



# TOXICOLOGY

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Lecture 2 - Thursday

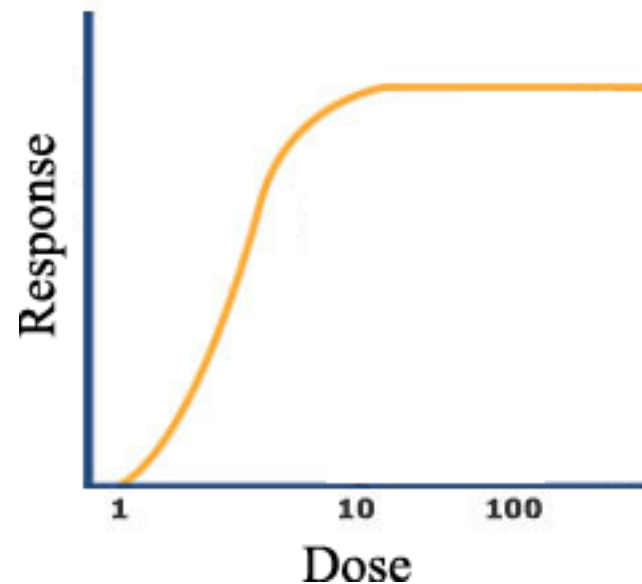
ENVH 111

11/03/11

Megan Cartwright

# Toxicology recap

- *Toxicant* – a man-made or natural substance exogenous (foreign) to the body that can kill or cause damage
- Damage is determined by:
  - Dose
  - Route of exposure
  - Duration of exposure
  - Toxicant's properties
  - Individual factors



# Toxicology recap

- Damage can occur through:
  - Alterations in cellular death (*apoptosis, necrosis*)
  - Damage to DNA, RNA, proteins, enzymes
  - Depletion of cellular protective mechanism
  - Allergic reaction to a chemical

# Toxicant case studies

- Pesticides: organophosphate insecticides
- Polycyclic aromatic hydrocarbons: benzo[a]pyrene
- Heavy metals: lead
- Mercury, thimerosal, and autism

# Pesticides

- Substance intended to destroy or repel pests
- Pests can include weeds, rodents, insects, fungi

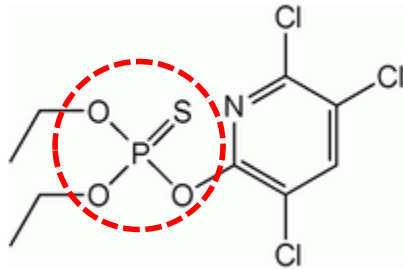


# Pesticides

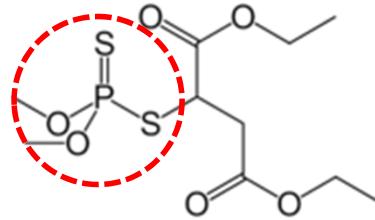
- Used in agriculture, home, garden, schools, offices, hospitals
- 2001: 4.9 billion lbs. of pesticides in U.S. (4.5 lbs./person!)
- Ideal pesticide would be highly specific, quick acting, and degrade quickly to harmless materials
- 2004: 3 million pesticide poisonings, 250,000 deaths worldwide

# Organophosphate insecticides

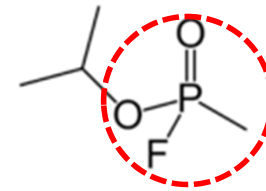
- > 50% of pesticides used are organophosphates (OPs)



