Environmental

Emerging Contaminants in Drinking Water

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Abraham Maslow

- ***What you don't know has power over you; knowing it brings it under your control, and makes it subject to your choice. Ignorance makes real choice impossible.***

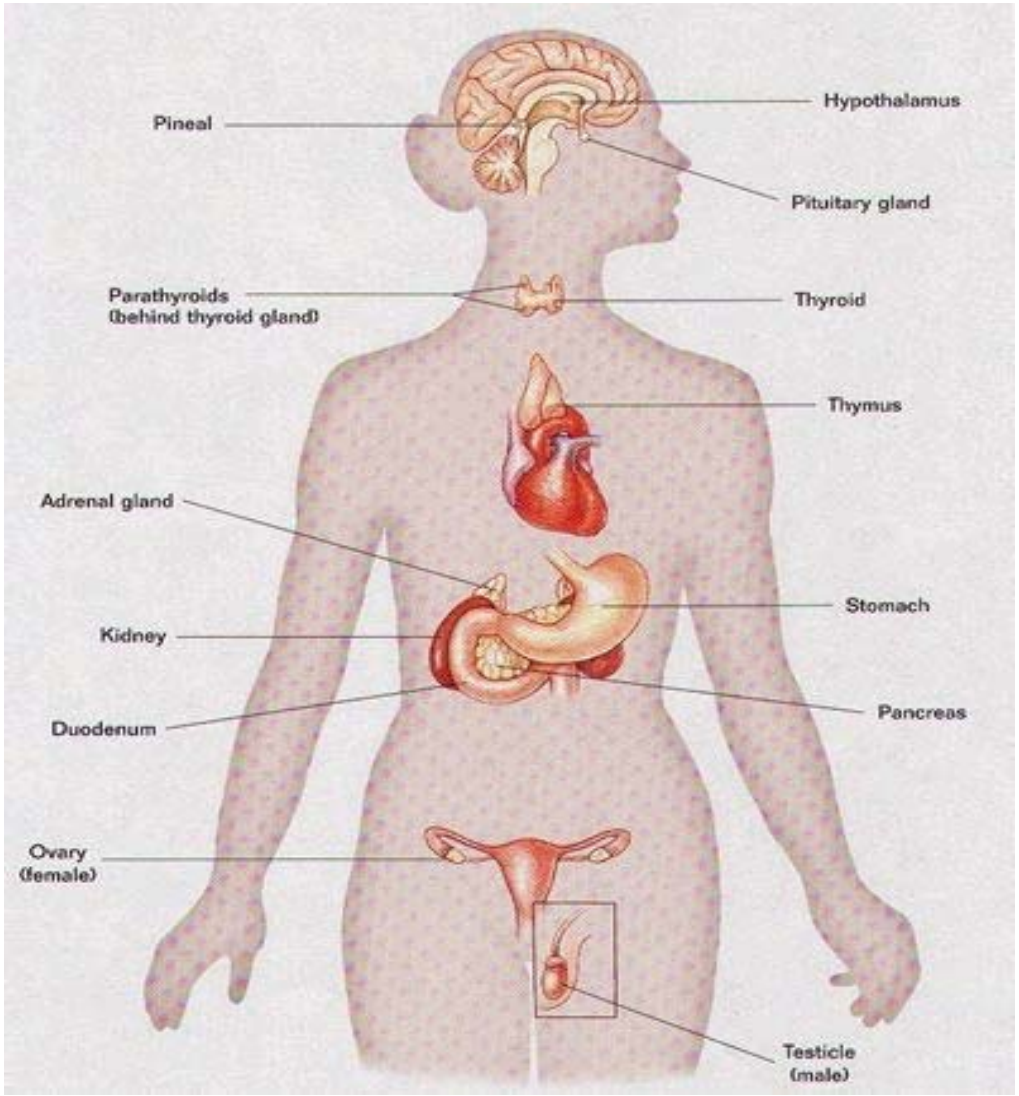
The Problem

- Credible scientific study is emerging, which raises disquieting evidence about the potential for environmental toxicants to profoundly affect the health and well-being of individuals at all stages of life—from the microscopic embryo within the amniotic sac to the toddler on the playground; from the child in a classroom to the robust adolescent and from the young adult in the workplace to the senior in a nursing home
- Ref: S.J. Genuis (2006). ***Human Reproduction***, 21: 2201-2208

Current Science

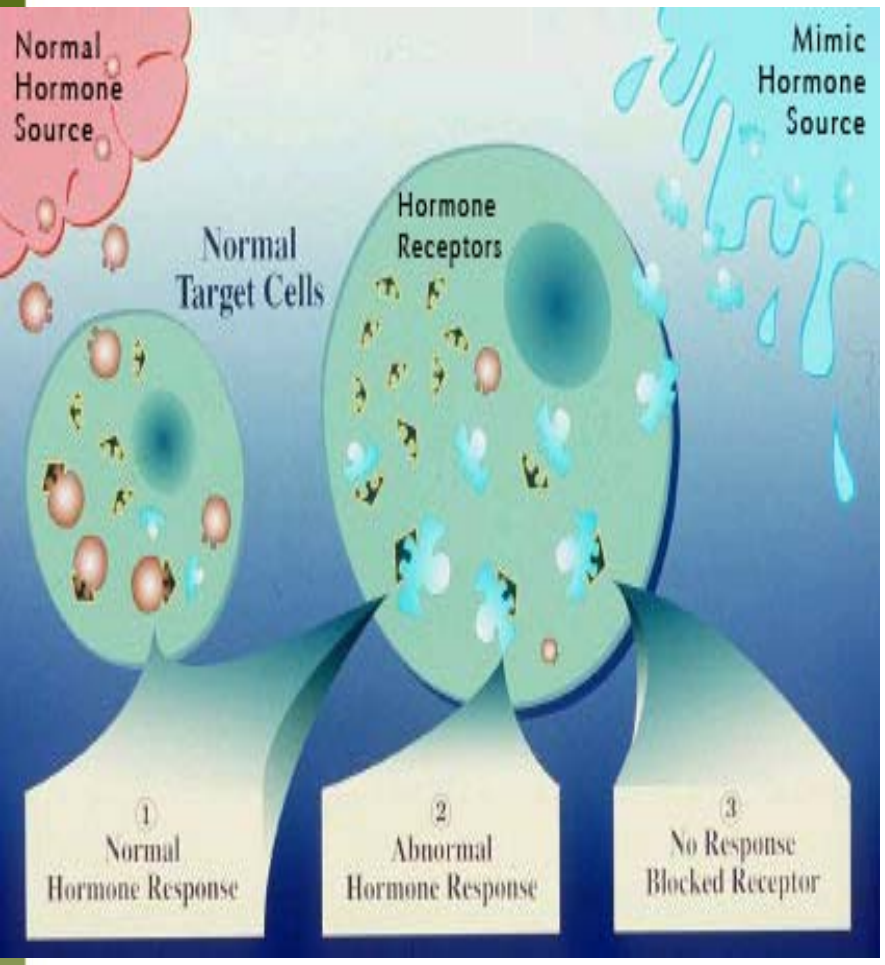
- We are now in an era where the effectiveness of technology and regulation to protect human and environmental exposure from unwanted chemicals is being questioned.
- There is an escalation of studies relating chemical bodyburdens to disease and the picture that is unfolding is cause for concern. Are escalating health costs one of the outcomes?
- A new branch of medicine is evolving looking at underlying causes of disease, chemical detoxification and the relationship to health improvement.
- These considerations beg the question where are these chemicals coming from and what can be done to mitigate future exposure
- Congressional hearings on “Emerging contaminants in drinking water. What to do?”

Endocrine System



- The endocrine system regulates all biological processes in the body from conception through adulthood and into old age, <u>including, development of the brain and nervous system, development of the immune system, the growth and function of all the reproductive system, as well as metabolism and blood sugar levels.</u>
- Major constituents of the endocrine system include: female ovaries, male testes, pituitary, thyroid and adrenal glands.

