Chemical Agents

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Chemical Case Studies:

• Dyes and Drugs
• POPs: DDT, PCBs, Dioxin and Pesticides
• Chemical Contaminants in Foods
Chemical Case Studies:

- **Dyes and Drugs**
  - The organic chemistry revolution starting in the 1850’s was motivated by the desire to develop "color-fast" dyes, often with arsenic, for cotton fabrics. This then led to the initiation of the modern pharmaceutical industry that has produced many life saving drugs. A downside of this revolution was the production of many toxic and carcinogenic chemicals.

Dyes and the Start of the Chemical Industry

- 1856: Perkin synthesizes mauveine
- Picric acid (yellow)
- Exchange –OH with methyl group
- Badische Anilin und Soda Fabrik, Bayer, IG Farben (Syndicate of Dyestuff industry Corp.)
From Dyes to Drugs

• In 1932, Gerhard Dogmak, a doctor working at IG Farben, decided to use protosil red to treat his 6-year old daughter who was desperately ill with a streptococcal infection.

• She recovered in a couple of days and the era of antibiotics was launched.

• Prontisil red and sulfanilamide.

• Ehrlich creates chemotherapy (Salvarsan)
Chemical Case Studies:

- **Persistent Organic Pollutants (POPs): DDT, PCBs, Dioxin and Pesticides**
  - The explosion of the synthetic organic chemistry revolution led to the design of agents for specific uses, e.g. pesticides, but this also led to the release into the environment collateral chemicals with untoward hazard to health.
Persistent Organic Pollutants (POPs)

- Remain in the environment for a long time
- Can travel long distances
- Resist degradation
- Have found their way into every living organism on earth
- Exhibit a spectrum of toxicities

Examples of POPs

- DDT
- Polychlorinated biphenyls (PCBs)
- Hexachlorobenzene
- Aldrin
- Polychlorinated
- Endrin
- Toxaphene
- Furans
- Mirex
- Dieldrin
- Dioxins
- Chlordane
- Heptachlor

[Images of DDT, Dioxin, and PCBs]
Polychlorinated biphenyls (PCBs)

Banned in 1977, Monsanto was manufacturing 40 million pounds per year.

DDT

- 1874 – First synthesized by Othmar Zeidler. Zeidler, a graduate student of Adolf von Baeyer who had synthesized the dye indigo (1905 Nobel Prize in Chemistry).
- 1939 – Paul Hermann Müller discovered insecticidal properties of DDT; awarded 1948 Nobel Prize in Chemistry.
- 1940s – Rapid development to combat malaria and other mosquito-borne diseases.
- 1950s – A WHO campaign to eradicate malaria was based on spraying DDT. Marked reduction in malaria mortality rate was found, but increasing resistance to DDT was discovered.
- 1950s – Marked decline of bird populations, especially raptors like the peregrine falcon, osprey, and eagles, were observed.
- 1962 – Rachel Carson publishes *Silent Spring.*
DDT and Rachel Carson, JHU ‘32

Dioxin: Chemical Structure

2,3,7,8 - Tetrachlorodibenzo - p - dioxin (TCDD)

- By-product in commercial and technical products
- High temperature industrial processes
- Incineration plants
- The pulp and paper industry
- Traffic exhausts
- Cigarette smoke
TCDD Toxicity Varies Greatly Among Species

<table>
<thead>
<tr>
<th>Species</th>
<th>$LD_{50}$ (µg per kg)</th>
</tr>
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<tbody>
<tr>
<td>Guinea pig</td>
<td>0.6 - 2.5</td>
</tr>
<tr>
<td>Mink</td>
<td>4</td>
</tr>
<tr>
<td>Rat</td>
<td>22 - 320</td>
</tr>
<tr>
<td>Monkey</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>Rabbit</td>
<td>115 - 275</td>
</tr>
<tr>
<td>Mouse</td>
<td>114 - 280</td>
</tr>
<tr>
<td>Dog</td>
<td>&gt;100 - &lt;3000</td>
</tr>
<tr>
<td>Hamster</td>
<td>1150 - 5000</td>
</tr>
</tbody>
</table>

Source: Environmental Protection Agency

Toxic Effects of TCDD

- Death
- Wasting syndrome
- Thymic atrophy
- Splenic atrophy
- Testicular atrophy
- Liver enlargement, fatty deposits, necrosis
- Hyperplasia: Gastric mucosa, urinary tract
- Bile duct
- Squamous metaplasia: Melbomian glands, sebaceous glands
- Chloracne: Hyperplasia, hyperkeratosis, altered pigmentation
- Teratogenesis
- Carcinogenesis
- Immunosuppression
- Enzyme induction
- Biochemical alterations
Major Human Exposures to Dioxin

• 1949: 250 workers exposed in Nitro, WV, 122 cases of chloracne.