chlorpyrifos



malathion

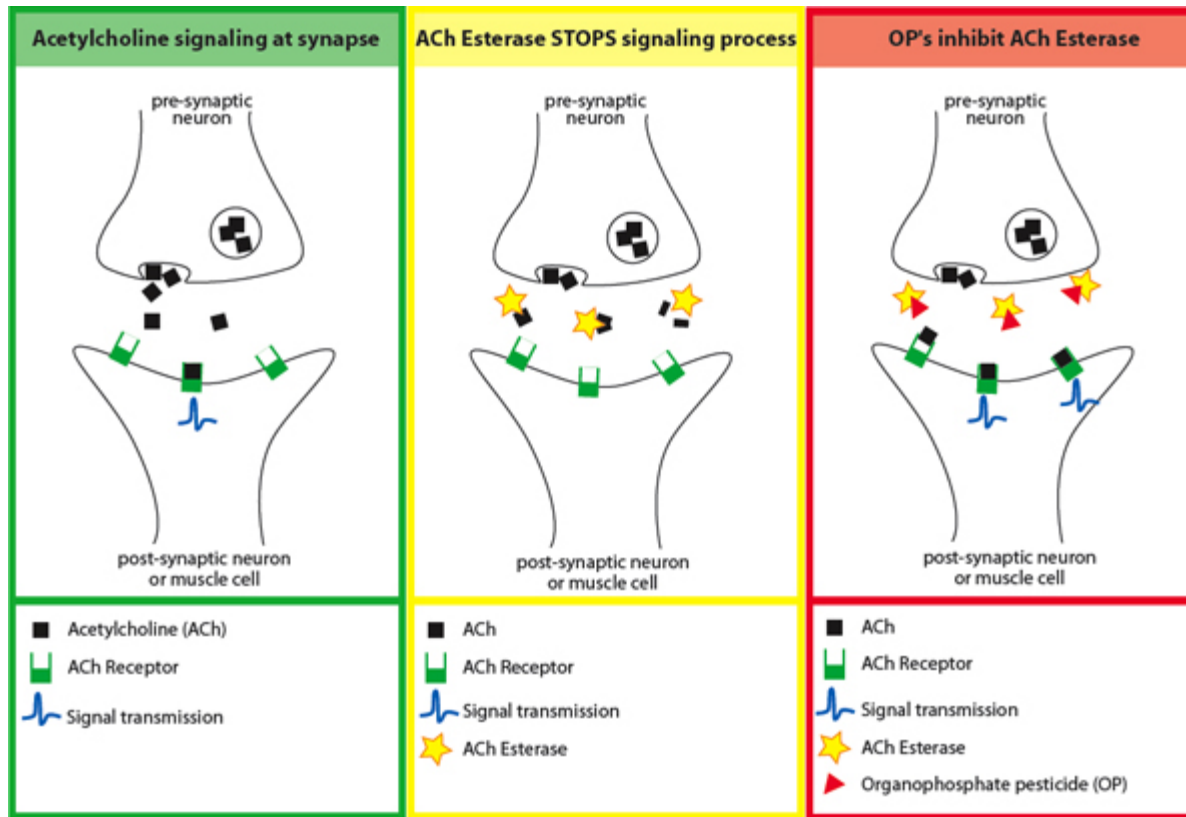


sarin

- Exposure through dermal, oral, inhalation routes usually among agricultural workers

# Organophosphate insecticides

- Target the nervous system by inhibiting *acetylcholinesterase* (AChE)



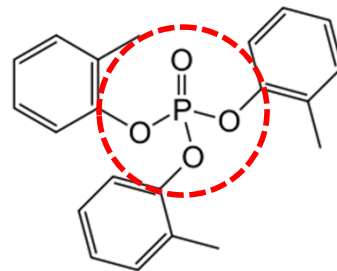


# Organophosphate insecticides

- Acute exposure leads to *cholinergic crisis* – sweating, salivation, tremors, paralysis, vomiting, convulsions
- Death due to inhibition of respiratory control in the brain and paralysis of respiratory muscles
- Only prompt treatment can prevent death:
  - Atropine – blocks excess acetylcholine from interacting with muscarinic receptors
  - Oximes – restore function of acetylcholinesterase

# Organophosphate insecticides

- Certain OPs can cause *OP-Induced Delayed Neuropathy* (OPIDN) by inhibiting *neuropathy target esterase*
- Degeneration of long axon terminals leads to paralysis
- 1930: “Ginger Jake” syndrome caused by contamination of bootleg “medicinal” liquor with an OP