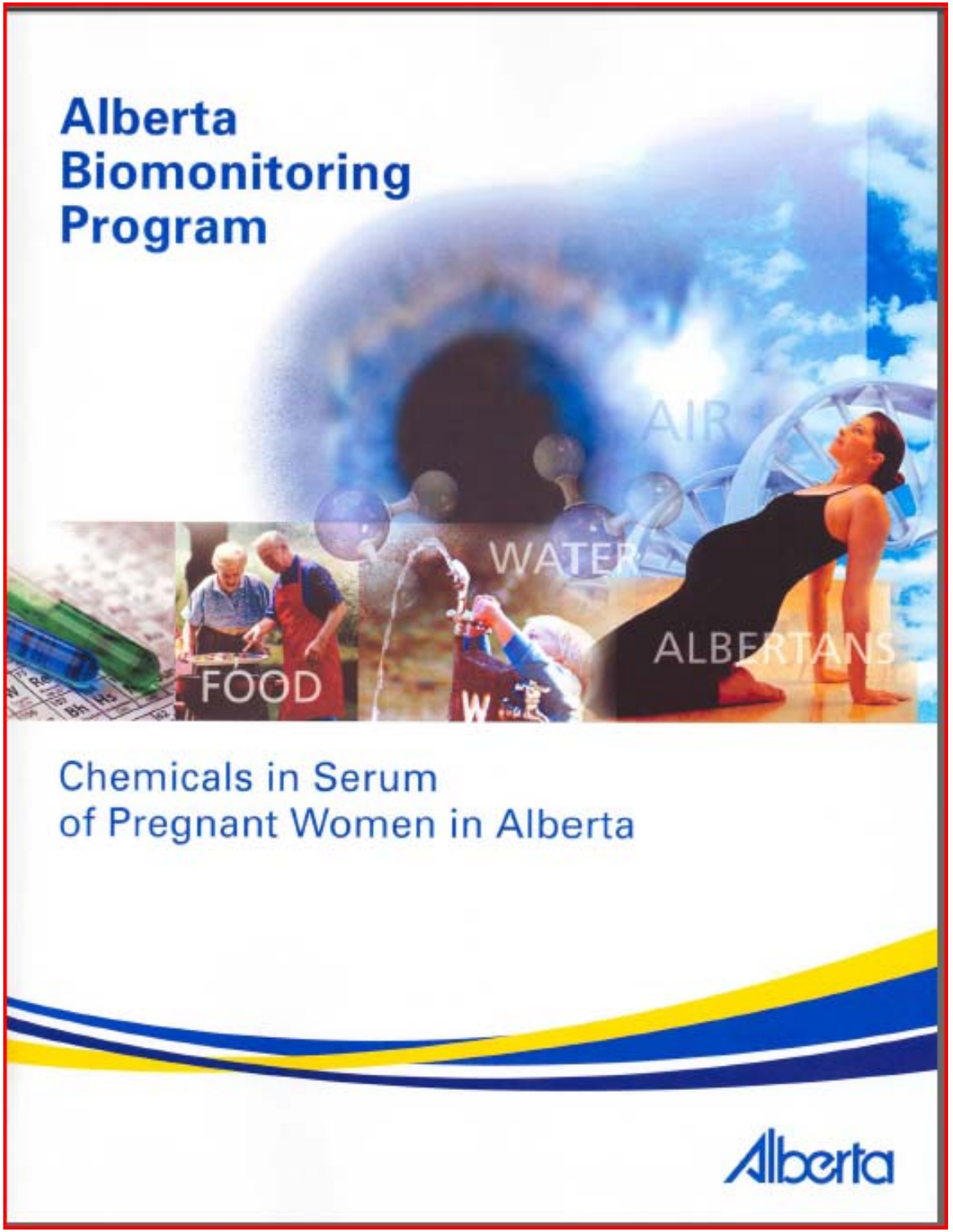
Endocrine Disruption



- Endocrine disrupters alter hormonal functions by several means.

Some chemicals can:

- ***mimic*** or partly mimic the natural hormone, fooling the body into over-responding to the stimulus e.g growth hormone that results in increased muscle mass
- ***block*** the effects of a hormone from certain receptors
- ***directly stimulate or inhibit*** the endocrine system and cause overproduction and underproduction of hormones, can be done by:
- altering the production and breakdown of natural hormones.
- modifying the making and function of hormone receptors.


Alberta
Biomonitoring
Program
AIR
WATER
FOOD
ALBERTANS
Chemicals in Serum
of Pregnant Women in Alberta
Alberta

Emerging Pollutants

- The term *Emerging Pollutants primarily refers to* those for which no regulations currently require monitoring or public reporting of their presence in our water supply

Pharmaceuticals

Studies carried out in Austria, Brazil, Canada, Croatia, England, Germany, Greece, Italy, Spain, Switzerland, the Netherlands and the U.S. have detected **> 80 pharmaceuticals and associated metabolites in the aquatic environment**

Drug traces found in cities' water

BY MARTIN MITTELSTAEDT
ENVIRONMENT REPORTER

Trace amounts of prescription drugs have been detected in the drinking water of four Canadian communities, including Montreal and Hamilton, the first time pharmaceutical products have been discovered in North America's municipal water supplies.

The drugs were found through laboratory tests funded jointly by The Globe and Mail and CTV of water samples taken from 10 Canadian communities.

The tests detected carbamazepine, an anticonvulsant given for epileptic seizures, in tap water from Montreal, Hamilton, and Brooks, a rural community in southern Alberta downstream of Calgary's sewage outflow.

Another drug, gemfibrozil, used to reduce cholesterol levels, was found in Portage La Prairie, a Manitoba community known for farming and food processing.

The tests, by Enviro-Test Laboratories of Ottawa, found the drug residues in concentrations in the 6.5- to 70-parts-per-trillion range.

One part per trillion is the equivalent of a grain of salt in an Olympic size swimming pool, and concentrations around this level are at the edge of what researchers can detect using modern laboratory equipment.

It is not known what health risk, if any, is posed by drinking or bathing in water containing trace amounts of drugs.

See WATER on page A6

JOHN ULAN/THE GLOBE AND MAIL

Detlef (Deib) Birkholz of Enviro-Test Laboratories watches as chemist Paul Houle prepares a water sample for testing in Edmonton.

Effects of drugs in trace amounts not known

WATER *from page A1*

"Right now, there [are] a lot of unanswered research questions, research that has to be conducted," said Detlef (Deib) Birkholz, vice-president of research at Enviro-Test and adjunct professor at the University of Alberta's faculty of pharmacy.

He said that "even though the concentrations are a thousand- or a million-fold below therapeutic levels, they could be having effects" on sensitive populations, such as fetuses and people with weakened immune systems.

Officials from the communities said they had no idea of why their water had drug residues.

The Globe-CTV tests were not intended to provide an exhaustive picture of drinking water supplies in Canada and researchers do not know if there are any ill effects for people exposed to extremely small quantities of pharmaceuticals.

But earlier studies have found trace amounts of drugs in some lakes and rivers, raising concerns that the chemical compounds could also be making their way into drinking water.

In Hamilton, the city draws water from a pipe that juts nearly a kilometre into Lake Ontario. The intake is far from any pollution source.

"It is strange. We are pretty far out in Lake Ontario," said Lou DiGironimo, director of Hamilton's municipal water department.

In Brooks, a community surrounded by vegetable and grain farms that draws on the Bow River to slake the thirst of its 12,500 residents, an official said the town's water is extensively treated and considered of good quality.

"We meet all Alberta environmental stuff and we chlorinate and filter and the whole thing," said Bill Prentice, manager of the town's works and utility department.

Health Canada's director of regulatory affairs, Karen Proud, cautions that research is so preliminary that regulators don't know whether the drug traces are hazardous. But she said there is enough evidence to warrant investigation.

"Whenever something turns up in drinking water that's not naturally there, there is a concern," she said.

In Europe, drugs have been detected in drinking water supplies, though similar research hasn't been published in Canada and the United States.

