AN INTRODUCTION TO ENVIRONMENTAL TOXICOLOGY

RACHEL NICOLL

WHAT IS ENVIRONMENTAL MEDICINE/TOXICOLOGY?

- From Wikipedia:

  'Environmental medicine is a multidisciplinary field…..studying the interactions between the environment and human health and the role of the environment in causing or mediating disease'.

- Overlapping with, but distinct from, Public, Environmental or Occupational Health

WHAT DOES ENVIRONMENTAL MEDICINE CONSIDER?

EM looks at the acute and chronic, short and long term effects of high and low dose exposures.

These effects may be direct or indirect and may result in long latency diseases.

KEY PRINCIPLES OF ENVIRONMENTAL MEDICINE (as distinct from orthodox medicine)

- The human body is a dynamic environment, subject to multiple exposures which can affect multiple systems, where everything is interconnected.
- There are only 2 causes of disease (excluding congenital):
  - Too many toxins which the body cannot metabolise *and/or*
  - Inadequate nutrients to protect against toxin damage.
- Exposure symptoms are not uniform; the same toxin exposure could manifest as IBS in person 1, depression in person 2 and no symptom at all in person 3.
- The problem is rarely 1 toxin; it is more likely total body burden, with 1 exposure tipping the body into a disease state.

THE EPIDEMIC OF CHRONIC DISEASE

- **2004 JAMA Editorial by Halsted Holman, MD of Stanford Medical School:**

  'Chronic disease is now the principal cause of disability and use of health services, consuming 78% of health expenditures….Chronic disease requires a practice of medicine quite different from that used for acute medicine'.

- **(Willett 2002) Despite the fact that potentially modifiable non-genetic factors (diet, weight, inactivity, smoking, environmental exposure) account for up to 70-90% of mortality in the US, clinical interventions are based primarily on drugs and surgery.**

AND THE COST: HUMAN AND FINANCIAL

- 2001 report: between US$568 billion and $793 billion is spent in the US and Canada on environmentally-caused disease.
- According to recent estimates between 5-10% of disease adjusted life years (DALYs) lost are due to environmental causes.

HOW HAS THIS COME ABOUT?

- There is a large gap between scientific research and integration of new knowledge into clinical practice, particularly in the area of complex chronic disease.
- Many of the companies that make toxic chemicals also manufacture the pharmaceuticals that are prescribed to treat the damage.
- Newspapers report industrial poisoning or chemical spills causing cancer as if each were an isolated and unique incident. They do not consider our continual daily toxin exposure.
- The interaction between toxins in the body is unknown.
- The outcome: Orthodox medicine's denial of environmental illness results in misdiagnosis, improper treatment and huge cost (because successive treatments fail).

ENVIRONMENTAL MEDICINE: A LOOK AT THE EVIDENCE

Rachel Nicoll, British Society for Ecological Medicine, 2016

THE PROBLEM

- There is a disconnect between science and orthodox medicine as in nutritional medicine:
  - orthodox medicine will not adopt nutritional remedies despite clear evidence of benefit.
- But also scientists cannot agree amongst themselves on environmental medicine. The evidence is unclear and it's not only because of political pressure and funding by 'Big Pharma'.

PROBLEMS WITH RESEARCH STUDIES

- We cannot conduct RCTs of toxins on humans for ethical reasons. In a world where the RCT is everything, this puts recognition of environmental toxins in a poor position.
- Humans are surrounded by toxins every day, so there can be no true non-exposed control group, although most researchers do not recognise this fact.

Nevertheless, there is no shortage of research studies into all types of toxins, mostly animal or epidemiological.

But there is no clear link between exposure and health conditions, not even between high dose exposure and acute conditions. Nothing is simple, and here's why…..

HIGH DOSE EXPOSURE – ACUTE CONDITIONS

- A precise measurement of exposure is almost impossible, particularly when it is being assessed retrospectively. Over time, researchers have improved research protocols and techniques but there are still many uncertainties.
- Toxins rarely occur in isolation and the combinations of toxins may have synergistic or antagonistic effects.
- The possibility of other causes of the condition in epidemiological or case control studies.
- Very few diseases are toxin specific (asbestosis is an exception).

LOW DOSE EXPOSURE (1)

Researchers have all the problems seen with high dose exposure, plus:

- **The dose/response relationship in the low dose range may not be linear. There may be a threshold or an adaptive response.**
- **For many low-dose exposures, the damage is initially very subtle, whereas most scientific research is constructed to measure gross and obvious changes in health from large and easily measurable exposures.**
- **Researchers tend to look for effects in specific organs. This ignores effects on DNA, mitochondria, the immune system etc.**
- **With low dose exposure the initial symptoms are generally non-specific (headache, IBS, fatigue, brain fog, sleep disturbance), which could relate to a number of conditions.**

LOW DOSE EXPOSURE (2)

- The incidence and extent of symptoms is more likely to be governed by individual patient status than the extent or duration of exposure.
- Toxins can induce hypersensitivities, which are not considered by researchers. Those not sensitised may not respond at any low dose, whereas those who are sensitised will respond at extremely low dose exposure.
- How would you tell the difference between a symptom due to low dose toxin exposure or due to hypersensitivity?

ANIMAL STUDIES: ARE THEY THE ANSWER?

Only animal studies can control for uncertainties but there are always difficulties extrapolating results to humans:

- **Animals use different metabolic pathways to humans**
- **Animals have a shorter lifespan so long latency diseases will not be detected.**

BIOMARKERS: ARE THEY THE ANSWER?

Biomarkers from blood, urine, hair/nails are now routinely used to assess exposure. But:

- **Blood and urine biomarkers can indicate very recent exposure or, with metals, past exposure if mobilised by a chelating agent.**
- **Blood lymphocyte testing can indicate a sensitivity, which is indicative of a current toxin load but not conclusive because one remains sensitive for a time after the toxin has been removed. It also does not measure body burden.**
- **Hair/nails only indicate exposure in the recent past.**
- **No biomarker is an accurate measure of past exposure.**
- **No biomarker is an accurate measure of total body burden.**

SAFEGUARDS:
THE PRECAUTIONARY PRINCIPLE

LEGAL SAFEGUARDS

The 1994 Maastricht Treaty established European environmental health policy to comprise:

- **the Precautionary Principle: shifts the presumption that specific chemicals or activities are safe until proven dangerous, to a presumption in favour of protecting public health and the environment in the face of uncertain risks.**
- **the prevention of pollution at its source**
- **the 'polluter pays' principle.**

SO WHAT IS STOPPING THE PRECAUTIONARY PRINCIPLE BEING PRACTISED?

- **UK government:** The UK lags the rest of the developed world with no single department with overall responsibility for the impact of environmental toxins on human health. The DOH and others have an advisory role on Public Health but comprise industry-friendly 'experts'. Basic pollution policy is set by the EU.
- **Economics:** No-one has yet found a mechanism to assign a monetary value to life, health or quality of life.
- **General public:** Believe that every substance in current use and on the market has been tested for toxicity, is safe and 'approved' for use. This is not the case.