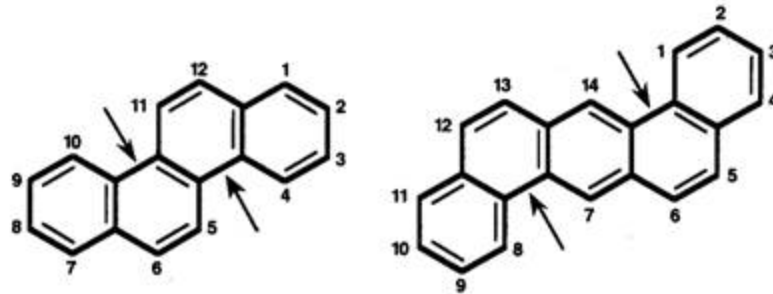
tri-ortho-cresyl phosphate

# Organophosphate insecticides

- OPs are neurotoxicants – targeting the nervous system
- Damage occurs through *inhibition of cellular enzymes*

# Polycyclic aromatic hydrocarbons

- Polycyclic aromatic hydrocarbons (PAHs) form when organic material not completely combusted

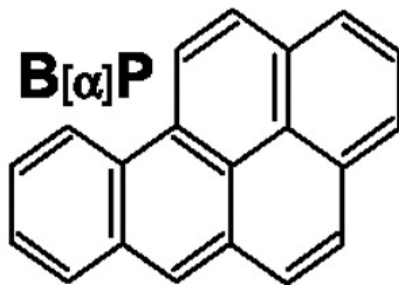


- Common sources include tobacco, wood, gas, oil, coal smoke
- Exposure usually occurs through inhalation



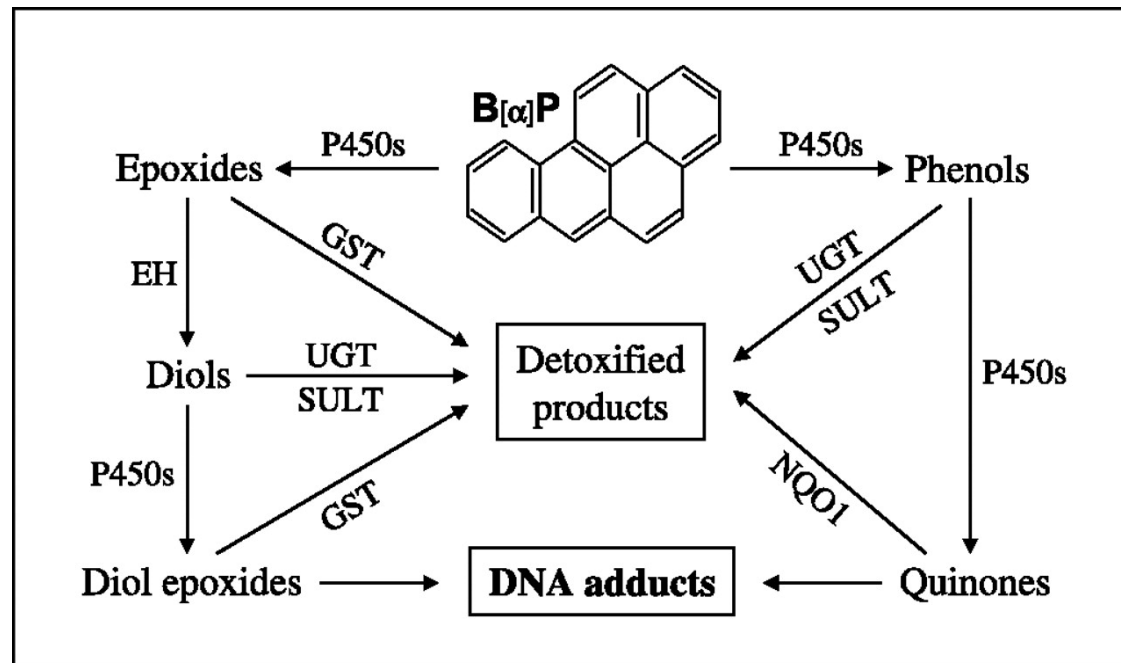
# PAHs – Benzo[a]pyrene

- Epidemiological association between occupational exposure to PAHs and lung, bladder, skin cancer
- Strong evidence in lab animals for PAHs being carcinogenic and *mutagenic* – altering or destroying DNA
- Benzo[a]pyrene is a classic PAH found in cigarette smoke, diesel exhaust, and asphalt mixing