Health Canada and Environment Canada are currently surveying 24 Ontario communities to check if drug residues have entered water supplies. The agencies are considering expanding their testing to the rest of Canada next year.

There is no requirement in Canada to test drinking water for drug residues and no regulatory limits on these contaminants.

"This is so new from a scientific perspective that nobody's even thought about it," said Mark Servos, a research scientist at Environment Canada who is heading the Ontario water study.

Drugs are entering the environment because many pharmaceuticals are not fully metabolized in the bodies of those using them.

For carbamazepine, about 30 per cent is excreted unaltered by users.

If there is good news in the survey, it is that most of the water Canadians draw from their taps appears to have no drug residues, or has them at such low concentrations that they are below laboratory detection limits.

Water samples were also taken from Edmonton, Calgary, Halifax, Vancouver, Toronto, and Walkerton, Ont., home of Canada's worst case of water-borne illness, the E. coli outbreak that killed seven residents and sickened thousands in May, 2000. In these communities no residues were found of the more than 40 commonly used drugs and chemicals that Enviro-Test checked for.

Globe and Mail Feb 10, 2003

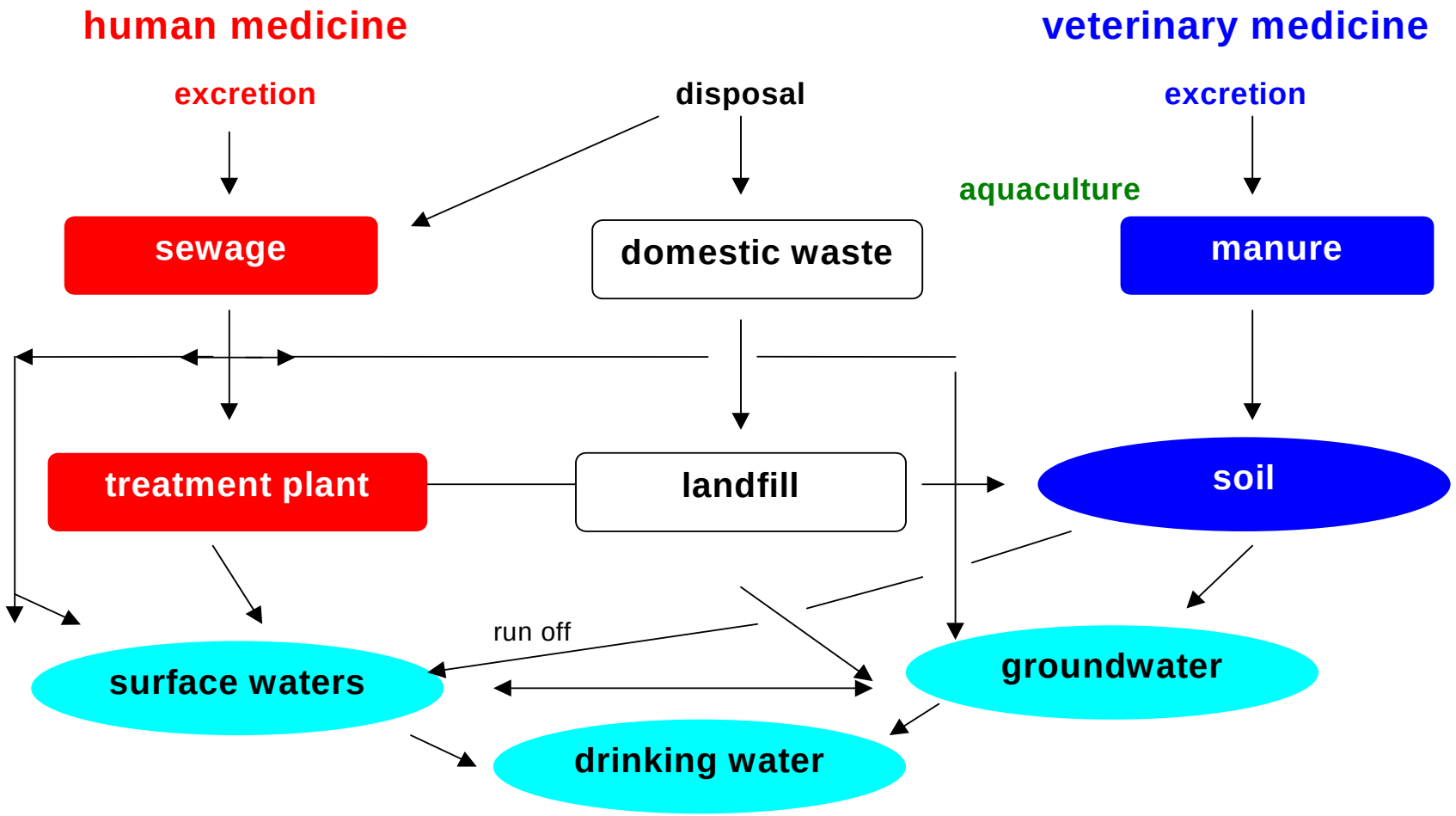
Canadian Drinking Water Survey

Carbamazepine: Brooks, Montreal, Hamilton 6.5 - 24 ng/L

Gemfibrozil: Portage La Prairie, 70 ng/L

Pharmaceuticals	
Therapeutic Classes	**Examples**
Veterinary and human antibiotics	***Examples***
β-lactams	Amoxicillin, ampicillin, benzylpenicillin
Macrolides	Erthomycin, azithromycin, tylosin
Sulfonamides	Sulfamethazine, sulfadiazine, sulfaguanidine
Tetracyclines	Oxytetracycline, tetracycline
Analagescis and Anti-inflammatories	Diclofenac, fenoprofen
Lipid regulators	Bezafibrate, clofibric acid, fenofibric acid
Pyschiatric drugs	Diazepam
β-blockers	Metoprolol, propranolol, timolol, solatol
X-ray contrast media	Lopromide, lopamidol, diatrizoate
Antidepressants	Fluoxetine
Hormones	Estradiol, estrone, estriol, ethinylestradiol
Anti-histamine	Cetirizine, acrivastine, fexofenadine
Anti-neoplastic drugs (cancer)	Platinum group elements, 5-fluorouracil
MRI contrast agents	Gadolinium, Gd
Illegal drugs	Amphetamine, methamphetamine, cannabinoids, morphine, codeine, cocaine, methylenedioxymethamphetamine (MDMA, ecstacy)

Exposure Routes



Canadian STP-Effluents (n=14)

Pharmaceutical	Type	Median Conc. (ng/L)	Maximum Conc. (ng/L)
ASA & SA	Analgesic - anti-inflammatory	3,600	59,600
Ibuprofen	Analgesic – anti-inflammatory	4,000	24,600
Naproxen	Analgesic – anti-inflammatory	9,500	33,900
Bezafibrate	Blood lipid regulator	200	600
Gemfibrozil	Blood lipid regulator	1,600	1,600
Pentoxyfylline	Vasodilator	500	600
Carbamazepine	Antiepileptic	740	2,200