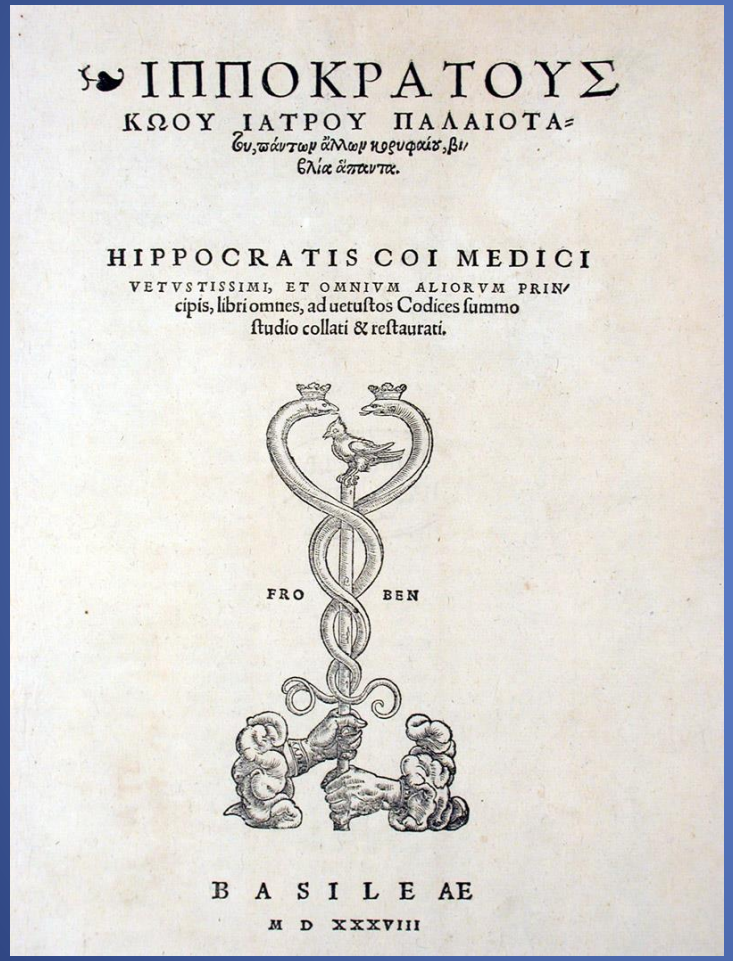
FURTHERMORE….

Just because there are headlines saying a toxin is being or has been banned, don't assume you can discount it as a source of disease:

- **It can take many years from a headline to actual banning (e.g. Minamata Convention)**
- **The ban may be disregarded as it is cheaper to pay the fine**
- **Many toxins have a long half life in the body**
- **The toxin may have been acquired in a country with no ban.**
- **The toxin may have been acquired from an import (e.g. lead in traditional Chinese medicines)**
- **Low dose exposure may take many years to manifest symptoms.**

WHY NOT EVERYONE WITH THE SAME EXPOSURE GETS SICK (SUSCEPTIBILITY)

THE FIRST ACKNOWLEDGEMENT OF SUSCEPTIBILITY?



Hippocrates (On Ancient Medicine) allegedly stated:

'Since some people who eat cheese do well on it, while others do not, the difference must lie in a constituent of the body which is hostile to cheese and is roused and stirred to action under its influence……But if cheese were bad for the human constitution, without exception it would have hurt all'.

THE CONCEPT OF INDIVIDUAL SUSCEPTIBILITY

- Current scientific thinking is that it is all due to gender and genetic factors affecting response to toxins.
- The new field of *toxicogenomics* investigates all the genes in the genome simultaneously to show the response to an environmental toxin.
- Although this research is growing, it is still in its infancy. So far the results are not encouraging.

RESULTS FROM GENETICS STUDIES

- The recent spate of research into the human genome has not brought about one single cure.
- Lichtenstein, Holm, Verkasalo 2000 on cancer susceptibility: ‘Inherited genetic factors make a minor contribution to susceptibility to most types of neoplasm. This finding indicates that the environment has the principal role in causing sporadic cancer’.
- But even this only recognises but does not explain susceptibility since environmental toxins affect different people differently.
- So the true answer to disease causation must be broader than just genetics.

FROM IFM TEXTBOOK OF FUNCTIONAL MEDICINE

‘Genetics is not destiny.

Merely because we have a susceptibility to a particular condition by virtue of our genes does not mean we will suffer from that condition – diseases are not hard-wired into our genes.

What determines whether or not we contract a disease is how our genes are expressed (epigenetics), which can be influenced by potentially modifiable factors (diet, weight, inactivity, smoking, environmental exposure).

This also determines our biochemical individuality’

FACTORS INFLUENCING DISEASE AETIOLOGY

- The "total load" concept: the total of all exposures in a susceptible individual contribute to a breakdown of homeostatic mechanisms.
- Multiplicative effect of certain toxins - see next
- Individual susceptibility: genetic predisposition (e.g. polymorphisms in detoxification enzymes), gender, age, nutritional status, microbiome status and emotional and physical stress.
- Adaptive ability: the ability of an organism to adjust to gradually changing circumstances.

EXAMPLE OF THE MULTIPLICATIVE EFFECT OF TOXINS

- Animals given mercury with lead at a dosage for both which would have been lethal in 1% of the animal population.
- Would expect 1-2% to die.
- Instead, 100% of the animals died.

(Schubert, Riley, 1978)

But very little research has been carried out on multiple exposures.

HOW DOES THE BODY PROTECT ITSELF AGAINST TOXINS?

THE BODY'S DEFENCES

- Immune system – see following slides
- Detoxification system – see following slides
- Endogenous antioxidant enzymes: glutathione peroxidase, SOD, catalase etc
- DNA repair mechanisms: methylation + nutrients
- Apoptosis: When DNA cannot be repaired, the cell may undergo programmed cell death before the altered DNA can be replicated.

THE IMMUNE SYSTEM

- 3 protective barriers: skin, GIT, lung membranes – but they can be penetrated
- GIT: toxins enter circulation through intestinal permeability and absorption through molecular mimicry.
- But we have gut-associated lymphoid tissue (GALT): 60% of immune system located in the mucosa, producing localised secretory IgA and systemic IgE or IgG.
- Healthy microflora are needed to support GALT.
- Mucosa-associated lymphoid tissue (MALT): Antigens penetrating mucosal surfaces activate MALT which generates B + T cells to circulate in search of target antigens.

THE BODY'S DEFENCES: DETOXIFICATION

- Occurs mainly in the liver followed by the intestinal mucosa. All cells have some capacity for metabolising toxins.
- Phase I: Biotransformation enzymes (e.g. cytochrome P450, alcohol dehydrogenase) convert lipid-soluble toxins to water-soluble (more polar) for conjugation through oxidation, reduction or hydrolysis.
- Phase II: Conjugation enzymes which attach polar groups (e.g. glutathione, glycine, glucuronic acid, taurine, methyl groups, sulphate) to the Phase I metabolites.

PROBLEMS WITH DETOXIFICATION

- Many toxins are lipophilic and can easily penetrate lipid cell membranes and accumulate in adipose tissue, particularly those that are resistant to biotransformation (e.g. PCBs).
- Phase I: The biotransformed metabolite may be more toxic than the original, binding to DNA, crosslinking with proteins or generating high levels of ROS. Many of these metabolites are known carcinogens.
- Phase I and II enzymes may have polymorphisms which make them more or less efficient.
- Upregulated Phase I and downregulated Phase II is the worst combination! Associated with many chronic diseases.