• 1964: 61 workers at Dow Chemical exposed, 49 cases of chloracne

• Between 1962 and 1971, the US military sprayed nearly 20,000,000 US gallons of chemical herbicides and defoliants in Vietnam, eastern Laos and parts of Cambodia, as part of Operation Ranch Hand.

• 1976: Servaso Italy, explosion at a 2,4,5-T plant.

• 1970s-1982: Times Beach, MO: roads sprayed with contaminated oil for dust control.

Organophosphate Pesticides:

Pesticides found in deadly school lunch in India, CNN, updated 11:17 AM EDT, July 20, 2013

• **Monocrotophos** is a highly toxic organophosphate insecticide that has been discontinued from use in the United States but is still used internationally.

• **Monocrotophos** is a highly toxic, broad spectrum, fast-acting cholinesterase inhibitor. It is highly toxic via all three routes of exposure - oral, dermal, and through inhalation. The oral LD₅₀ 17 mg/kg in male rats and 20 mg/kg in female rats.

• Early symptoms of poisoning may include excessive sweating, headache, weakness, giddiness, nausea, vomiting, hypersalivation, abdominal cramps, diarrhea, blurred vision and slurred speech.

• These compounds are responsible for about 250,000 deaths each year, major agent in suicides around the world (WHO, 2007).

http://toxipedia.org/display/toxipedia/Monocrotophos
Easy availability of pesticides has made self-poisoning the most common means to commit suicide in Sri Lanka.

Comparison of methods used for fatal self harm in England and Wales, Australia, and Asia.
Chemical Case Studies:

- **Chemical Contaminants in Foods**
  
  - Over a century ago, legislation in response to toxicity of food additives and bacterial contamination led to the implementation of food safety laws. This has become much more complicated in the last 25 years due to globalization of the food supply. Further, concerns are now raised from how foods are processed leading to the generation of toxic chemicals.
"To enable the Secretary of Agriculture to investigate the character of food preservatives, coloring matters, and other substances added to foods, to determine their relation to digestion and to health, and to establish the principles which should guide their use."

The Poison Squad

Borax, Salicylic acid, Sulfuric acid, Sodium benzoate, Formaldehyde

Candy Color

- Red sulfuret (mercury sulfide)
- Verdigris (copper acetate)
- Blue vitriol (copper sulfate)
  - Sugar of lead (lead acetate)
  - White lead (lead carbonate)
- Scheele’s green (copper arsenite)
Food Safety Over the Last 100 Years

- **Food and Drug Act of 1906**: Dr. Harvey Wiley, then director of the USDA’s Bureau of Chemistry, spurred Congress to pass and President Theodore Roosevelt to sign the 1906 Food and Drug Act. The 1906 Act prohibited the marketing of adulterated and misbranded food and drugs.

- **Federal Food, Drug and Cosmetic Act of 1938**: In 1937, nearly 100 people died after ingesting a product called Elixir Sulfanilamide, which was prepared using diethylene glycol.
  - Although the manufacturer technically violated the 1906 Act because the product was called an elixir (by definition this is supposed to contain alcohol, and this product did not), the company’s failure to test the product for safety and to label the product adequately were not violations of the law.
  - The 1938 Act compelled manufacturers to demonstrate to the FDA the safety of new drugs...; set tolerances for substances such as pesticides; extended regulation to color additives and cosmetics.

- **Food Additive Amendment of 1958 and Color Additive Amendments of 1960**: These amendments required pre-market approval by the FDA of food components and color additives not "generally recognized as safe" by the scientific community. The use of additives that are shown to be carcinogenic in animals or humans is prohibited.