Ref: Metcalfe, (2002) TSRI Project 337

Canadian Surface Waters

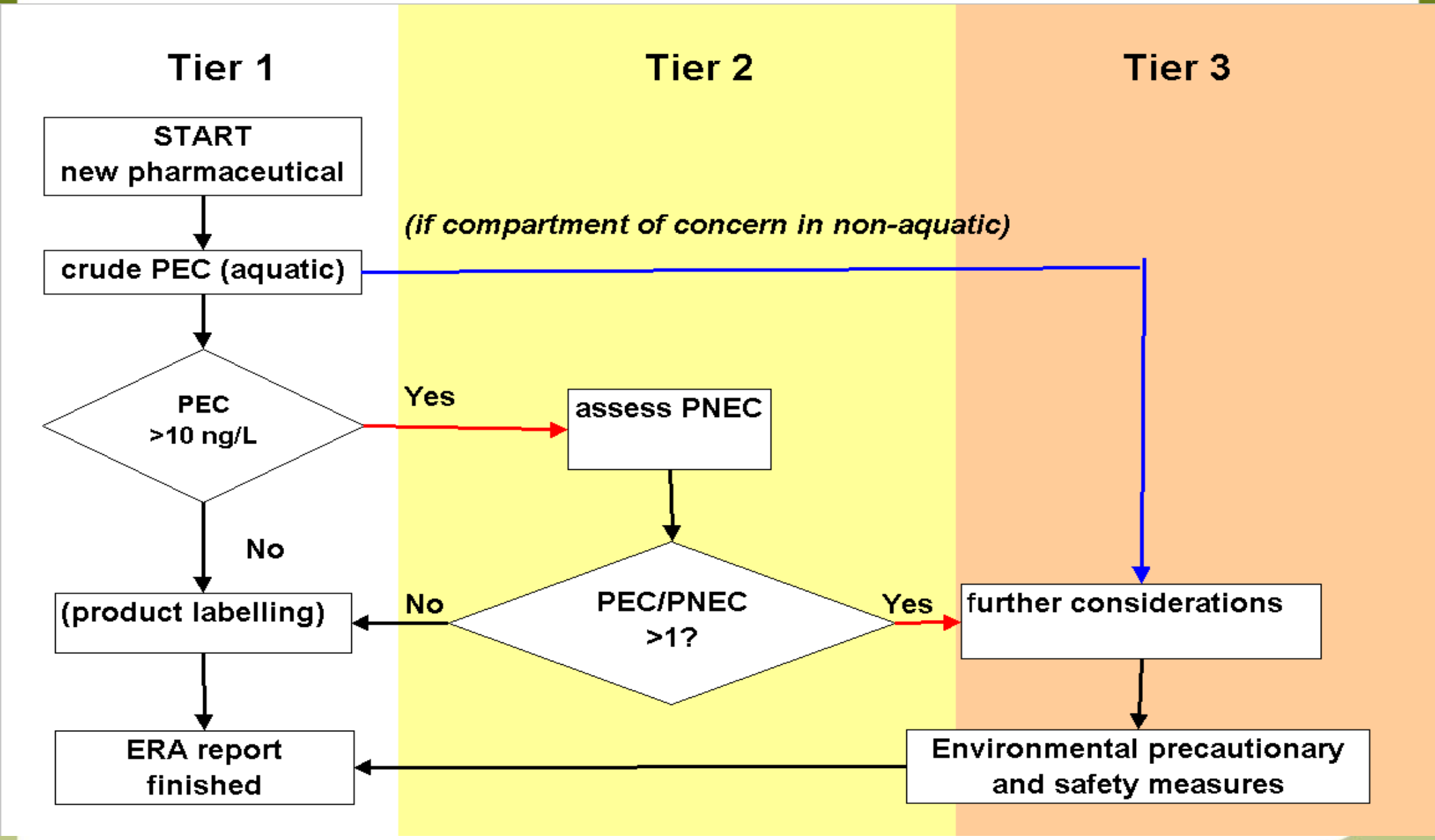
Pharmaceutical	Detriot River Med., Max., n (ng/L)	Hamilton Harbour Med., Max., n (ng/L)	Other Sites Lake Ontario Med., Max, n (ng/L)
ASA & SA	478, 2115, 13	Nd, Nd, 14	Nd, ND, 17
Clofibric acid	59, 175, 13	77, 101, 14	15, 15, 17
Ibuprofen	141, 790, 13	64, 93, 14	Nd, Nd, 17
Gemfibrozil	66, 112, 13	12, 67, 14	Nd, Nd, 17
Fenoprofen	Nd, Nd, 13	45, 64, 14	59, 59, 17
Naproxen	207, 551, 13	94, 139, 14	Nd, Nd, 17
Ketoprofen	12, 17, 13	31, 47, 14	50, 50, 17
Diclofenac	26, 42, 13	194, 194, 14	Nd, Nd, 17
Bezafibrate	52, 200, 13	Nd, Nd, 14	Nd, Nd, 17
Carbamazepine	185, 650, 11	120, 310, 14	20, 20, 15

Ref: Metcalfe (2002) TSRI Project #337

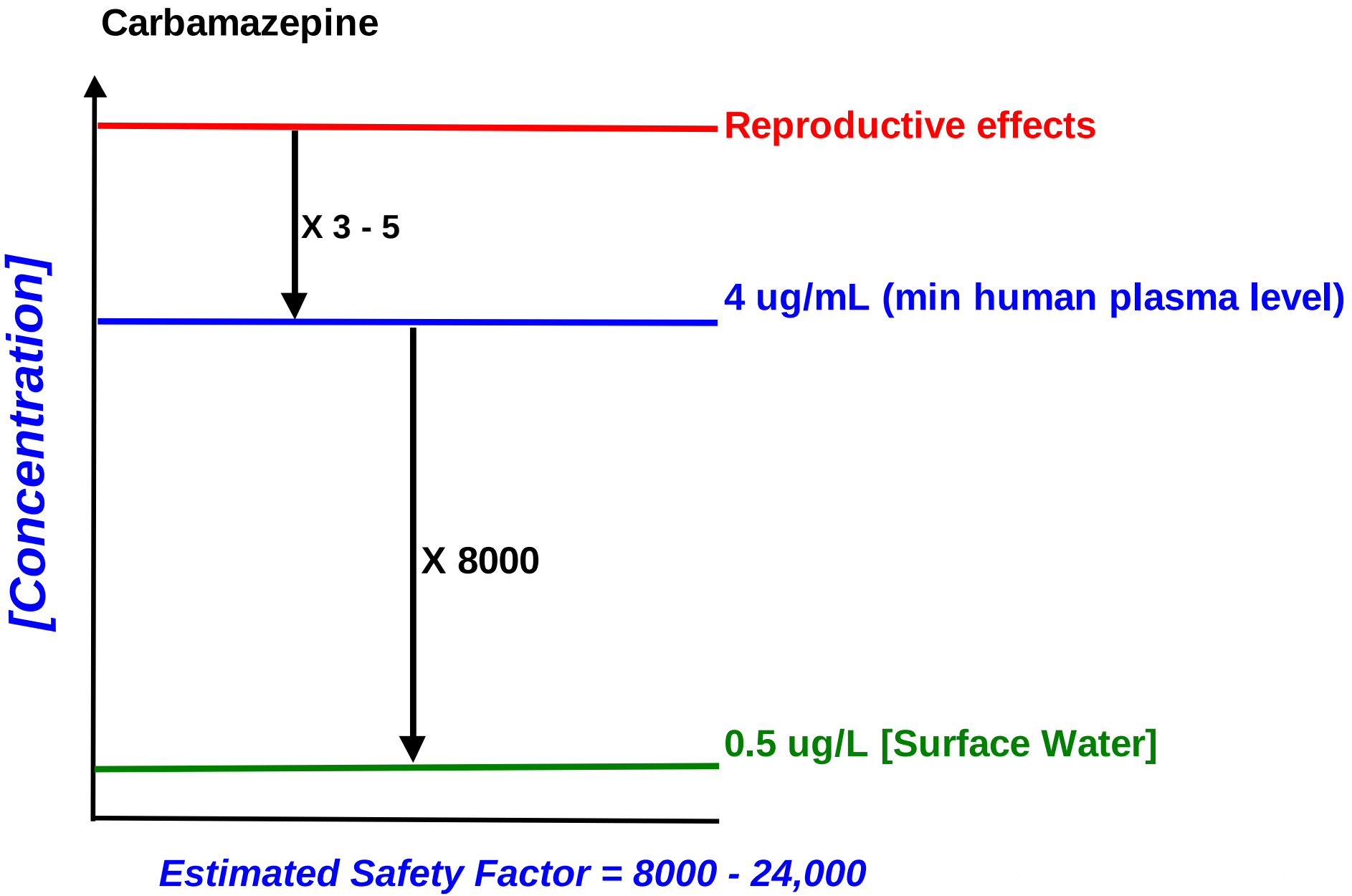
Drug Residues Found in 17 Groundwater Wells of a Drinking Water Plant