INTRODUCTION TO OUTDOOR AIR POLLUTION

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SOURCES OF OUTDOOR AIR POLLUTION

Outdoor air pollution is a complex mixture of multiple pollutants, gases and particles.

Concentration depends on emission sources, weather, land patterns

- **Natural:** Radon, VOCs
- **Vehicle emissions:** NO_2, CO, PMs, O_3, VOCs
- **Industrial emissions:** As vehicle emissions + SO_2, CO_2, toxic metals
- **Landfill/hazardous waste sites:** CO_2, hydrogen sulphide, methane, ammonia, VOCs
- **Incinerators:** As industrial emissions + HCl, PCBs, dioxins, furans, PAHs

WHAT IS PARTICULATE MATTER (PM)?

- PMs are microscopic solid or liquid particles suspended in air. They may be derived from combustion sources (industrial emissions or vehicle emissions, particularly diesel) or from dust.
- Almost any pollutant can have a particulate form, which makes them particularly toxic because they can penetrate deep into the lungs and enter the circulation, whereas a filter system exists in the body for larger pollutants. The smaller particles may also penetrate indoors.
- PMs are generally described by aerodynamic diameter: PM10 means the particles have a diameter of 10 microns. The larger PMs will be PM10 or greater, while smaller particles may be 'fine' (PM2.5) or 'ultrafine' (PM0.1).

Volkswagen diesel emissions scandal

But it's all going to be OK because……

Leonardo DiCaprio to produce Volkswagen Scandal film

VEHICLE EXHAUSTS: PROBLEMS NEW AND OLD

- **New:** Diesel engines are more efficient than petrol engines but their airborne emissions are greater, releasing a combination of gases (nitrogen oxides), ultrafine particles, benzene, formaldehyde and polycyclic aromatic hydrocarbons (PAHs) (Kagawa J, Toxicology, 2002).
- **Client Impact:** Exposure for anyone in an urban environment

- **Old:** Lead used to be added to petrol as an anti-knocking agent. Although banned in Europe and much of the world on health grounds, there are still countries where lead is still added to petrol: Afghanistan, Algeria, Iraq, Myanmar, North Korea, Yemen
- **Client Impact:** You may have clients born in these countries.

IMPACT OF GLOBAL WARMING

- Since urban air pollution depends in part on temperature, higher temperatures will only increase concentrations
- Because ozone is formed through the reaction of solar radiation and other pollutants, increased solar radiation will increase ozone concentrations.

STUDIES INVESTIGATING THE HEALTH EFFECTS OF OUTDOOR AIR POLLUTION (1)

- Most studies investigate air pollution as a whole or by a surrogate marker, so the exact impact of each gas is unclear.
- Many epidemiological studies fail to correct for temperature, weather, population characteristics, presence of other pollutants etc.
- And a confounding factor will always be individual exposure to indoor air pollution – no study controls for this.
- While these epidemiological studies often show associations, the criticisms relating to confounders devalue the message of the studies.
- Only controlled human exposure studies can allow for confounders but these are unethical.

STUDIES INVESTIGATING THE HEALTH EFFECTS OF OUTDOOR AIR POLLUTION (2)

- The best known health problems are respiratory disease and MIs and related mortality (Dockery DW 1993; 1994; Katsouyanni K 1997);
- Emergency hospital admissions are known to increase significantly during times of high air pollution (Samet, Cohen, 1999; Wolkoff P 2000).
- Those particularly at risk: the elderly, children, those with COPD (Zanobetti A 2000).
- Children are particularly at risk because they breathe more rapidly than adults, allowing for the inhalation of more pollutants per kilogram of body weight, and they spend more time playing outdoors and close to the ground, increasing the likelihood of exposure.
- Exacerbating factors: asthma, pre-existing respiratory infection.

STUDIES INVESTIGATING THE HEALTH EFFECTS OF OUTDOOR AIR POLLUTION (3)

- There is a 40% increased lung cancer risk from vehicle NO2 emissions (Nyberg F, Epidemiology, 2000).
- Children residing within 750 feet of roads with the highest traffic density (>20,000 vehicles per day) had a >6-fold increase in risk of all cancers and >8-fold increase in risk of leukaemia compared to children with the lowest traffic density exposures (Pearson RL, 2000).
- Vehicle emissions are also associated with neurodevelopmental deficits (Calderon-Garciduenas 2008; Perera 2009).
- Proximity to traffic during pregnancy was associated with asthma development in offspring up to age 5 (Sbihi H, Eur Rep J, 2016).

HEALTH EFFECTS OF INHALED PARTICULATE MATTER

- The WHO has designated PMs a Group 1 carcinogen, causing permanent DNA mutations, as well as MIs and premature death
- In 2013, a study involving 312,944 people in nine European countries revealed that there was no safe level of particulate matter and that for every increase of 10 µg/m3 in PM10, lung cancer rates rose 22%. The smaller PM2.5 were associated with a 36% increase in lung cancer per 10 µg/m3 (Raaschou-Nielsen O, Lancet Oncology, 2013).
- Increased daily PM levels are associated with increased mortality, which peaks within a few days of exposure, and CV mortality (Laden, Neas, Dockery, Schwartz, 2000; Frampton, Utell, Zareba 2004).
- A UK study found associations between PM10 and all respiratory admissions, pneumonia and deaths from COPD (Wordley J, Walters S, Ayres JG, 1997).
- Asthmatic children are particularly at risk (Delfino RJ, Zeiger RS, Seltzer JM, 2002).

HEALTH EFFECTS OF OZONE

- The APHEA project showed a 2.9% increase in mortality associated with a 50µg/m3 increase in daily ozone (Touloumi G 1997).
- Long term exposure may be a risk factor for asthma (McConnell R 2002; McDonnell WF 1999) and lung cancer incidence and mortality (Beeson WI 1998; Abbey DE 1999).
- Increase of 100µg/m3 in daily ozone concentration was associated with admissions for pneumonia (Schwartz J, Arch Environ Health, 1994).

HEALTH EFFECTS OF NITROGEN DIOXIDE

- **Increased accident and emergency room visits** (Kesten S, Szalai, J, Dzyngel B, 1995; Buchdahl, R, Parker A, Stebbings T, 1996)
- **Increased hospital admissions** (Bates DV, Sizto R, Environ Res 1987; Ponka A, Virtanen M, Environ Res 1994)
- **Increased respiratory symptoms** (Braun-Fahrlander C, Schwartz J, Gnehm HP, 1992; Mukala K, Pekkanen J, Tiittanen P, 1996)
- **Reduced lung function** (Frischer TM, Kuehr J, Pullwitt A, 1993; Scarlett JF, Abbott KJ, Peacock JL, 1996)
- **An increase of 50µg/m3 was associated with a 2.6% increase in asthma admissions and a 1.3% increase in daily all-cause mortality** (Touloumi G, Katsouyanni K, Zmirou D, 1997).

WHAT CAN BE DONE ABOUT OUTDOOR AIR POLLUTION?

