*	*M*§	*M*§		*H*§	*M*§	*H*	*H*	*H*	*L*
	Pergafast 201 N-(p-Toluenesulfonyl)-N'-(3-p-toluenesulfonyloxyphenyl)urea	232938-43-1	L	*M*	L	M	H	*L*	M	L		L	VL	H	H	VH	L

Growing Community of Practice

Others are conducting Alternatives Assessments using related methods:

- States and NGOs
  - Washington, Maine and TURI in Massachusetts
  - Clean Production Action's (CPA) GreenScreen®
  - Green Chemistry & Commerce Council (GC3)
- Companies and trade associations
  - HP
  - Nike
  - Phosphorous, Inorganic & Nitrogen Flame Retardants Association (PINFA)

DfE Links

DfE Home Page

http://www.epa.gov/dfe/

DfE Alternatives Assessments:

http://www.epa.gov/dfe/alternative_assessments.html

DfE Alternatives Assessments Criteria:

http://www.epa.gov/dfe/alternatives_assessment_criteria_for_hazard_eval.pdf

Cal Baier-Anderson

baier-anderson.caroline@epa.gov

Toxicology and Alternatives Assessment

Robert Roy, PhD, DABT and Robert Skoglund PhD, DABT, CIH

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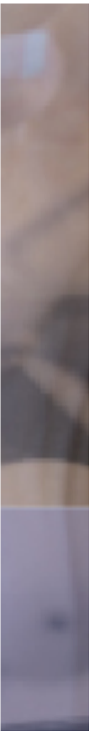
3M

Alternatives Assessment (AA)



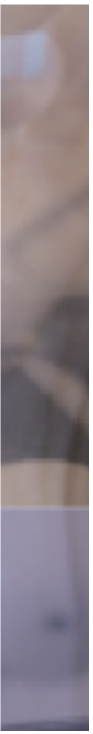
- The process for identifying and comparing potential chemical and non-chemical alternatives that can be used as substitutes to replace chemicals or technologies of high concern*

Goal: Reduce risk by reducing hazard

Risk = (Hazard) x (Exposure)

* Dr. Ken Geiser, Lowell Center for Sustainable Production

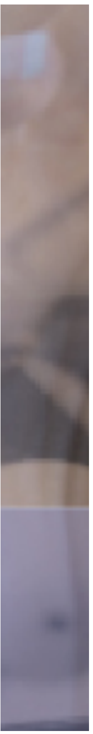
AA: Toxicologist's Roles/Responsibilities



- The primary responsibility of the toxicologist* is to carryout, document and communicate the *[chemical]* health hazard assessment
  - Also consider attributes beyond hazard, especially health risk
- The toxicologist may also be involved to a limited degree in the initial identification and/or prioritization of chemical alternatives (that will need health hazard assessment)
  - However, this step most is often performed by product developers, etc. and results communicated to the toxicologist

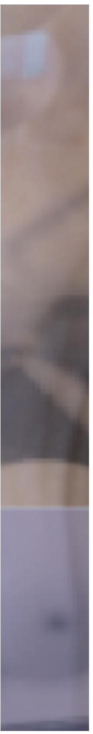
*Preferred attributes: 1) a formal educational background in the sciences; 2) further training via continuing education (internal and external); 3) practical toxicological/health hazard assessment experience; and 4) professional certification(s) [or working towards]

AA: Toxicologist's Roles/Responsibilities



- The toxicologist needs to ensure that the chemical alternative is an improvement
  - Can't simply move away from a chemical of concern $\longrightarrow$ need to move to a better option
    - Hazard (need to balance multiple health endpoints)
    - Performance (make sure the chemical still "works")
    - Cost
  - Need to avoid "regrettable" chemical substitutions

AA: Chemical Hazard Assessment



- 3M has a long history of preparing comprehensive, toxicologically defensible and transparent chemical hazard assessments
  - Health, physical and environmental assessments
- Chemical health hazard assessments used for (examples):
  - Hazard communication
    - SDSs, labels and training (workers, customers, other technical staff, etc.)
  - Risk (safety) assessment preparation
  - Helping 3M to make informed decisions regarding chemical use