- Clofibric acid - 70 - 7300 ng/L - lipid regulator
- Diclofenac - nd - 380 ng/L - analgesic / anti-inflammatory
- Fenofibrate - nd - 45 ng/L - lipid regulator
- Ibuprofen - nd - 200 ng/L - analgesic / anti-inflammatory
- phenazone - <10 - 1250 ng/L - analgesic / anti-inflammatory
- propiphenazone - nd - 1465 ng/L - analgesic / anti-inflammatory
- clofibric acid derivative - 50 - 2900 ng/L - lipid regulator
- N-methylphenacetin - <5 - 470 ng/L - analgesic / anti-inflammatory
- N-(phenylsulfonyl)sarcosine - 165 - 1440 ng/L
- **ref: Herberer et al (1998)**

EU Environmental Risk Assessment Decision Tree



Human Risk Assessment



Risk Assessment

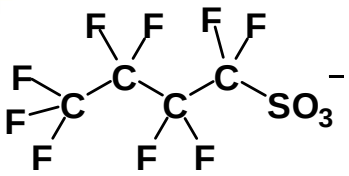
- Cunningham et al. (2009) conducted a risk assessment for potential impact to human health from environmental exposures for 44 active pharmaceutical ingredients (APIs), representing approximately 22 general pharmacological classes exhibiting a broad spectrum of therapeutic activities. Acceptable daily intake values were used to generate predicted no-effect concentrations from environmental exposure for human health (PNECHHs) from drinking water or fish consumption. PNECs were compared to predicted environmental concentrations (PECs) calculated using the regional assessment models PhATETM for North America and GREAT-ER for Europe. PEC/PNEC risk ratios were determined to be less than 1.

Pharmaceuticals

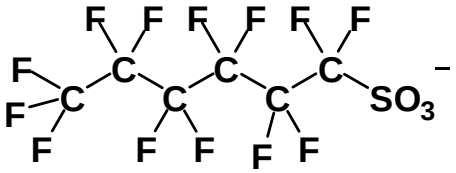
- The fact is that there are only 3 ways to reduce concentrations of pharmaceutical agents in drinking water. **Reducing the burden by reducing the release into wastewater** will not solve the problem because people will certainly continue to take drugs and many upriver communities are growing. **"Take-back" programs to divert drugs from being flushed down the toilet** or drain would have a marginal effect compared to the much greater mass of drugs that pass through the body. **Reducing the intake of human beings by upgraded water treatment** may be good for human health but the greater problem is probably ecosystem toxicity; this does nothing for effects on aquatic species, such as the endocrine effect on fish documented in many bodies of water. **Reducing the effluent into bodies of water by upgraded wastewater treatment is really the only solution**, and it depends on infrastructure support, capital to upgrade, and technology.
- Ref: Guidotti, (2009). **Testimony before The House Committee on Transportation and Infrastructure Subcommittee on Water Resources and Environment,** a working group of the US Congress, September 18, 2008,.

Perfluorinated Compounds

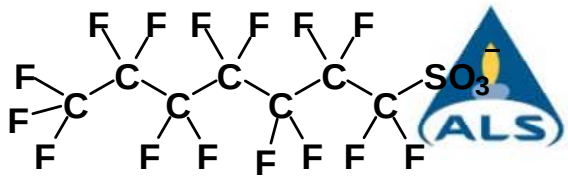
- PFCs are a family of commonly used synthetic compounds with many applications, including repelling oil and stains on furniture, clothing, carpets and food packaging, as well as in the manufacturing of polytetrafluoroethylene– a non-stick surfacing often used in cookware, e.g. Teflon^{R}
- The most commonly studied PFC classes are the perfluorinated sulfonates (PFSAs) and the perfluorinated carboxylates (PFCAs) and the most commonly measured compounds in these classes are perfluorooctane sulfonate (PFOS), perfluorohexanesulfonate (PFHxS) and perfluorooctanoic acid (PFOA)
- Ref: Genius et al (2010). Public Health, 124: 367-375
- Ref: Trudel et al (2008). Risk Analysis, 28: 251-269



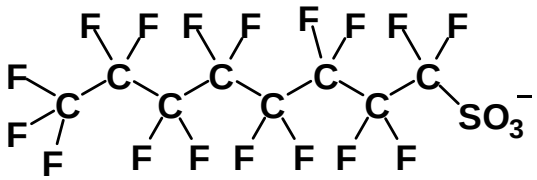
perfluoro-1-butanesulfonate



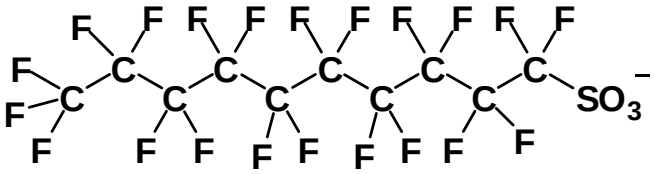
perfluoro-1-hexanesulfonate



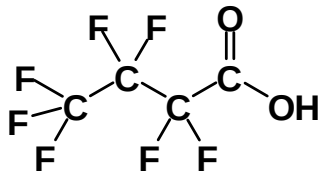
perflouro-1-heptanesulfonate



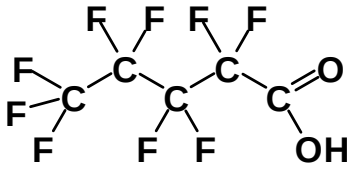
perfluoro-1-octanesulfonate



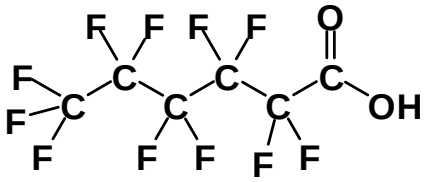
perfluoro-1-decanesulfonate



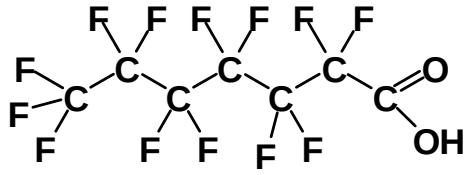
perfluoro-n-butanoic acid



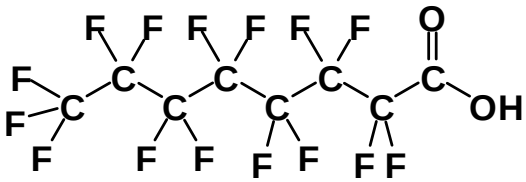
perfluoro-n-pentanoic acid



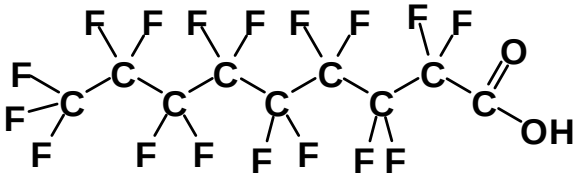
perfluoro-n-hexanoic acid



pefluoro-n-heptanoic acid



perfluoro-n-octanoic acid



perfluoro-n-nonanoic acid

Medium serum half-lives

- The median human serum half-lives for common
- PFCs are:
- PFHxS, 8.8 years (range 2.8–27);
- PFOS, 5.4 years (range 2.4–21.7);
- PFOA, 3.8 years (range 1.5–9.1)
- Between individuals, there may be variation in biological breakdown of precursors and elimination of PFAs due to differences in individual biochemistry and physiology based on genomic and metabolic variation.
- A gender difference in elimination of PFCs in humans has not been observed thus far

Toxicity

- Most PFC toxicity work thus far has been done on animals. In animal research, common PFCs such as PFOA and PFOS appear to be potentially carcinogenic, induce functional alteration in cellular organelles, and cause neurotoxicity and hepatotoxicity.
- The literature also confirms significant PFC adverse effects on immune system function, cell membrane potential, neuroendocrine function, and gestational and developmental processes. In summary, animal research evidence to date confirms that some PFCs have potential for hepatotoxicity, developmental toxicity, immunotoxicity, hormonal disruption, and genomic and biochemical impact.
- Potential human thresholds for harm are currently unknown.