- Clean Air Acts made a significant difference in reducing adverse health effects and reducing the burden of respiratory disease.
- But it's not just our air pollution: New York City has mercury and aluminium dust, which has been carried on the air from China, while western Europe suffered the Chernobyl fall-out from Ukraine.
- Traffic reduction measures work: with deliberate reduction in traffic density for the 2000 Olympic Games in Atlanta, GA, hospital asthma admissions were significantly reduced (Friedman MS, Powell KE, Hutwagner L, 2001).
- But in the end we have to reduce the pollution from vehicle exhausts, industry and incinerators.

INTRODUCTION TO VOLATILE ORGANIC COMPOUNDS

RACHEL NICOLL

WHAT ARE VOLATILE ORGANIC COMPOUNDS (VOCs)?

- VOCs are organic (i.e. carbon-containing) chemicals that have a high vapour pressure at room temperature.
- This means they can easily evaporate as gases into the air from some solids or liquids.
- Many of them are solvents, which may be smelled to induce intoxication e.g. glue sniffing.
- Because they are ingredients in many commonly used products, they are present in virtually all indoor air, particularly from cleaning products, toiletries and perfume.
- Levels of VOCs increase as temperature rises, so if a building is deemed 'safe' on a cold day, it says nothing about its condition on a hot day.

PRINCIPAL SOURCES OF VOCs

Formaldehyde	Embalming, paints, adhesives, plastics, soft furnishings, building materials, insulation, natural gas, kerosene, cigarette smoke
Vinyl, polyvinyl chloride (PVC)	Wallpaper, upholstery, carpets, building materials, vehicles, plastic products, rubber, paper, glass.
Polycyclic aromatic hydrocarbons (PAHs)	All forms of cooking, incense, cigarette smoking, vehicle exhausts, industrial emissions, mothballs, tar, pitch, creosote, pesticides, toiletries, synthetic turf. Incineration of plastic waste such as PVC.
Ethanol (alcohol)	Perfume, air fresheners, toiletries, hairspray, nail polish/removers, detergents, paints, varnishes/removers, industrial cleaners, de-icers.
Benzene	Cigarette smoke, fuels, vehicle exhausts, plastics, adhesives, cleaners.
Perchloroethylene	Also tri- or tetrachloroethylene. Dry cleaning, carpets, paints, degreasing.

VOCs: ROUTES INTO AND OUT OF THE BODY

- VOCs are highly lipophilic and have small molecule size, so they can easily enter the lungs and be absorbed across the lung membranes and enter the blood supply. Blood from the lungs moves directly to the brain and other organs before reaching the liver, where metabolism of the VOC occurs.
- VOCs are also well absorbed from the gut, although the presence of food may delay absorption.
- The skin offers little barrier to lipophilic VOCs and skin exposure can result in local irritation and increased blood levels of the chemical.
- VOCs are eliminated from the body by metabolism or exhalation.
- Metabolism occurs mainly in the liver by CYP450 enzymes. Generally this results in reduced toxicity and increased elimination but not in the case of benzene, which is metabolised to a more toxic chemical.

EXTENT OF VOCs IN THE BODY

- A US study found that xylene, dichlorobenzene, ethylphenol and styrene were present in 100% of tissue samples tested across the country (EPA 1982).
- The US EPA studied fat tissues from corpses and liposuction patients and found that:
  - 100% of samples contained styrene, 1,4-dichlorobenzene, xylene and ethylphenol
  - 91-98% of samples contained benzene, toluene and ethylbenzene

ACUTE EFFECTS OF VOCs

- Dizziness, drowsiness, sleepiness, headache, confusion, nausea, ear, nose, throat and eye irritation.
- If the source persists, exposure can lead to poor sleep, impaired memory and concentration, persistent flu-like symptoms, difficulty in speaking and walking, unconsciousness and death.
- Skin irritation and rash may result from repeated or extended skin contact.

(Molhave L 1986; Kjaergaard SK 1991; Hudnell HK 1992; Prah JD 1998; Molhave L 1986; Kjaergaard SK 1991; Hodgson, Levin, Wolkoff, 1994; Koren HS 1992).

- A beneficial use of an acute effect: anaesthetics (ether, nitrous oxide, chloroform, cyclopropane, halothane).

LONGER-TERM HEALTH EFFECTS OF CHRONIC EXPOSURE

Formaldehyde	Childhood asthma (McGwin, Lienert, 2011); miscarriage and birth defects (Duong A, Mutat Res, 2011); cancer (Nielsen GD, Wolkoff P, 2010)
Vinyl/polyvinyl chloride (PVC)	Cancers of liver and brain (Kielhorn J, Melber C, 2000); lung cancer mortality (Wagoner JK, 1983)
Polycyclic aromatic hydrocarbons	Lung cancer (Bolm-Audorff U, 1996); DNA adducts and strand-breakage (Fu PP, Xia Q, Sun X, 2012)
Ethanol (alcohol)	Intestinal permeability (Elamin EE, Nutr Rev, 2013); neurotoxicity (Luo J, Autophagy, 2014; Yang JY, Xue X, Tian H, 2014); liver cancer and disease (Shukla SD, Lim RW, 2013)
Benzene	Leukaemia (Irons RD, Kerzic PJ, 2014); reproductive, immune, nervous, endocrine, CV and respiratory conditions (Bahadar H, 2014); asthma and allergy (Nurmatov UB, 2015)
Perchloroethylene	Cancer (Lash LH, Parker JC, 2001; Weiss NS, 1995); congenital heart defects (Bukowski J, 2014); skin disorders (Cooper GS, 2009)

WATCH OUT FOR OCCUPATIONAL EXPOSURE

- In the 18th century the connection was made between cancer of the scrotum and soot exposure among chimney sweeps. The carcinogen is the polycyclic aromatic hydrocarbons (PAHs) in the coal tar.
- Modern occupational exposure includes painters, hairdressers, manicurists, manufacturers, dry cleaners, cleaners, mechanics.

INTRODUCTION TO TOXINS FROM LANDFILL OR HAZARDOUS WASTE SITES AND INCINERATORS

RACHEL NICOLL

TYPES OF HEALTH HAZARD FROM LANDFILL AND HAZARDOUS WASTE SITES

- Biological and food wastes: diseases spread by microorganisms, insects and rodents
- Poorly lined landfill sites: microorganisms, toxic metals and chemicals (PCBs, dioxins, chlorinated hydrocarbons, hydrogen sulphide, pesticides, asbestos, pharmaceutical drugs) can leach out, contaminating the soil and water sources
- Air pollution from landfill sites: toxic gases (methane, hydrogen sulphide, carbon dioxide), mercury vapour (mercaptans), VOCs including ammonia, tri- and tetrachloroethylene and petroleum distillates. Landfills account for 5-20% of methane emissions into the atmosphere.

In addition, microbial degradation of garbage and vegetative waste in a landfill site can produce organic acids, which lower the pH of the site, making metals more soluble.

EXAMPLE FROM NORTH CAROLINA, USA

- In an incident in North Carolina in 1969, methane gas from a landfill site migrated underground through the soil to the basement of an armoury building adjacent to the landfill.
- The methane gas built up to a dangerous level in the basement and a lit cigarette triggered an explosion that killed 3 men and injured 5 others.