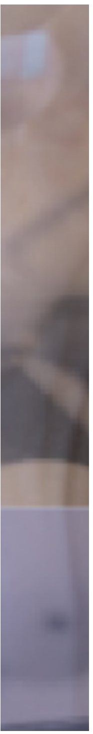
Chemical Hazard Assessment

- Comprehensive evaluation of the available scientific evidence *[of a chemical]* in order to determine its human health effects (designated as health hazard endpoints)
  - Need to access (and interpret) available data
  - Important considerations (examples):
    - Data scientifically validated (or can they be)? → Reliability

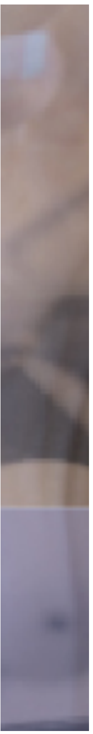
      Example: Assignment of a Klimisch score (*RTP* **25**: 1-5, 1997)
    - Statistical significance of the results
    - Biologically plausible?
    - Determination of an "adverse" health effect vs. a "non-adverse" effect
    - Weight of Evidence (WoE) evaluation

      WoE → evaluation of all (+), (-) and equivocal data together

Adverse vs Non-Adverse Health Effect



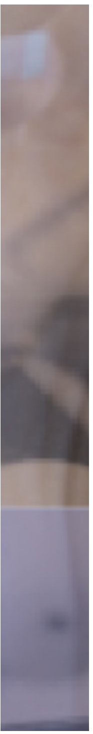
- A change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, or an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (OECD; REACH)
- Change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences (WHO/IPCS)



Adverse vs Non-Adverse Health Effect

- <u>Critical</u> to health hazard assessment that the assessment is based on adverse health effects and not non-adverse (*e.g.* "adaptive effects)
  - Doing this can involve a significant amount of work
  - Involves use of available guidance and professional judgment and experience
- Guidance resources:
  - GHS Chapter 3 sections 3.9.2.7.3 and 3.9.2.8.
  - ECETOC Technical Report 85 (2002)
  - *Toxicologic Pathology* **30(1)**: 66-74 (2002)

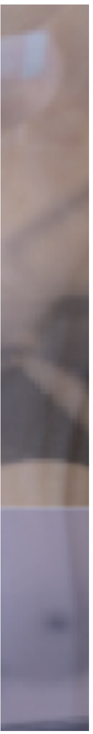
Health Hazard Assessment - Process



(1) Gather available health hazard data on the chemical(s)

- Tiered Literature Search Strategy (CAS # specific)
  - Tier 1 – 3M data and comprehensive, peer-reviewed, regularly updated, authoritative/reliable, easily accessed secondary sources and chemical classifications (examples):
    - Ariel WebInsight
    - ECHA REACH Registration database
    - ATSDR Toxicology Profiles
    - EPA IRIS
    - EU RARs
    - IPCS – INCHEM
    - *Documentation* for OELs (TERA/OARS WEELs; ACGIH TLVs, etc.)

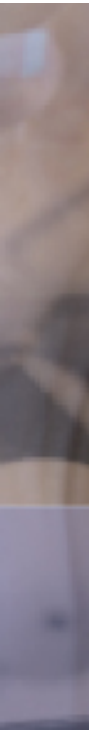
Health Hazard Assessment - Process



- Tiered Literature Search Strategy
  - Tier 2 – Other secondary sources (examples):
    - IUCLID datasheets;
    - IARC Monographs and List; Prop65; other “lists”
    - NTP study data/abstracts/reports
    - OECD SIDS Documents
  - Tier 3* – Factual and bibliographic databases (including primary literature) (examples):
    - NLM TOXNET ; NLM PubMED; SCOPUS
    - TSCA Test Submissions (TSCA 8e submissions – test reports, etc.)
    - Vendor raw material SDSs, technical data sheets, etc.
    - Internet search (be careful)

*Search Tier 3 for significant new information and to fill in data gaps

Health Hazard Assessment - Process



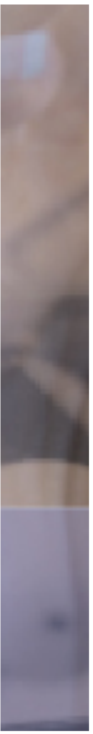
(2) Conduct a comprehensive review of the assembled toxicology/health hazard data

- Data on the chemical in question
- Data on an analog (single chemical and chemical class/group)
- Data from models

Practical reality: May need to use all these because of data gaps

- All *[adverse]* health hazard endpoints are considered
  - Remember: "Considerations" (see: slide 5)
    - "Adverse" health effect vs. a "non-adverse" effect is very important!