Brominated Flame Retardants (BFR)

Many type of BFR

- Polybrominated biphenyl (PBB)
- Polybrominated diphenyl ether (PBDE)
- Tetrabromobisphenol-A (TBBPA)
- Hexabromocyclododecane (HBCD) - textiles

Classes of BFR

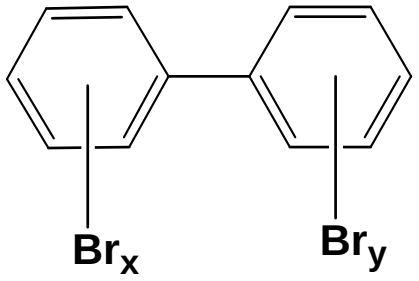
- Additive - mixed into polymers, not chemically bound to plastic (PBB and PBDE)
- Reactive - chemically bound to plastic (TBBPA)

Uses

- Plastic components of computers and televisions
- Circuit boards
- Seats of cars and buses
- Textiles

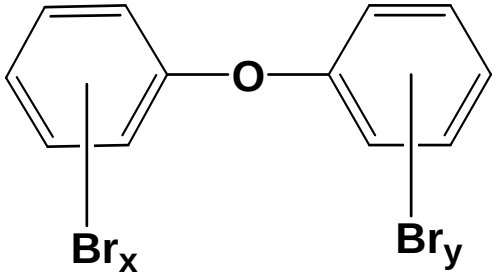
Brominated flame retardants

Polybrominated biphenyls PBBs
209 congeners



x + y = 1-10

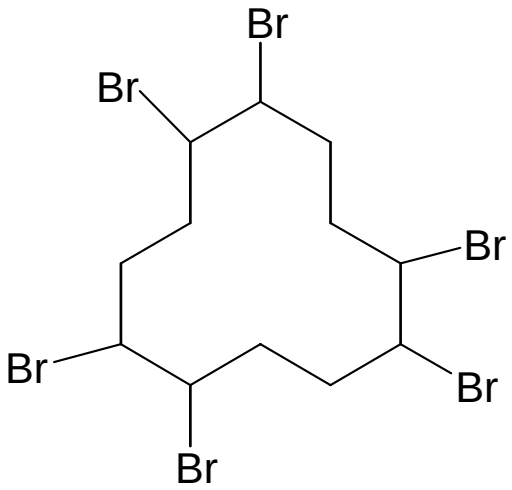
Polybrominated diphenylethers PBDEs



x + y = 1-10

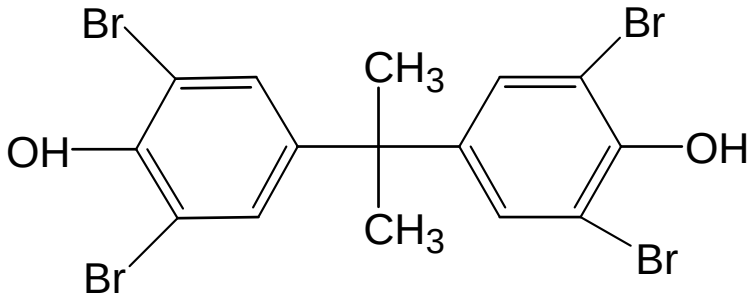
Hexabromocyclododecane HBCD
3-isomers

be



α–HBCD β–HBCD γ-HBCD

Tetrabromobiosphenol A TBBPA



Hormone disrupting effects of BFR

- Heating (for example during manufacture of plastics) and burning of materials containing PBBs and other brominated flame retardants can produce polybrominated dibenzo-p-dioxins, which have similar toxicological effects to chlorinated dioxins.

- Low level ***exposure of young mice to PBDEs causes permanent disturbances in behaviour, memory and learning***

- ***PBDEs have been shown to disrupt the tyroid hormone system in rats and mice; these systems are a crucial part of the development of the brain and body***

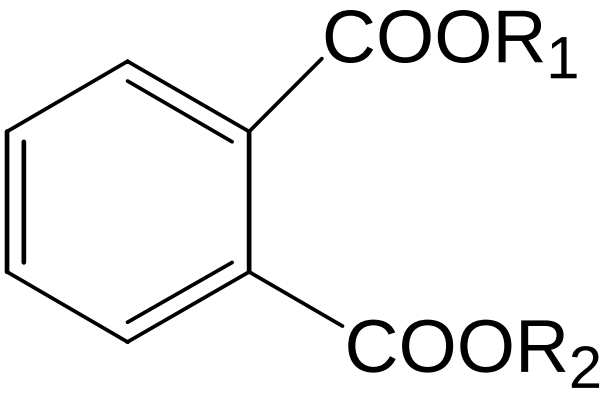
- TBBPA is active in a breast cancer cell assay (MCF-7 growth promotion E-screen)

- TBBPA was found to have a high potential for out-competing the natural hormone thyroxine

Nanoparticles

- Can have effects on cellular levels, i.e. affect protein structure through binding
- Not toxic but can effect reproduction
- May soon be ubiquitous
- Silver particles bactericidal
- Used indiscriminantly – no regulations
- Difficult to measure, Si, CdSe, TiO2, Zno, Au,

Phthalates



Plasticizers used in the manufacturing of PVC, epoxy resins and cellulose esters, adhesive formulations

-medical products, cosmetics, packaging of food (limited extent)

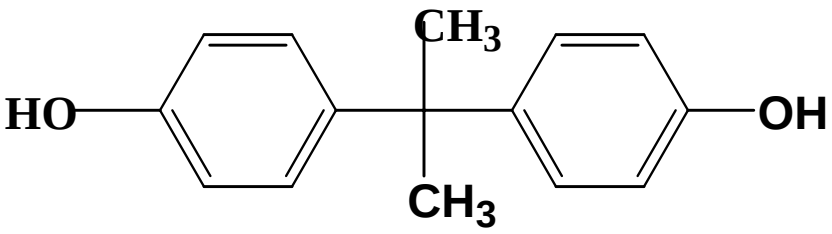
Phthalates from the “Priority pollutant” list according to the US EPA

R_1	R_2	Name	Acronym
CH_3		Dimethyl phthalate	DMP
CH_2CH_3		Diethyl phthalate	DEP
$(CH_2)_3CH_3$		Dibutyl phthalate	DBP
$(CH_2)_3CH_3$	$CH_2C_6H_5$	Butylbenzyl phthalate	BBP
$CH_2CH(CH_2CH_3)(CH_2)_3CH_3$		Bis (2-ethylhexyl) phthalate	DEHP
C_8H_{17}		Di-n-octyl phthalate	DnOP

Phthalates in Humans

Units	6 – 11	12 –19	20 and older
Urine, ug/g creatinine	1614	1746	2495

Bisphenol A (BPA)