PROBLEMS WITH CONDUCTING STUDIES OF THE HEALTH EFFECTS OF LANDFILL, HAZARDOUS WASTE AND INCINERATORS

- Distance from the site is usually taken as a surrogate measure of exposure but this can lead to misclassification of exposure and underestimation of the true relative risk. Factors other than distance may be critical, e.g. wind speed and direction, direction of flow of groundwater.
- Dose levels at hazardous waste sites are particularly hard to estimate and it is usually not known which chemicals may be responsible.
- Because of the latency period for cancer and other chronic diseases can be 10-40 years, it is difficult to establish patterns of exposure and to gather data on a sufficiently large population group to confirm a definitive relationship.
- Most evaluations are carried out for single toxicants and take no account of combinations of toxicants as is usually the case in hazardous waste.

HEALTH EFFECTS FROM LANDFILL AND HAZARDOUS WASTE SITES

- **Symptoms of low dose exposure: headache, malaise, minor skin irritation, respiratory tract complaints, but these are common to many conditions.**

Rachel Nicoll, British Society for Ecological Medicine, 2016

HEALTH EFFECTS FROM LANDFILL AND HAZARDOUS WASTE SITES

- **Cancer:**
  - **Increased gastrointestinal, oesophageal, stomach, colon and rectal cancers (Najem GR 1983; Griffith J 1989);**
  - **increased risk of cancers of the liver, kidney and pancreas and non-Hodgkin's lymphoma (Goldberg MS 1995; Goldberg MS 1999).**
- **Congenital abnormalities:**
  - **a dose-dependent 12% increase in malformations of the nervous and musculoskeletal systems in those living within 1 mile of a site (Geschwind SA, Stolwijk JAJ. Am J Epidemiol. 1992).**
  - **neural tube defects and cardiac malformations in those residing within 3km of hazardous waste sites (Dolk H, Vrijheid M. Lancet 1998).**

INCINERATORS AS SOURCES OF TOXINS

- Incinerators can emit particles, acidic gases and aerosols, hydrochloric acid, toxic metals, dioxins, furans, PCBs and polycyclic aromatic hydrocarbons (PAHs).
- Modern incinerators show much reduced emissions compared to old uncontrolled incineration facilities but an incinerator will always emit some dioxins.
- Domestic bonfires may also release dioxins into the atmosphere.

HEALTH EFFECTS OF INCINERATOR EMISSIONS

- Cancer: Increased lung and laryngeal cancer (Hu S, Shy CM. 2001). A UK study found increased risk of liver cancer among those living within 1km of a site (Elliott P, Br J Cancer, 2000). In Sweden, there was increased mortality due to lung cancer and ischaemic heart disease among incinerator workers (Gustavsson P 1989).
- Birth defects: A UK study found increased infant mortality due to spina bifida and heart defects near incinerators and crematoriums (Dummer TJ, Dickinson HO. J Epidemiol Community Health. 2003).
- Heart disease: Increased CV mortality among incinerator workers (Gustavsson P 1989); increased ischaemic heart disease (Hu S, Shy CM. 2001).

INTRODUCTION TO INDOOR AIR POLLUTION

RACHEL NICOLL

WHY IS INDOOR AIR POLLUTION IMPORTANT?

- Often it is ignored while the focus is on outdoor pollution.
- But…most people spend a significant proportion of their time indoors, particularly the most vulnerable: the very young, the elderly, the infirm.
- In many cities, indoor air pollutant concentrations exceed those outdoors.
- The US EPA ranks poor indoor air quality among the top 5 environmental risks to public health; they found concentrations of VOCs in indoor air to be up to 5 times greater than in outdoor air and sometimes far greater.
- And the levels of VOCs in personal air space was highest at night, the time when the body should be resting and repairing.
- A 1993 study found that indoor air provided more pesticide exposure than outdoor air (Whitemore RW, Arch Environ Contam Toxicol 1994).
- A US EPA study found that dichlorobenzene, found in mothballs and air fresheners, was present in the urine of 96% of children and 98% of adults.
- But there are no standards for indoor air pollution, as there are for outdoor air pollution – the public fear 'Big Brother', plus legislation would be virtually unenforceable.

HOW HAS INDOOR AIR POLLUTION BECOME SUCH A PROBLEM?

- Energy conservation measures, largely since the energy crisis of the 1970s, has dramatically decreased ventilation.
- Instead of opening windows, we live and work in a hermetically sealed, double glazed, weather-proofed environment, controlled by heating, humidifiers and air conditioning.
- This has increased the moisture content of the air, leading to the growth of moulds and release of spores and mycotoxins, which are harmful if inhaled, ingested or absorbed through the skin. All excess moisture problems (leaks, floods, excessive humidity) allow these organisms to thrive.
- The lack of ventilation means that no toxins can escape the home, leading to a build-up of VOCs, pesticides, tobacco smoke and toxic metals in air and dust, which settle on floors and soft furnishings, particularly carpets.
- Toddlers and infants are most at risk from chemicals in the carpet, as they spend much of their time on the floor and tend to put objects and fingers into their mouth.
- Sweeping, vacuuming and dusting may remove large particles but increase circulation of the more dangerous minute and easily inhaled particles.

SOURCES OF INDOOR AIR POLLUTION

- Fossil fuel combustion: CO, SO2, NO2, hydrogen chloride (HCl), particulates (PM), ozone
- Off-gassing of new building materials, carpets, furniture and furnishings: Formaldehyde, pesticides, brominated flame retardants and other VOCs
- Home office equipment and supplies: VOCs: formaldehyde, benzene
- Dry cleaning: Tetrachloroethylene
- Spraying for pest control: Insecticides
- Mothballs, air fresheners: Dichlorobenzene, naphthalene (hazardous waste!)
- Cleaning agents, perfume: Benzene, acetaldehydes, terpenes (d-limonene; d-pinene)
- All plastics: Phthalates
- Tobacco smoke: PMs, toxic metals, toxic gases, VOCs, nitrosamines
- Radon: In certain areas of the UK, particularly Cornwall
- Bioaerosols: Mould/fungus spores, bacteria, pollen, mites, algae, animal dander
- Dust: Toxic metals, pesticides, asbestos, fibre glass

USE OF BIOMASS FUELS

- Biomass fuels comprise coal, coke, wood, charcoal, kerosene, paraffin, crop waste, animal dung, heating oil.
- In the developed world, use is decreasing but it is still the principal means of cooking and heating in the developing world.
- Many of your clients may have grown up in just such a home.
- Biomass fuel combustion produces the same pollutants as vehicle exhausts, with the addition of carbon monoxide.
- Developing countries also tend to have a higher incidence of smoking and greater use of pesticide sprays and mosquito coils, making the air highly toxic.
- It is estimated that 1.4 billion urban residents breathe air with contaminant levels that exceed WHO air quality guidelines.
- In 2002, the 'brown cloud', produced by the combustion of biomass fuels, covered southern Asia and was estimated to be 2 miles thick.

Smoke from indoor cooking fires kills one person every 20 seconds in the developing world, UK campaigners say (BBC, 2003).