Health Hazard Endpoints[1]



- Acute Toxicity
  - Oral (LD_{50}), Dermal (LD_{50}), Inhalation (LC_{50})
- Skin Irritation or Corrosion
- Eye irritation or Corrosion
  - Serious Eye Damage
- Sensitization
  - Dermal and Respiratory
- Genotoxicity/Mutagenicity
  - Germ Cell Mutagenicity
- Carcinogenicity
- Reproductive Toxicity
- Specific Target Organ Toxicity - Single Exposure
- Specific Target Organ Toxicity - Repeated Exposure
- Aspiration Hazard

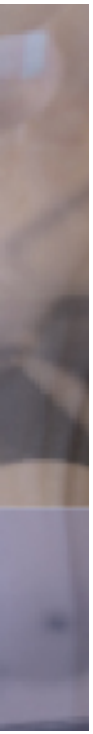
[1]See : Appendix A to 2012 OSHA HazCom Standard (1910.1200) and GHS (5th edition; 2013) for more detailed information on each endpoint

Health Hazard Assessment - Process

(3) Try to “fill” data gaps

- Often requires experience and professional judgment
- Re-visit the literature search strategy
  - Primary literature; updated databases, etc.
- Read-Across approach
  - Really brought to the forefront because of REACH
- QSAR
  - Involves computer modeling (*in silico* approaches)
    - Require specialized training, and equipment, etc.

Health Hazard Assessment - Process

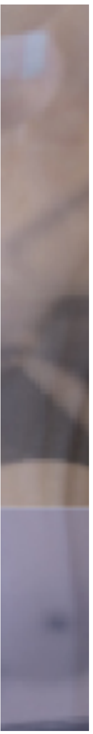


Read-Across (Analog Approach)

- A technique for data-gap filling where endpoint information from one chemical (source) is used to predict the same endpoint for another chemical (target) which is considered to be similar in some important aspect relating to that endpoint, *e.g. mode of action,* toxicokinetics, metabolism etc.
  - May be for a qualitative or quantitative

Source Chemical → Target Chemical

Health Hazard Assessment - Process



- Read-Across (Category Approach)
- Substances whose physicochemical and/or toxicological and/or ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity, may be considered as a group, or ‘category’ of substances
  - One very common “similarity” is a common functional group
    - Example: N=C=O (isocyante functional group)

Health Hazard Assessment - Process

(4) Document and Use the Health Hazard

- Can be done with the Health Hazard Profile (HHP)
  - Is a comprehensive document for a chemical for all endpoints assessed
  - Is peer-reviewed by at least two other toxicologists
  - Results (with interpretation, etc.) communicated to requestor(s)
    - Updating HazCom documents, labels, etc.
    - Regulatory classification of chemicals
    - Use in product development (safer alternative)
  - Results are also used as a starting point for risk/safety assessment by other toxicologists