# PAHs – Benzo[a]pyrene

- Benzo[a]pyrene (B[a]P) is metabolized by the same enzymes (cytochrome P450s, epoxide hydrolases) to different metabolites



# PAHs – Benzo[a]pyrene

- B[a]P's toxic metabolite interacts with DNA to form an *adduct* - a bulky structure that blocks or alters DNA's normal functions
- B[a]P is both a mutagen – because it alters the chemical structure of DNA – and a carcinogen, because it is associated with cancer development



# PAHs – Benzo[a]pyrene

- B[a]P is a mutagen and a carcinogen
- Damage occurs through *alteration of DNA* and ultimately carcinogenesis



# Heavy metals


- Many metals (Cu, Zn, Fe) essential to life, e.g. proper enzyme function, oxygen transport, etc.
- Metal toxicity typically due to:
  - Excess of an essential metal – e.g. iron poisoning
  - The body mistaking a non-essential metal for an essential element

# Heavy metals

- “Mistakes” due to similar chemical properties between different elements, e.g. charge, size, etc.

**IUPAC Periodic Table of the Elements**

1																		2														
1 H hydrogen 1.007 94(7)																		2 He helium 4.002 602(2)														
3 Li lithium 6.941(2)	4 Be beryllium 9.012 182(3)																	5 B boron 10.811(7)	6 C carbon 12.0107(8)	7 N nitrogen 14.0067(2)	8 O oxygen 15.9994(3)	9 F fluorine 18.998 4032(5)	10 Ne neon 20.1797(6)									
11 Na sodium 22.989 769 28(2)	12 Mg magnesium 24.3050(6)																	13 Al aluminium 26.981 538 6(8)	14 Si silicon 28.0855(3)	15 P phosphorus 30.973 762(2)	16 S sulfur 32.065(5)	17 Cl chlorine 35.453(2)	18 Ar argon 39.948(1)									
19 K potassium 39.0983(1)	20 Ca calcium 40.078(4)	21 Sc scandium 44.955 912(6)	22 Ti titanium 47.867(1)	23 V vanadium 50.9415(1)	24 Cr chromium 51.9961(6)	25 Mn manganese 54.938 045(5)	26 Fe iron 55.845(2)	27 Co cobalt 58.933 195(5)	28 Ni nickel 58.6934(2)	29 Cu copper 63.546(3)	30 Zn zinc 65.409(4)	31 Ga gallium 69.723(1)	32 Ge germanium 72.64(1)	33 As arsenic 74.921 60(2)	34 Se selenium 78.96(3)	35 Br bromine 79.904(1)	36 Kr krypton 83.798(2)															
37 Rb rubidium 85.4678(3)	38 Sr strontium 87.62(1)	39 Y yttrium 88.905 85(2)	40 Zr zirconium 91.224(2)	41 Nb niobium 92.906 38(2)	42 Mo molybdenum 95.94(2)	43 Tc technetium [98]	44 Ru ruthenium 101.07(2)	45 Rh rhodium 102.905 50(2)	46 Pd palladium 106.42(1)	47 Ag silver 107.8682(2)	48 Cd cadmium 112.411(8)	49 In indium 114.818(3)	50 Sn tin 118.710(7)	51 Sb antimony 121.760(1)	52 Te tellurium 127.60(3)	53 I iodine 126.904 47(3)	54 Xe xenon 131.293(6)															
55 Cs caesium 132.905 451 9(2)	56 Ba barium 137.327(7)	57-71 lanthanoids	72 Hf hafnium 178.49(2)	73 Ta tantalum 180.947 88(2)	74 W tungsten 183.84(1)	75 Re rhenium 186.207(1)	76 Os osmium 190.23(3)	77 Ir iridium 192.217(3)	78 Pt platinum 195.084(9)	79 Au gold 196.966 569(4)	80 Hg mercury 200.59(2)	81 Tl thallium 204.3833(2)	82 Pb lead 207.2(1)	83 Bi bismuth 208.980 40(1)	84 Po polonium [209]	85 At astatine [210]	86 Rn radon [222]															
87 Fr francium [223]	88 Ra radium [226]	89-103 actinoids	104 Rf rutherfordium [261]	105 Db dubnium [262]	106 Sg seaborgium [266]	107 Bh bohrium [264]	108 Hs hassium [277]	109 Mt meitnerium [268]	110 Ds darmstadtium [271]	111 Rg roentgenium [272]																						
																		57 La lanthanum 138.905 47(7)	58 Ce cerium 140.116(1)	59 Pr praseodymium 140.907 65(2)	60 Nd neodymium 144.242(3)	61 Pm promethium [145]	62 Sm samarium 150.36(2)	63 Eu europium 151.964(1)	64 Gd gadolinium 157.25(3)	65 Tb terbium 158.925 35(2)	66 Dy dysprosium 162.500(1)	67 Ho holmium 164.930 32(2)	68 Er erbium 167.259(3)	69 Tm thulium 168.934 21(2)	70 Yb ytterbium 173.04(3)	71 Lu lutetium 174.967(1)
																		89 Ac actinium [227]	90 Th thorium 232.038 06(2)	91 Pa protactinium 231.036 88(2)	92 U uranium 238.028 91(3)	93 Np neptunium [237]	94 Pu plutonium [244]	95 Am americium [243]	96 Cm curium [247]	97 Bk berkelium [247]	98 Cf californium [251]	99 Es einsteinium [252]	100 Fm fermium [257]	101 Md mendelevium [258]	102 No nobelium [259]	103 Lr lawrencium [262]