The US Secretary of State Hillary Clinton has announced a global partnership to tackle the scourge of toxic smoke from indoor cooking fires (BBC 2010)

SYNTHETIC BUILDING MATERIALS AND FURNISHINGS

- There are now very few natural materials used for building, furniture and soft furnishings. Those that are natural will have been treated with pesticides or flame retardants.
- A UK study found that new carpets contained significant levels of brominated flame retardant, pesticides and formaldehyde (Allsop M, Greenpeace Research Laboratories 2001).
- This results in 'off-gassing', a process which may take several months.

EXTERNAL POLLUTANTS BROUGHT INDOORS

- All external air pollutants can travel indoors, particularly in summer. External ultra-fine particulate matter can migrate into even the most tightly sealed building.
- In air conditioned buildings, an air intake near ground level will bring vehicle emissions indoors.
- Petrol/diesel fuels, oil and pesticides can be walked indoors on shoes.
- Clothes newly returned from the cleaners give off tetrachloroethylene.

WHO IS AT RISK?

- Toddlers, infants, the sick and the elderly are at high risk, as well as the increasing number of people now working from home.
- A study comparing women who work outside the home with women who work at home found a 54% higher risk of developing cancer in those who work at home.

HEALTH EFFECTS OF CARBON MONOXIDE (CO)

- Mechanism: CO has a high affinity with haemoglobin (Hb), 200-250 times that of oxygen. This means it will preferentially bind with Hb to form carboxyhaemoglobin (COHb), thereby lowering oxygen transport and hence availability.
- The brain and heart are particularly vulnerable to low oxygen.
- Acute exposure results in visual impairment, fatigue, decreased dexterity, dizziness, nausea, CV and neurological symptoms and mortality.
- In controlled human exposure studies in patients with CAD, increased COHb levels were associated with shortening of time to onset of angina, increased cardiac arrhythmia, hospital admissions for cardiac disease and CV mortality (Peters A 2000; Schwartz J 1999; Touloumi G 1996; Samet J 2000).

BIOMASS/FOSSIL FUELS

- Exposure to biomass fuels in developing countries may be responsible for nearly 2 million deaths and represents 4% of the global burden of disease (Bruce N 2000).
- Evidence from 13 studies from developing countries indicates that young children living in biomass fuel-using households have 2-3 times higher risk of acute respiratory infection than unexposed children (Smith KR 2000); women are also at risk (Golshan, Faghihi, Marandi 2002).
- Smoke from biomass fuels is a clear risk factor for acute respiratory and other infections, COPD, asthma, TB, low birth weight, cataract, blindness and lung and other cancers (Smith KR 2002; Bruce, Perez-Padilla, Albalak, 2000; Ezzati, Kammen 2002; Balakrishnan 2002) and around 5% of global mortality (Ezzati, Kammen, 2002).
- A Los Angeles study (i.e. not in the developing world!) showed that coal use for cooking and heating during childhood and adolescence was associated with an odds ratio of 2.3 for adenocarcinoma (Wu AH, Henderson BE, Pike MC, 1985).
- Ozone may react with terpenes (d-limonene; d-pinene ,which add fragrance to cleaning products) to form ultra-fine/fine particles, aldehydes, hydrogen peroxide, carboxylic acids, reactive intermediates and free radicals (Fan Z 2003; Weschler CJ 1996; Wainman T 2000). Animal studies suggest that these contribute to health effects (Wolkoff P 2000).

HEALTH EFFECTS OF INDOOR AIR POLLUTION: MOULD

- Moulds are microorganisms which manufacture biotoxins, which can form into bioaerosols.
- Mould toxins enter the body through the lungs, so they generally affect the respiratory system as well as inducing hypersensitivity by stimulating an allergic response. Once the hypersensitivity response has been established, even a tiny amount of the antigen may cause a severe reaction.
- In susceptible people (HLA gene?), they bind to fat-cell receptors causing continually upregulated production of cytokines.
- Chronic exposure can induce autoimmunity and systemic inflammation, resulting in MS or idiopathic peripheral neuropathy (Campbell AW, Thrasher JD 2003).
- Idiopathic pulmonary haemorrhage may be associated with the mould *Stachybotrys chartarum* (Hodgson, Dearborn 2002).

HEALTH EFFECTS OF SMOKING

- Globally, tobacco use causes >4 million deaths each year, c11,000 each day (Meister 2003). Years of life lost through smoking: males 13; females 14.
- Many cancers are linked to cigarette smoke. Two meta-analyses of studies of lung cancer and adult exposure showed that RRs were around 1.20 in women and 1.30 in men (IARC 2003; Hackshaw AK, Law, MR, BMJ 1997).
- Passive smoking delivers the same toxic compounds as active smoking (Boffetta P, Scand J Work Environ Health, 2002; Strachan DP, Cook DG. Health Effects of Passive Smoking, Parts 1,4 and 6, 1997 and 1998; Thun M 1999; Hackshaw AK 1997; Anderson HR 1997; Windham GC 1999).
- A 1997 study found that by age 65, the risk of developing heart disease if you live with a smoker was 30% higher than if you did not and was equivalent to the risk of smoking 20 a day (Law MR, BMJ 1997).
- Passive smoking may also be associated with breast cancer and TB (Khuder SA 2000; Alcaide J 1996; Altet MN 1996).

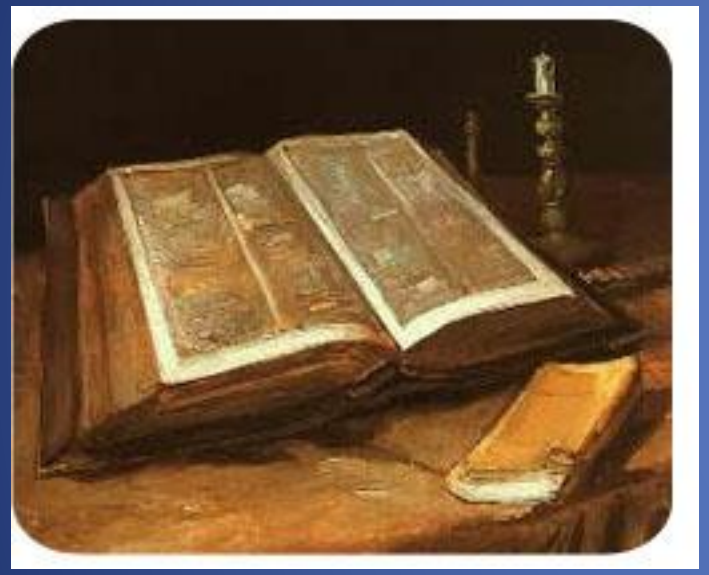
And a quote from Mark Twain

‘To cease smoking is the easiest thing I ever did. I ought to know, I’ve done it a thousand times.’ Mark Twain

INTRODUCTION TO SICK BUILDING SYNDROME

RACHEL NICOLL

EARLIEST WRITTEN ACCOUNT OF SICK BUILDING SYNDROME AND A HAZARDOUS WASTE SITE



Leviticus 14: 33-45

'I put the plague of leprosy in a house….and he that owneth the house shall come and tell the priest…and the priest shall command that they empty the house….and the priest shall go in... and, behold, if the plague be in the walls of the house….then the priest shall shut up the house for seven days. And the priest shall come again the seventh day…and behold, if the plague be spread in the walls…then the priest shall command that they take away the stones in which the plague is, and they shall cast them into an unseen place without the city.'