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**Melamine**

- Used to make urea
- Used for melamine resins
- Flame retardant
- Causes renal failure

\[
\text{Melamine: } \begin{array}{c}
\text{N} \\
\text{N} \\
\text{H}_2\text{N} \\
\text{\textbf{H}_2\text{N}} \\
\text{\textbf{NH}_2}
\end{array}
\]
Melamine

- Wheat/rice/corn washed with water to remove starch leaving gluten (protein)
- Thickener, elasticity and meat substitute
- Very inexpensive
Melamine in Milk Products for Humans

- Melamine contaminated milk blamed for 4 deaths and 54,000 sick children
  (Washington Post, October 6, 2008)
- Melamine found in 31 brands of milk in China
  (Washington Post, October 1, 2008)
- Melamine found in Cadbury Chocolates in Hong Kong
  (NY Times, October 5, 2008)

Melamine: Why is it a food adulterant?
Protein Content in Foods Measured by Kjeldahl Method

- Kjeldahl Method for Nitrogen Determination developed nearly 125 years ago
- Digest protein with sulfuric acid, neutralize with base and distill off the ammonia that is trapped
- Ammonia content is surrogate for nitrogen content in protein

Food Safety Over the Last 100 Years

- **Food and Drug Act of 1906:**
- **Federal Food, Drug and Cosmetic Act of 1938:**
- **Food Additive Amendment of 1958 and Color Additive Amendments of 1960:**
- **Dietary Supplement & Health Act of 1994 (DSHEA):**
Dietary Supplement & Health Act of 1994 (DSHEA)

- Drugs: Intensively regulated by U.S. Food & Drug Administration (FDA).
- Dietary supplements: Limited regulation by FDA.
  - Can only be withdrawn if FDA can prove clear and present danger
  - Unlike drugs, onus is on FDA to prove danger, not manufacturer to prove safety
  - Supplement must pose “a significant or unreasonable risk of illness or injury” before FDA can take action
- Congress recently added new requirements for certification of purity of dietary supplements to current law – DSHEA.

Special thanks to Dr. Harold Lieberman
Dietary Supplement & Health Act of 1994 (DSHEA): Consequences

• Dietary supplements are not subject to pre-market FDA approval unless they contain a “New Dietary Ingredient”.

• Demonstration of Safety & Efficacy by manufacturer is not required; but claims are restricted

• Most naturally-occurring substances, except those already classified as drugs, can be labeled as a dietary supplement.
  – For example: ephedra, melatonin

• Clinical trials of supplements are not regulated by the FDA.

• Without “National Standards” that establish safety and efficacy, what processes for monitoring supplement use and abuse since ~70% of young adults regularly take a DS or related product.

Special thanks to Dr. Harold Lieberman

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Emergency Department Visits for Adverse Events Related to Dietary Supplements


**ABSTRACT**

**BACKGROUND**

Dietary supplements, such as herbal or complementary nutritional products and micronutrients (vitamins and minerals), are commonly used in the United States, yet national data on adverse effects are limited.

**METHODS**

We used nationally representative surveillance data from 63 emergency departments obtained from 2004 through 2013 to describe visits to U.S. emergency departments because of adverse events related to dietary supplements.

**RESULTS**

On the basis of 3667 cases, we estimated that 23,095 (95% confidence interval [CI], 18,611 to 27,998) emergency department visits per year were attributed to adverse events related to dietary supplements. These visits resulted in an estimated 2154 hospitalizations (95% CI, 1342 to 2967) annually. Such visits frequently involved young adults between the ages of 20 and 34 years (28.0% of visits; 95% CI, 23.7% to 32.4%) and non-Hispanic white children (9.8% of visits; 95% CI, 4.3% to 15.4%).

From the Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention (A.I.G., N.J.W., M.C.L., D.S.B.), and change Government Consulting (R.P.M.) — both in Atlanta; and the Center for Food Safety and Applied Nutrition and the Division of Public Health Informatics and Analytics (R.B.M., B.S.T.) and the Division of Dietary Supplement Programs (R.B.M.), Food and Drug Administration, Rockville, MD. Address reprint requests to Dr. Geller at the Division of Healthcare Quality Promotion, CDC, 1825 Century Blvd, NE, Mailstop G-26, Atlanta, GA 30341, or at ageller@dcd.gov.

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Large, Well-Controlled Clinical Trials of Promising Dietary Supplements and a Meta-Analysis

1. Effect of *Hypericum perforatum* (St. John’s Wort) in Major Depressive Disorder: A Randomized Controlled Study; *Journal of the American Medical Association*, 2002.
   - **No beneficial effect**

2. Effects of Long-Term Vitamin E Supplementation on Cardiovascular Events and Cancer: A Randomized Controlled Trial; The HOPE and HOPE-TOO Trial; *Journal of the American Medical Association*, 2005.
   - **Significant adverse effects** (13% greater incidence of heart failure in patients at high risk for cardiovascular disease)

Special thanks to Dr. Harold Lieberman

Large, Well-Controlled Clinical Trials of Promising Dietary Supplements and a Meta-Analysis