**Notes**

- 'Aluminium' and 'caesium' are commonly used alternative spellings for 'aluminum' and 'caesrium'.
- IUPAC 2005 standard atomic weights (mean relative atomic masses) are listed with uncertainties in the last figure in parentheses [M. E. Wieser, Pure Appl. Chem. 78, 2051 (2006)].
- These values correspond to current best knowledge of the elements in natural terrestrial sources. For elements that have no stable or long-lived nuclides, the mass number of the nuclide with the longest confirmed half-life is listed between square brackets.
- Elements with atomic numbers 112 and above have been reported but not fully authenticated.

Copyright © 2007 IUPAC, the International Union of Pure and Applied Chemistry. For updates to this table, see [http://www.iupac.org/reports/periodic\\_table/](http://www.iupac.org/reports/periodic_table/). This version is dated 22 June 2007.

# Heavy metals - lead

- Used in metal alloys, glazes and paints, batteries, radiation shields, water pipes, gasoline additives, etc.



# Heavy metals - lead

- Lead associated with renal (kidney) toxicity, hypertension, immune alterations, brain, stomach, lung, and bladder cancer
- Lead has different neurotoxic and skeletal effects in adults and children



# Heavy metals - lead

- Adults:
  - Occupational exposures
  - Degeneration of myelin sheaths on neurons leads to peripheral neuropathy, e.g. house painter “wristdrop”
- Children:
  - Ingestion of paint chips
  - Lead absorbed in place of calcium
  - Disruption of calcium homeostasis affects neurotransmitters, neurons, and leads to mental retardation
  - Lead taken up into bone instead of calcium

# Heavy metals - lead

- Lead is a developmental toxicant, neurotoxicant, renal toxicant, immunotoxicant, and carcinogen
- Damage caused through *interactions with proteins* and *depletion of protective mechanisms*