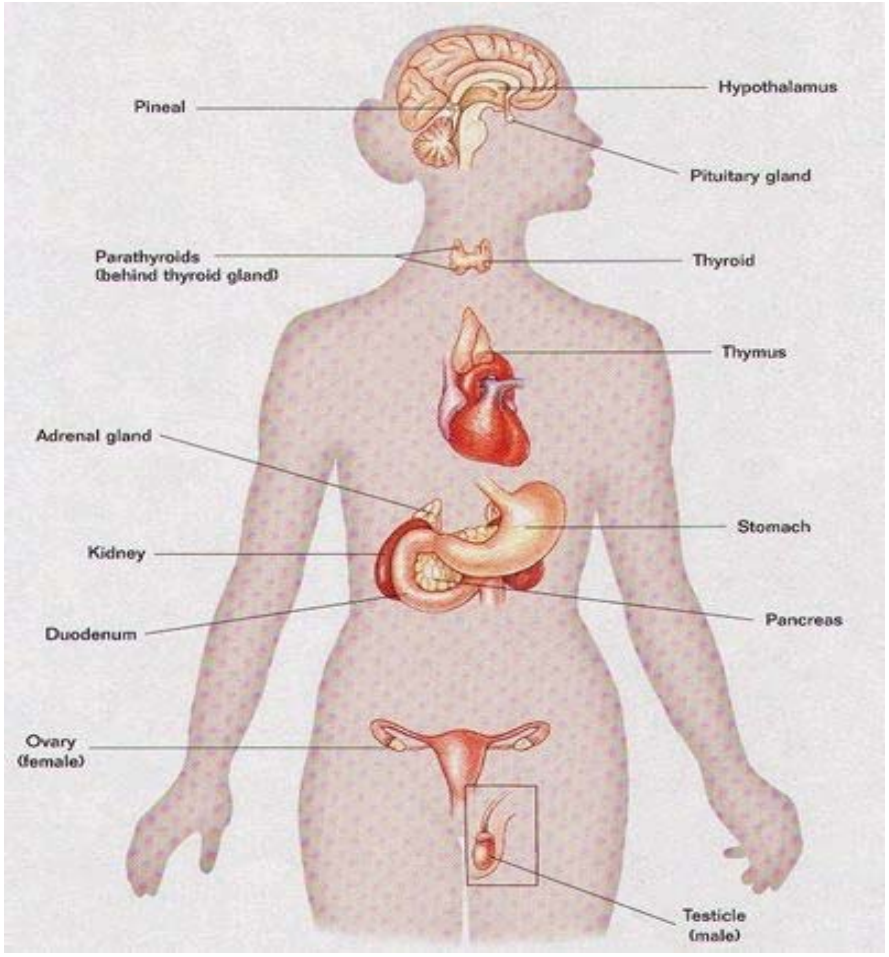
Plasticizer

Bisphenol A is used in the production of epoxy resin and polycarbonate plastics
These plastics are used in many food and drink packaging applications, whilst the resins are commonly used as lacquers to coat metal products such as food cans, bottle tops and water supply pipes.

Some polymers used in dental treatment contain Bisphenol-A

Global production is more than one million tons per year

Bisphenol A in Human Blood



- 1.05 +/- 0.1 ng/mL
- 1.17 +/- 0.16 ng/mL
- Women with ovarian dysfunction and obesity
- Correlation statistical only

Circulating Levels of Bisphenol A and Phthalates are related to Carotid Atherosclerosis in the Elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study

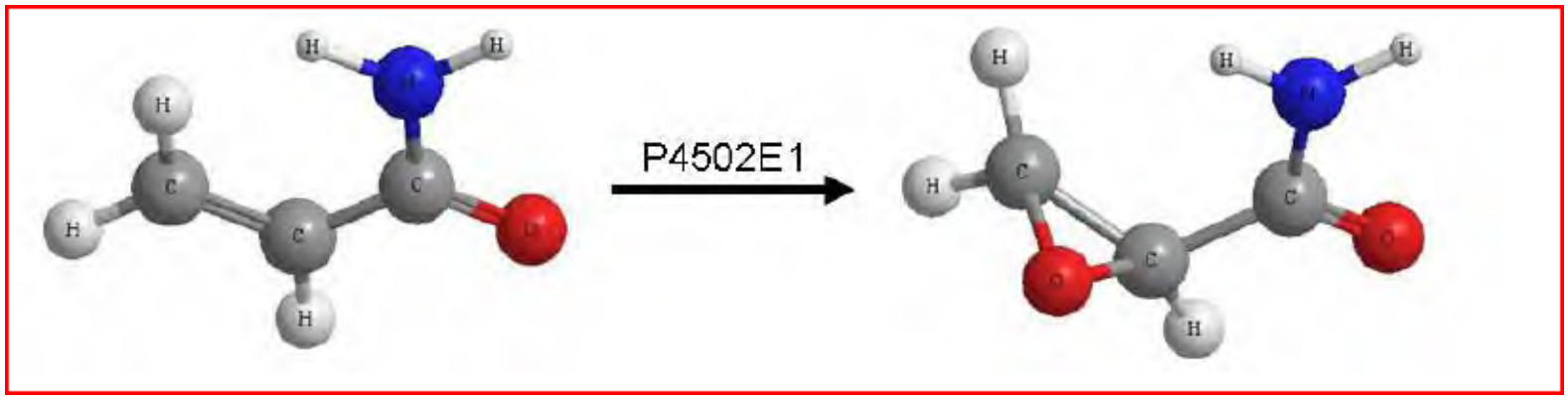
P. Monica Lind, PhD1, Detlef A. Birkholz, PhD2 and Lars Lind, MD, PhD3

Circulating levels of phthalates and bisphenol A (BPA) in an elderly population in Sweden– Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)

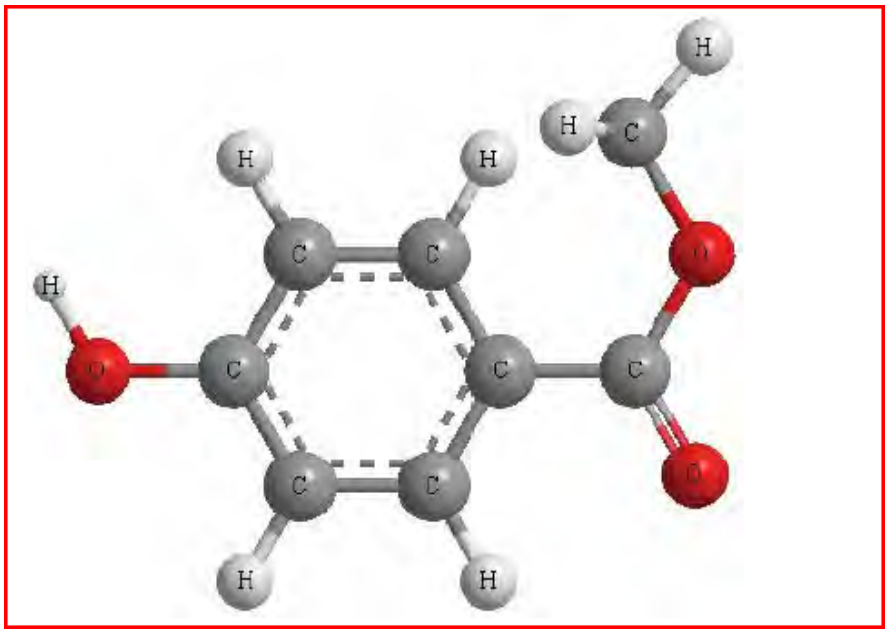
Lena Olsén[1], Erik Lampa[1], Detlef A. Birkholz[2], Lars Lind[3], P. Monica Lind[1]

Acrylamide

- Exposure to small reactive, carcinogenic, mutagenic compounds like acrylamide and its mutagenic metabolite glycidamide, has been a serious health concern for some time.
- Once exposed to acrylamide, it is rapidly metabolized by the cytochrome P4502E1 enzymes to its metabolite, glycidamide. Both compounds readily bind to form stable adducts with hemoglobin.