3. Effect of Raw Garlic vs. Commercial Garlic Supplements on Plasma Lipid Concentrations in Adults with Moderate Hypercholesterolemia: A Randomized Clinical Trial; *Archives of Internal Medicine*, 2007.
   - **No beneficial effects**

   - **Treatment with beta carotene, vitamin A and vitamin E may increase mortality**

   - **No beneficial effects**

Special thanks to Dr. Harold Lieberman
Extracts of *Ginkgo biloba* tree are used as an herbal remedy and dietary supplement purported to improve memory and brain function

- 2013 Toxicology and Carcinogenesis Studies of *Ginkgo biloba* Extract in Rats and Mice; conducted by National Toxicology Program, NIH

- **Increased prevalence of thyroid and liver cancer; especially in males**

  $\text{N} = \text{over 1000 animals}$

  ~$250$ million in US sales

Special thanks to Dr. Harold Lieberman

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*The Package*
Bisphenol A (BPA) Production and Use

- Annual worldwide production: >6 billion lbs.
- Found in items made of polycarbonate plastic or lined with epoxy resin. Also found in surface coating of thermal printing papers.
  - Electronics, car parts, dental sealants, food and drink cans, water bottles, medical equipment, recycled paper, paper receipts.

Adapted from R. Nachman

BPA Exposure in Humans

- NHANES: Detectable in the urine of >90% of U.S. population age 6 yrs & older
- Diet is main route of exposure (NTP 2008)
- Main source of exposure in general population is food packaging
  - Canned food
  - Reusable water bottles
  - Baby bottles
  - Formula packaging
  - Baby food packaging
  - Breast milk

Adapted from R. Nachman
Bisphenol A (BPA): An Endocrine Disruptor

Health endpoints of concern
- Diabetes
- Heart disease
- Cancer
- Obesity
- Thyroid effects
- Reproductive effects
- Developmental effects (brain and prostate)

In Situ Production of Toxins
Acrylamide: A Carcinogen

Emerging issues of carcinogens formed by cooking foods
Health risks?

Acrylamide

- MW = 71.08, MP = 84.5°C, BP = 125°C
- Acrylamide (water-soluble polymers) used for water treatment, flocculants, contact lenses, and permanent press fabrics.
- The largest use for polyacrylamide is in treating municipal drinking water and wastewater.
- Acrylamide is classified as a carcinogen by US EPA. Damages the testes, the nervous system, causes numbness and "pins and needles".
- Exposure to acrylamide irritates the eyes, nose, throat, skin and can also cause loss of balance, slurred speech, and heavy sweating.
Markers of Biologically-Effective Dose

Assessment of the interactions of toxicants with their molecular targets

• DNA adducts
  – Cellular DNA: e.g., benzo[a]pyrene-DNA adducts in peripheral lymphocytes of coke oven workers; cisplatinum-DNA adducts in WBC of chemotherapy patients;

• Protein adducts
  – Hemoglobin: Ethylene oxide, aromatic amines, tobacco-specific nitrosamines, cisplatinum
  – Albumin: Aflatoxin B₁

Sample Survey Results

<table>
<thead>
<tr>
<th>Food Product</th>
<th>Acrylamide (μg/kg, ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toasted English Muffin, 5min</td>
<td>50</td>
</tr>
<tr>
<td>Tortilla Chips</td>
<td>97</td>
</tr>
<tr>
<td>Baby Food Potatoes</td>
<td>101</td>
</tr>
<tr>
<td>Banana Chips</td>
<td>125</td>
</tr>
<tr>
<td>Roasted Asparagus</td>
<td>143</td>
</tr>
<tr>
<td>Pretzels</td>
<td>196</td>
</tr>
<tr>
<td>Hearty Rye Crispbread</td>
<td>242</td>
</tr>
<tr>
<td>Baked Potato Chips</td>
<td>317</td>
</tr>
<tr>
<td>Corn Chips</td>
<td>331</td>
</tr>
<tr>
<td>Cooked Taco Shell</td>
<td>559</td>
</tr>
<tr>
<td>Blue Potato Chips</td>
<td>736</td>
</tr>
<tr>
<td>Kettle Potato Chips</td>
<td>3400</td>
</tr>
</tbody>
</table>
Effect of Temperature on Acrylamide Formation (ppb)

Temperature (°C) 110 130 150
Acrylamide: A Carcinogen

Acrylamide Formation from frying
- Potato starch <50 ppb
- Potato starch + asparagine 117 ppb
- Potato starch + dextrose + asparagine 9270 ppb

* 6 in 10,000 lifetime cancer risk