# Mercury, thimerosal, and autism

- Autism spectrum disorders (ASDs) are developmental disabilities associated with the brain
- Associated with social and communication impairments
- Also associated with mental retardation
- Prevalence of 0.6 – 1.0% (36,500 out of 4 million born every year in U.S.)
- Rates of diagnosis have increased through heightened awareness and screening

# Mercury, thimerosal, and autism

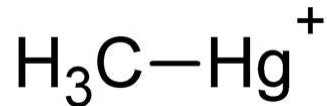
- Methyl mercury long recognized as developmental toxicant and neurotoxicant
- Infamously associated with 1956 Minamata Bay disaster, which permanently damaged or killed > 2,000 people in Japan



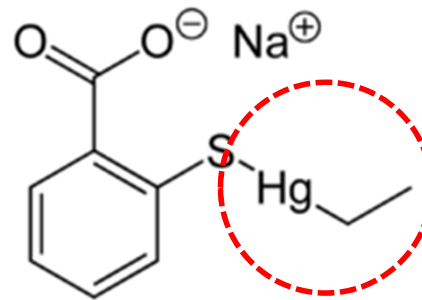


# Mercury, thimerosal, and autism

- Thimerosal is an antimicrobial preservative used since 1930 to prevent contamination of vaccines
- Contains ethyl mercury, not methyl mercury



methyl  
mercury



ethyl  
mercury

- Never previously associated with human poisonings
- No to minimal renal toxicity observed in lab animals

Offit PA. "Thimerosal and Vaccines – A Cautionary Tale." *N Engl J Med* 2007; 357:1278-1279.

Liu J et al. "Toxic Effects of Metals." *Casarett & Doull's Toxicology: The Basic Science of Poisons*. Ed. Klassen, CD. New York: McGraw Hill Medical, 2008. 931-979. Print

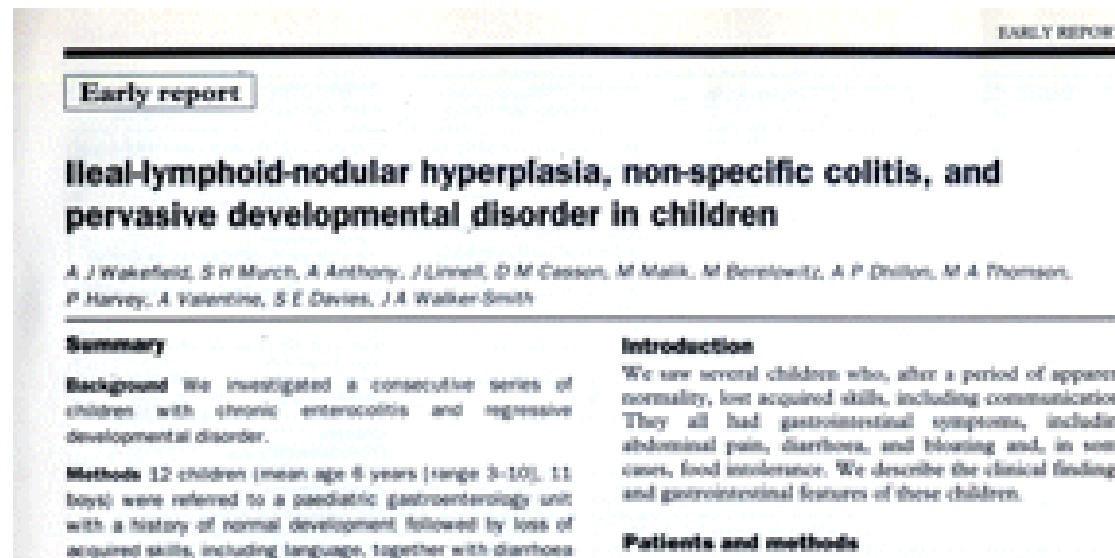
Clarkson TW et al. "The Toxicology of Mercury – Current Exposures and Clinical Manifestations." *N Engl J Med* 2003; 349:1731-1737.