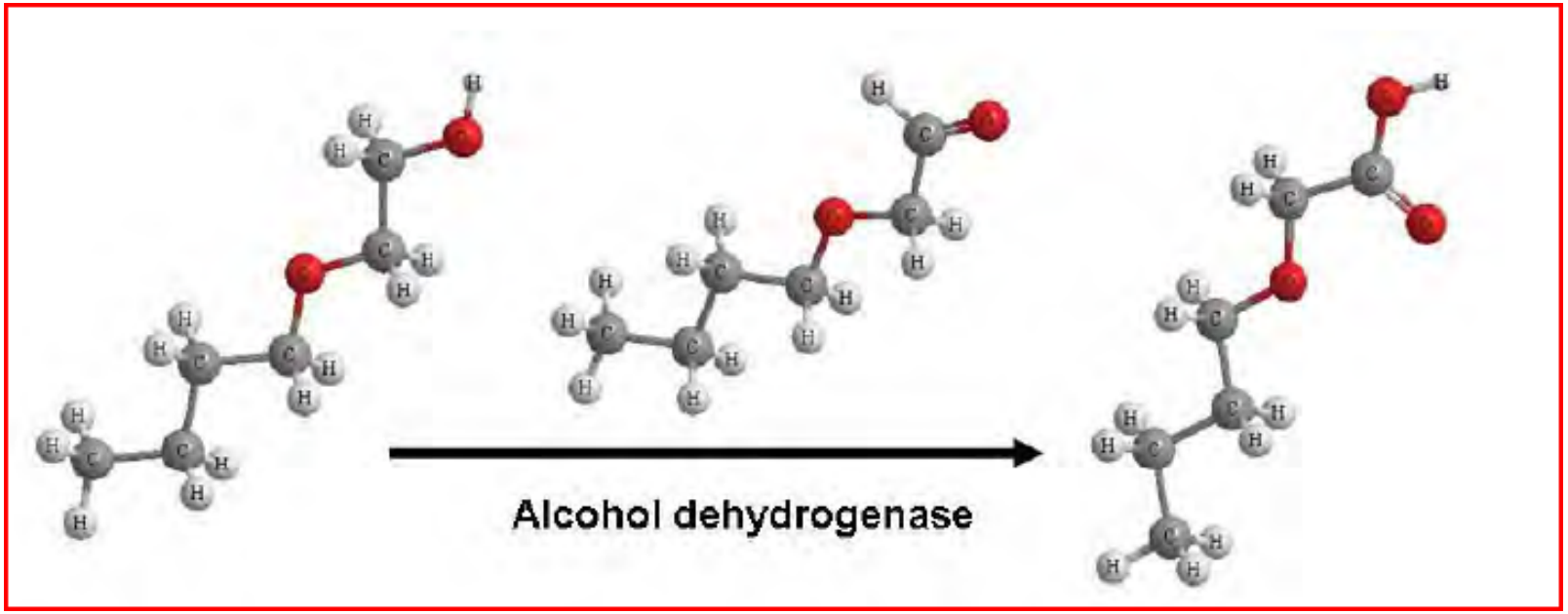
Parabens



- Parabens are widely used as antimicrobial preservatives in pharmaceuticals, cosmetics, and food and beverage processing.
- Commonly found in surface water

2-Butoxyethanol

- 2-Butoxyethanol (BE) has many industrial uses and is a component in many commonly used formulations. Its main use is in paints, surface coatings, and inks, but it is also used in numerous household cleaning products and aerosols.



Others

- N-nitrosodimethylamine (NDMA), is a semi-volatile organic chemical that is highly toxic and is a suspected human carcinogen. The US Environmental Protection Agency has determined that the maximum admissible concentration of NDMA in drinking water is 7 ng L
- 1,4-dioxane is a colorless liquid that is mainly used as a stabilizer for the solvent trichloroethane. It is an occasionally used solvent for a variety of practical applications as well as in the laboratory
- 1,2,3-trichloropropane, was used historically as a paint and varnish remover, cleaning and degreasing agent, and a cleaning and maintenance solvent, and more currently as a chemical intermediate (NTP, 2005). Its use as a pesticide was in formulations with dichloropropenes in the manufacture of D-D, a soil fumigant

Emerging Contaminants

- These other, point-source emerging contaminants need to be handled through a different program, which should include the following:
- 1. Systematic research and tracking where they are known or most likely to occur;
- 2. Further toxicological investigation to support risk assessment, in order to determine the level of risk they present;
- 3. Targeted development of remediation technology, which of necessity is likely to be site-specific.
- Ref: Guidotti, (2009). Testimony before The House Committee on Transportation and Infrastructure Subcommittee on Water Resources and Environment, a working group of the US Congress, September 18, 2008,.

How Do Analyze for EDCs

- Bioassays (in vitro and in vivo)
- US-EPA Endocrine Disruptors Screening Program http://www.epa.gov/scipoly/oscpendo
- Chemical analyses: GC/MS, HPLC/tandem MS
- Forensic approach - integrated bioassays/chemical analyses

Test	Endpoint	Ailment
Salmonella/microsome	Initiation	Cancer – increase bacterial counts for histidine deficient bacteria
EROD induction – Clone 9 cells	Activation prior to initiation	Cancer – resorufin measurements
Chick Embryo Screening test – fertilized white leghorn hen's eggs	Promotion	Cancer – 18d look for liver necrosis and green liver
Gap Junction Intercellular Communication Clone 9 cells	Promotion	Cancer, rate constant of dye transfer between cells
SOS-chromotest	Initiation	Cancer, E. Coli measures DNA damage
T4-TTR binding	Thyroid hormone metabolism and transport	Learning, memory, behavior

Test	Endpoint	Ailment
ER and transient gene expression in MCF-7 cells	Estrogenic response	Potent pseudoestrogens
ER CALUX, YES, YAS	Estrogenic and androgenic response	Potent pseudoestrogens, androgens
Frog embryo Teratogenesis Assay Xenopus (FETAX)	Screening teratogens	
Spisula solidissima, Atlantic surfclam	neuronal development	Possible link to autism Carol Reinisch
Elliptiocomplanata – freshwater mussel	Hemolymphs tested for phagocytic activity, intracellular esterase activity, cell adherence and lipid perodixation	Immune compromise

Conclusions

- The list of emerging contaminants of concern is much larger than presented
- The chemicals presented represent those identified by the US Congressional hearing on emerging contaminants of concern in drinking water
- Researchers have identified many more chemicals, however, toxicological data is largely lacking.
- Although ecological data is accumulating at an exponential rate, how do we relate this to human risk? That is the challenge.
- The field of genomics and proteinomics is expanding at a huge rate. A lot of the effort is targeted towards drug design
- The same technology may well have a place in providing the sorely needed toxicological data for identified emerging contaminants.

Conclusions

- While most contaminants of emerging concern are not likely to be concentrated enough to induce acute toxicity, chronic effects may occur from exposure to mixtures of contaminants at environmentally realistic concentrations. It is proposed that the primary challenges to emerging pollutants relate to their potency, reactivity and interactions with biological systems, and that a framework for risk management is needed.

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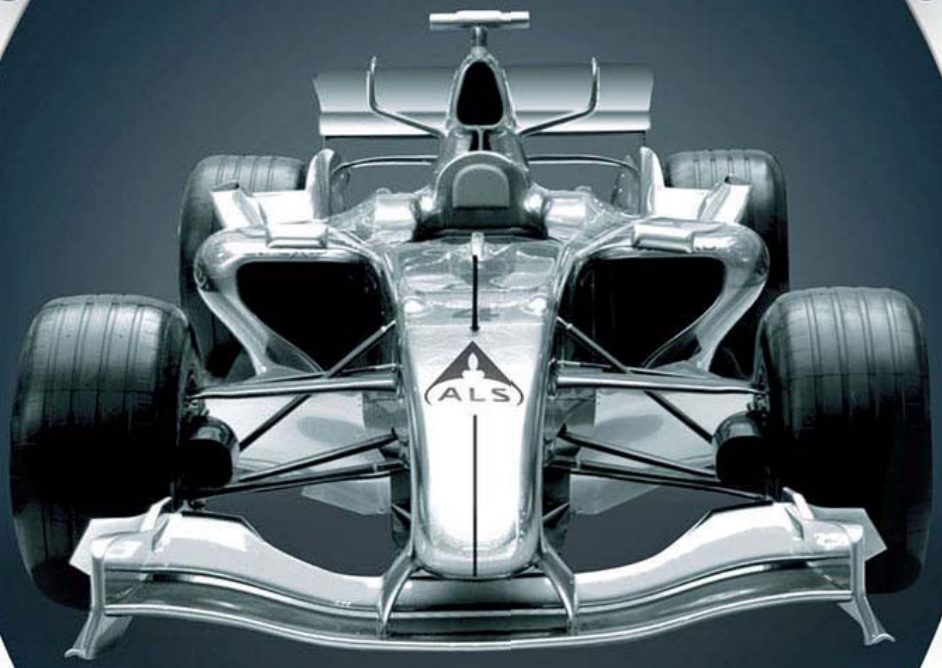

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