WHAT IS SICK BUILDING SYNDROME (SBS)?

- There is no precise definition of SBS.
- It may also be known as non-specific building-related illness (NSBRI).
- It was originally called ‘tight building syndrome’ as it resulted from living in a hermetically sealed environment with little ventilation.
- Any building can become a ‘sick building’, particularly a new or remodelled building, which has a substantial amount of chemical off-gassing.
- Modern buildings seal the chemicals into the building, particularly those with automated climate control systems, that continuously recirculate the toxic gases, dust and bacteria.
- There may be complaints about indoor air quality.

PRINCIPAL SOURCES OF SICK BUILDING SYNDROME

- Micro-organisms (bacteria, viruses, moulds and spores),
- Allergens,
- High humidity; moisture/damp sources,
- Radon,
- Tobacco smoke,
- Office cleaning supplies
- Wood dust, fibreglass, asbestos
- Office machinery, particularly photocopying
- Air intake systems sited at street level which suck in vehicle exhaust gases.
- VOCs off-gassing from building material and furnishings, particularly formaldehyde and benzene
- Heating and air conditioning, humidification, associated bacterial growth

IS VENTILATION THE KEY?

- Investigations in several countries consistently show an association between complaint frequency and a poor ventilation system (Mendell, Fisk, 1997).
- An important randomised controlled trial indicated that bacterial growth on damp cooling coils within the building, may be the cause of many symptoms; amelioration was achieved by irradiating the cooling coils (Menzies, 2003).
- In schools, studies show that the air in may contain moulds, formaldehyde, benzene and other VOCs.
- And in offices, the source is largely VOCs from new furnishings, wall coverings and office equipment.
- In healthcare facilities, low ventilation rates are associated with transmission of viral illness (Menzies, Fanning, Yuan, FitzGerald, 2000; Myatt TA, 2004) and moisture and fungi are a risk for immunosuppressed patients (Streifel AJ, 2002).
- So poor ventilation may be a significant factor but without the mould and off-gassing of VOCs, improved ventilation would not be needed.

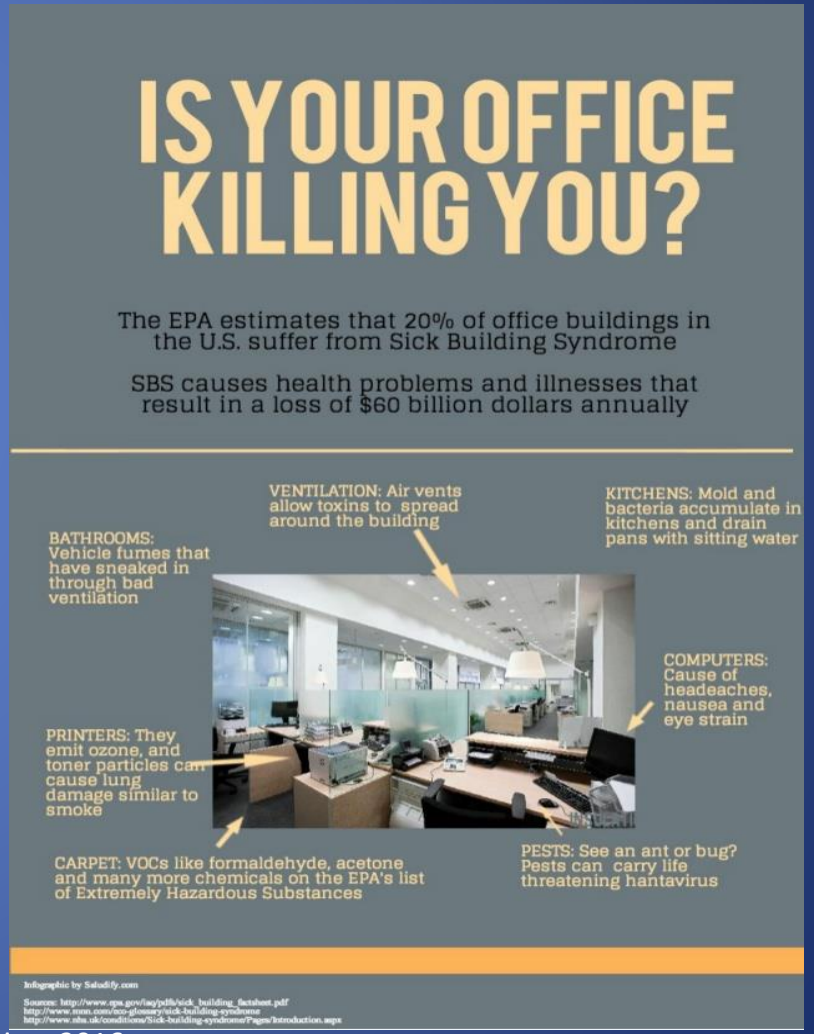
Acute health effects

Headaches, fatigue, concentration loss, memory loss, confusion, shortness of breath, cough, dysosmia (distorted sense of smell).

Chronic health effects	
Rhinitis/sinusitis	Allergens, moulds, spores, chemicals, cleaning agents, VOCs
Asthma	Cleaning agents, VOCs, allergens, moulds, phthalates
Hypersensitivity pneumonitis	Moulds, bacteria, wood dust, methylene diisocyanate (MDI), other VOCs
Infectious agents and diseases	Legionella pneumophila, mycobacterium tuberculosis, viruses
Lung cancer	Radon, tobacco smoke, asbestos, combustion products
Dermatitis	Fibreglass, VOCs, low humidity, formaldehyde, fungal allergens, equipment emissions
Organic dust toxic syndrome/inhalation fever	Gram negative bacteria, moulds

WHO IS MORE SUSCEPTIBLE?

- Those with pre-existing allergies and sensitivities describe higher symptom frequencies. They also respond to irritants at lower levels and have lower irritant thresholds (Kjaergaard, Pedersen, Molhave, 1992).
- Health care workers have the highest rates of asthma of any occupational group in the US.
- Stress can make SBS symptoms worse (Ooi PL, Goh KT. Int J Epidemiol 1997; Skov P Scand J Work Environ Health 1989).



DAMP AND MOULD

- If everyone in the building is getting sick, it is probably mould.
- Several studies have found that the common symptoms of SBS were associated with presence of moisture (Bornehag CG, 2001; Bornehag, Sundell, Sigsgaard, 2004; Pommer L, 2004).
- Chronic exposure from water-damaged buildings can induce neuronal autoimmunity and systemic inflammation, resulting in multiple sclerosis or idiopathic peripheral neuropathy (Campbell AW, Thrasher JD 2003).
- Symptoms of fatigue, headache, lethargy and other non-specific symptoms may be associated with moisture or humidity (Teeuw, Vandenbroucke-Grauls, Verhoef, 1994; Schwartz, Stewart, Lipton, 1997; Warshaw, Burton, 1998).
- Mould mycotoxins damage the mitochondria, affecting energy production. The gut lining is particularly vulnerable to lack of ATP.