# Mercury, thimerosal, and autism

- 1997: U.S. Congressman Frank Pallone added a rider to the FDA Modernization Act of 1997
- FDA given 2 years to “*compile a list of drugs and foods that contain intentionally introduced mercury compounds and [to] provide a quantitative and qualitative analysis of the mercury compounds in the list*”

# Mercury, thimerosal, and autism

- 1998: *The Lancet* publishes case series article by Wakefield *et al.* implying a link between the measles, mumps, and rubella (MMR) vaccine and a new syndrome of autism and bowel disease



# Mercury, thimerosal, and autism

- May 1999: FDA found that by 6 months of age, infants could receive up to 187.5 ug of ethyl mercury from vaccines
- While EPA and Agency for Toxic Substances and Disease Registry had safety guidelines for methyl mercury, did not have guidelines set for ethyl mercury
- July 1999: CDC and American Academy of Pediatrics decide to go with *precautionary principle* and, using the guidelines for methyl mercury, asked manufacturers to remove thimerosal from vaccines

# Mercury, thimerosal, and autism

- Precautionary principle assumes no harm in being cautious
- 2000: anti-vaccine advocacy groups formed around belief that thimerosal had caused autism in children



# Mercury, thimerosal, and autism

- Vaccines provide protection for both the vaccinated and the unvaccinated through *herd immunity*
- Vaccines are essential in preventing harm and death
  - 2002: 2 million child deaths worldwide from vaccine-preventable diseases (294,000 pertussis, 386,000 Hib, 540,000 measles)
  - 2002: 600,000 deaths in adults due to Hep B
- It is not possible to stop vaccinating without serious harm

# Mercury, thimerosal, and autism

- 2004: first epidemiological studies from U.K. examining thimerosal in vaccines found no association with neurodevelopmental or psychological problems
- 2007: additional epidemiological studies in both U.K. and U.S. found no association

# Mercury, thimerosal, and autism

- Parents of 4800 autistic and developmentally delayed children filed cases for compensation through federal Vaccine Injury Compensation Program (VICP)
- VICP has broad authority to legally determine injury causation



# Mercury, thimerosal, and autism

- Three test cases considered to have the best claims were heard by the VICP
- Over 28 medical experts, 50 expert reviews, 900 scientific articles, and 5000 pages of proceedings used to come to decision
- 2009: *“The overall weight of the evidence is overwhelmingly contrary to the petitioners’ causation theories...Unfortunately, the Cedillos [a family filing suit] have been misled by physicians who are guilty...of gross medical misjudgment”*

# Mercury, thimerosal, and autism

- 2010: *The Lancet* formally retracts Wakefield's 1998 paper linking MMR and developmental disorders
- While writing the final draft, Wakefield altered patients' case histories and falsified lab data
- Wakefield also did not disclose a conflict of interest – he was financially involved in a lawsuit against MMR vaccine manufacturers, and had instigated the study at the request of attorneys

# Mercury, thimerosal, and autism

- 2007 – 2011: in U.S., >84,000 vaccine-preventable illnesses, 738 deaths attributed to unvaccinated
- 2011: U.K. vaccination rates still below herd immunity levels (95%)
  - WHO declared measles endemic in England and Wales

## Further reading

- “Wakefield’s article linking MMR vaccine and autism was fraudulent.” Godlee et al., *British Medical Journal* 2011:  
<<http://www.bmj.com/content/342/bmj.c7452.full>>
- “Thimerosal and Vaccines – A Cautionary Tale.” Offit, *N Engl J Med* 2007:  
<<http://www.nejm.org/doi/full/10.1056/NEJMp078187>>
- “How the case against the MMR vaccine was fixed.” Deer, *British Medical Journal* 2011:  
<<http://www.bmj.com/content/342/bmj.c5347.full>>

## Further reading

- *Autism's False Prophets: Bad Science, Risky Medicine, and the Search for a Cure* by Dr. Paul Offit
- *The Poisoner's Handbook: Murder and the Birth of Forensic Medicine in Jazz Age New York* by Deborah Blum
- *Silent Spring* by Rachel Carson
- *Intuition* by Allegra Goodman