Emerging Contaminants in Drinking Water

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• 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

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 body burdens 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, 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.

- Major constituents of the endocrine system include: female ovaries, male testes, pituitary, thyroid and adrenal glands.
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

Chemicals in Serum of Pregnant Women in 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

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

<table>
<thead>
<tr>
<th>Therapeutic Classes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Veterinary and human antibiotics</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td>β-lactams</td>
<td>Amoxicillin, ampicillin, benzylpenicillin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erthomycin, azithromycin, tylosin</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Sulfamethazine, sulfadiazine, sulfaguanidine</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Oxytetracycline, tetracycline</td>
</tr>
<tr>
<td><strong>Analgesics and Anti-inflammatories</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Diclofenac, fenoprofen</td>
</tr>
<tr>
<td><strong>Lipid regulators</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Bezafibrate, clofibrirc acid, fenofibrirc acid</td>
</tr>
<tr>
<td><strong>Psychiatric drugs</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Metoprolol, propranolol, timolol, solatol</td>
</tr>
<tr>
<td><strong>X-ray contrast media</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Lopromide, lopamidol, diatrizoate</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Estradiol, estrone, estriol, ethinylestradiol</td>
</tr>
<tr>
<td><strong>Anti-histamine</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Cetirizine, acrivastine, fexofenadine</td>
</tr>
<tr>
<td><strong>Anti-neoplastic drugs (cancer)</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Platinum group elements, 5-fluorouracil</td>
</tr>
<tr>
<td><strong>MRI contrast agents</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Gadolinium, Gd</td>
</tr>
<tr>
<td><strong>Illegal drugs</strong></td>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td></td>
<td>Amphetamine, methamphetamine, cannabinoids, morphine, codeine, cocaine, methylenedioxymethamphetamine (MDMA, ecstasy)</td>
</tr>
</tbody>
</table>
## Canadian STP-Effluents (n=14)

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

Ref: Metcalfe, (2002) TSRI Project 337
### Canadian Surface Waters

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

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

EU Environmental Risk Assessment Decision Tree

Tier 1

START new pharmaceutical

- crude PEC (aquatic)
  - PEC >10 ng/L
    - No (product labelling)
    - Yes (if compartment of concern in non-aquatic)

Tier 2

- assess PNEC
  - Yes
    - further considerations
  - No
    - PEC/PNEC >1?
      - Yes
        - Environmental precautionary and safety measures
      - No
        - ERA report finished
Human Risk Assessment

Carbamazepine

Reproductive effects

$\times 3 - 5$

4 ug/mL (min human plasma level)

$\times 8000$

0.5 ug/L [Surface Water]

Estimated Safety Factor = 8000 - 24,000
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®

- 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)


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 television
- Circuit boards
- Seats of cars and buses
- Textiles
Brominated flame retardants

Polybrominated biphenyls PBBs
209 congeners

\[ \text{Br}_x \quad \text{Br}_y \]

\[ x + y = 1-10 \]

Hexabromocyclododecane HBCD
3-isomers

\[ \alpha-\text{HBCD} \quad \beta-\text{HBCD} \quad \gamma-\text{HBCD} \]

Polybrominated diphenylethers PBDEs

\[ \text{Br}_x \quad \text{Br}_y \]

\[ x + y = 1-10 \]

Tetrabromobisphenol 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 thyroid 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)

| R₁         | R₂                     | Name                                           | Acronym |
|------------|------------------------|                                                |         |
| CH₃        | (CH₂)₃CH₃              | Dimethyl phthalate                            | DMP     |
| CH₂CH₃     | (CH₂)₃CH₃              | Diethyl phthalate                             | DEP     |
| (CH₂)₃CH₃ | CH₂C₆H₅                | Dibutyl phthalate                             | DBP     |
| (CH₂)₃CH₃ | CH₂CH(CH₂CH₃)(CH₂)₃CH₃ | Butylbenzyl phthalate                         | BBP     |
| C₈H₁₇      |                        | Bis (2-ethylhexyl) phthalate                   | DEHP    |
|            |                        | Di-n-octyl phthalate                          | DnOP    |
## Phthalates in Humans

<table>
<thead>
<tr>
<th>Units</th>
<th>6 – 11</th>
<th>12 – 19</th>
<th>20 and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine, ug/g creatinine</td>
<td>1614</td>
<td>1746</td>
<td>2495</td>
</tr>
</tbody>
</table>
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 Olsén¹, Erik Lampa¹, Detlef A. Birkholz², Lars Lind³, P. Monica Lind¹
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-Butoxoyethanol

- 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
<table>
<thead>
<tr>
<th>Test</th>
<th>Endpoint</th>
<th>Ailment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella/microsome</td>
<td>Initiation</td>
<td>Cancer – increase bacterial counts for histidine deficient bacteria</td>
</tr>
<tr>
<td>EROD induction – Clone 9 cells</td>
<td>Activation prior to initiation</td>
<td>Cancer – resorufin measurements</td>
</tr>
<tr>
<td>Chick Embryo Screening test – fertilized white leghorn hen’s eggs</td>
<td>Promotion</td>
<td>Cancer – 18d look for liver necrosis and green liver</td>
</tr>
<tr>
<td>Gap Junction Intercellular Communication Clone 9 cells</td>
<td>Promotion</td>
<td>Cancer, rate constant of dye transfer between cells</td>
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<tr>
<td>SOS-chromotest</td>
<td>Initiation</td>
<td>Cancer, E. Coli measures DNA damage</td>
</tr>
<tr>
<td>T4-TTR binding</td>
<td>Thyroid hormone metabolism and transport</td>
<td>Learning, memory, behavior</td>
</tr>
<tr>
<td>Test</td>
<td>Endpoint</td>
<td>Ailment</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>---------------------------------</td>
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</tr>
<tr>
<td>ER and transient gene expression in MCF-7 cells</td>
<td>Estrogenic response</td>
<td>Potent pseudoestrogens</td>
</tr>
<tr>
<td>ER CALUX, YES, YAS</td>
<td>Estrogenic and androgenic response</td>
<td>Potent pseudoestrogens, androgens</td>
</tr>
<tr>
<td>Frog embryo Teratogenesis Assay Xenopus (FETAX)</td>
<td>Screening teratogens</td>
<td></td>
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<tr>
<td>Spisula solidissima, Atlantic surfclam</td>
<td>neuronal development</td>
<td>Possible link to autism</td>
</tr>
<tr>
<td>Elliptiocomplanata – freshwater mussel</td>
<td>Hemolymphs tested for phagocytic activity, intracellular esterase activity, cell adherence and lipid peroxidation</td>
<td>Immune compromise</td>
</tr>
</tbody>
</table>
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.