Documentation: HHP

PARTIAL VIEW OF A SUBSTANCE HHP

Endpoint	Route	3M Hazard Code [GHS Classification]	Test Qualifier	Test Result	Endpoint Summary	Species	Exposure Duration
CAN Carcino-genicity	Inhalation	2 [Carcinogen, Category 2]	Carcino-genicity	Positive	EXPERIMENTAL/OCCUPATIONAL CONDITIONS & OBSERVATIONS: Ethylbenzene was tested by inhalation exposure in mice and rats. In mice, it increased the incidence of lung adenomas in males and of liver adenomas in females. In male rats, it increased the incidence of renal tubule adenomas and carcinomas. An increase in the incidence of renal adenomas was seen in females only after step-sectioning. Ethylbenzene is considered to be possibly carcinogenic to humans (IARC Group 2B). REFERENCE: IARC (2000). IARC Monographs, Volume 77. AUTHOR: [redacted] PEER REVIEWER: [redacted]	Multiple animal species	
CAR Cardiac (general) - P/R	Inhalation	0 [Not classified for Specific Target Organ Toxicity (Repeat Exposure)]	NOAEL	3.2 mg/L	EXPERIMENTAL/OCCUPATIONAL CONDITIONS & OBSERVATIONS: Male and female Fischer 344 rats exposed to ethylbenzene concentrations of 0, 75, 250, or 750 ppm (= 0, 0.32, 1.1, or 3.2 mg/L) for 6 hours/day, 5 days/week, for up to 2 years (103-104 weeks) displayed no adverse cardiovascular effects. REFERENCE: ATSDR (1999). Toxicological Profile for Ethylbenzene. AUTHOR: [redacted] PEER REVIEWER: [redacted]	Rat	2 years
NEU CNS depression	Inhalation	4 [Specific Target Organ Toxicity (Single Exposure), Category 3]	LOAEL	>0.43 mg/L	EXPERIMENTAL/OCCUPATIONAL CONDITIONS & OBSERVATIONS: In a human study, an 8-hour exposure above the occupational exposure limit value (100 ppm) generated complaints of fatigue, sleepiness, headache, and irritation of the eyes and respiratory tract. The LOAEL was therefore >100ppm (>0.43 mg/L). REFERENCE: IPCS (1996). EHC Monograph 186: Ethylbenzene. AUTHOR: [redacted] PEER REVIEWER: [redacted]	Human	8 hours

12 Principles of Green Chemistry

1. **Prevention**
   - It's better to prevent waste than to treat or clean up waste afterwards.
2. **Atom Economy**
   - Design synthetic methods to maximize the incorporation of all materials used in the process into the final product.
3. **Less Hazardous Chemical Syntheses**
   - Design synthetic methods to use and generate substances that minimize toxicity to human health and the environment
4. **Designing Safer Chemicals**
   - Design chemical products to affect their desired function while minimizing their toxicity.
5. **Safer Solvents and Auxiliaries**
   - Minimize the use of auxiliary substances wherever possible make them innocuous when used.
6. **Design for Energy Efficiency**
   - Minimize the energy requirements of chemical processes and conduct synthetic methods at ambient temperature and pressure if possible.
7. **Use of Renewable Feedstocks**
   - Use renewable raw material or feedstock rather whenever practicable.
8. **Reduce Derivatives**
   - Minimize or avoid unnecessary derivatization if possible, which requires additional reagents and generate waste.
9. **Catalysis**
   - Catalytic reagents are superior to stoichiometric reagents.
10. **Design for Degradation**
    - Design chemical products so they break down into innocuous products that do not persist in the environment.
11. **Real-time Analysis for Pollution Prevention**
    - Develop analytical methodologies needed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention**
    - Choose substances and the form of a substance used in a chemical process to minimize the potential for chemical accidents, including releases, explosions, and fires.

3M Products Designed Based on Green Chemistry Principles*

Made with 67% plant-based adhesive and recycled material **(# 5 & 7)**

3M™ Greener Post-it™

50% of the scrubbing fibers are made from agave plant **(# 7)**

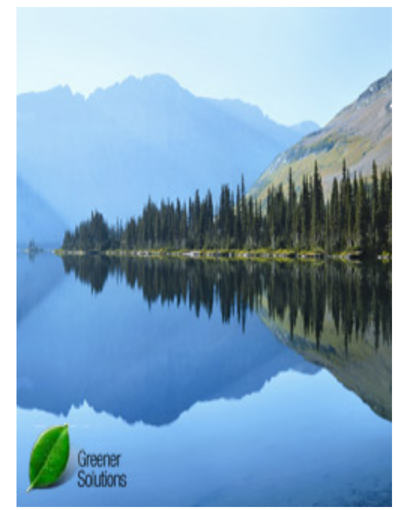
3M™ Scotchbrite™ Greener Clean™

Tape made from over 53% plant-based materials **(# 5 & 7)**

3M™ Greener Magic™

Zero solvent adhesive is non-flammable in its wet state, and contains no polychloroprene **(# 5)**

3M™ Fast Tack Water Based Adhesive 1000NF



non-polyvinyl chloride (non-PVC) graphic films **(# 3)**

3M™ Envision™ Products

*Courtesy of Keith Miller, 3M Sustainability

Thanks for joining us!

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