TRANSPORTATION

Motor vehicle interiors:

- Petrol and diesel combustion generates particulate matter and VOCs (benzene, acetone, cyclohexane, ethyl benzene, MIKB and xylene), some of which seep into the interior, particularly during rush hour traffic.
- Cars also contain plastics, PVC, stain resistant chemicals, synthetic carpets and furnishings manufactured with pesticides. The 'new car smell' is neurotoxic solvents. Even after four months, levels inside cars were 4 times the accepted safe level.
- CO2 is generated by breathing if the windows are closed.

Aircraft interiors

- Can contain elevated CO2 concentrations, pesticide sprays, perchloroethylene from dry cleaned uniforms, toxic metals from instruments and toxic gases from oil seepage.
- In addition, most airlines have a policy of recycling at least 50% of the aircraft air.
- On long haul flights, passengers and crew are sealed for hours in a poorly ventilated chamber that has recently been gassed.
- Is severe jet lag merely air toxin poisoning?

INTRODUCTION TO PERSISTENT ORGANIC POLLUTANTS

RACHEL NICOLL

WHAT ARE PERSISTENT ORGANIC POLLUTANTS (POPs)?

- They are pollutants, which are organic (carbon-based) and persistent in the environment. They are also persistent in our bodies (normally adipose tissue) but people seem to care less about that!
- They may comprise some pesticides, solvents, industrial chemicals, metals and pharmaceuticals.
- Some POPs are also volatile organic compounds (VOCs) or semi-VOCs and may travel thousands of miles before depositing on the earth or water.
- Degradation can take up to 100 years
- The UN Binding Convention on Persistent Organic Pollutants in 2001 banned 11 POPs but many others remain in use.
- Because they are 'persistent', even those banned 15 years ago remain in the environment and our bodies.

THE PRINCIPAL POPs

Note: ***I am not talking about POPs that are also VOCs as I have covered those under VOCs.***

- **Polychlorinated biphenyls (PCBs): Used in insulation; found in much old electrical equipment, office products and pesticides. Foods: meat, fish, dairy. Also found in cord blood and breast milk.**
- **Polychlorinated dibenzofurans (PCDFs, furans): Produced by incineration of organochlorine chemicals: paints, solvents, pesticides, plastics. Also found in electrical equipment.**
- **Polychlorinated dibenzo-*p*-dioxins (PCDDs, dioxins): Also produced by incineration of organochlorine chemicals: paints, solvents, pesticides, plastics. Used in manufacture of pesticides and white paper products. Found in animal fat.**
- **Phthalates: Used in any plastics, including cling film and other food packaging and manufacture of cosmetics, pharmaceuticals, toiletries and pesticides. Found in air, food and water.**

CLEAN-UP COSTS OF POPs

- Removal of PCB-contaminated sites in Sweden would cost $400-650 million 10 years ago. Extrapolating to all sites in the EU, clean up would cost around $23 billion.
- These costs do not include expenses associated with renovation costs of removing all PCBs in caulking or other building materials.
- In the US, removal of PCB-contaminated sediments from the Hudson River had by 2010 cost General Electric $830 million and the project was not completed.
- A PCB-polluted harbour cost an electrical component plant $366 million in 2012 – fishing had been banned there since 1979.

EXAMPLE OF PREVALENCE OF POPs IN THE BODY

- A US NHANES study found that 75% of participants aged >5 had phthalate metabolites in urine; concentrations differed by racial groups, gender and age (Silva, Environ Health Perspect, 2004).
- The US EPA studied fat tissues from corpses and liposuction patients and found that:
  - 100% of samples contained OCDD (a dioxin), styrene, 1,4-dichlorobenzene, xylene and ethylphenol
  - 91-98% of samples contained benzene, toluene, ethylbenzene, DDE (a breakdown product of DDT, banned in US since 1972), 3 dioxins and 1 furan.
  - 83% of the samples contained polychlorinated biphenyls (PCBs)
- The World Wildlife Fund 2004 conducted the Bad Blood Study by testing the blood of 14 EU environment and health ministers. All the ministers were contaminated with PCBs, pesticide residues, brominated flame retardants and perfluorinated chemicals and most were contaminated with phthalates.
- Many of these chemicals had already been banned but have a long half-life in the body.

HEALTH EFFECTS OF POLYCHLORINATED BIPHENYLS (PCBs)

- *In utero* exposure: impaired brain development, lower IQ scores, ADHD and impaired thyroid function (Jacobson, Fein, Jacobson, 1985; Jacobson JL, Jacobson SW. 1996; Stewart, Fitzgerald, Reihman, 2003; Porterfield SP 1994).
- Less masculinised play in boys and more in girls (Vreugdenhil, Slijper, Mulder. 2002).
- Metabolic disturbance: Altered insulin/glucose metabolism and pancreatic damage (Longnecker MP, Diabetes Care, 2001)
- Breast cancer: (Leng L, Environ Int, 2016; Zhang J, PLoS One, 2015)
- Fertility: Longer TTP from eating polluted fish (Buck G, Vena J. Epidemiology 2000).

POLYCHLORINATED BIPHENYLS (PCBs): HEALTH EFFECTS

Children are not 'little adults':

- **In a famous legal case regarding compensation for PCB poisoning, the poisoned children received only $2,000 while adult claimants received 5 times as much.**
- **This was because the award was made on blood PCB levels and medical conditions developed.**
- **But….the children's serum PCB levels were considerably lower and associated medical conditions developed later.**

HEALTH EFFECTS OF POLYCHLORINATED DIBENZO-*P*-DIOXINS (DIOXINS)

- ***In utero*** **exposure: impaired sperm production and development and thyroid abnormalities** (Faqi AS, Dalsenter PR, Toxicol Appl Pharmacol, 1998; Porterfield SP 1994)
- **Lower testosterone and raised FSH and LH in males** (Egeland GM, Sweeney MH, Am J Epidemiol. 1994)
- **Altered glucose/insulin metabolism** (Longnecker MP, Michalek JE, Epidemiology, 2000)
- **Increased cancer and cancer mortality** (Steenland, Deddens, Piacitelli, 2001)

AIRBORNE DIOXIN EMISSIONS, SEVESO, ITALY, 1976

BBC 25 May, 2000:

‘Dioxin exposure 'cuts number of boy babies'

The number of baby boys born to parents affected by dioxin poisoning fell significantly, scientists report. And the younger the person was at the time of their exposure, the less likely were their children to be boys.

- 135 cases of chloracne (acute)
- Fathers exposed when aged <19 sired more girls than boys. 8 years after the accident 12 daughters and no sons were born to 9 couples with the highest dioxin exposure. (Mocarelli P, Gerthoux PM, Ferrari E. Lancet 2000)
- 20 years after the accident, exposed women with the highest blood levels of TCDD had a 20-110% higher risk of developing endometriosis. (Eskenazi B, Environ Health Perspect, 2002)
- Exposed women had greatly increased breast cancer risk (Warner M, Environ Health Perspect, 2002).

HEALTH EFFECTS OF FURANS AND PTHALATES

- **Furans:** ***In utero*** **exposure: reduced sperm motility in males, shorter stature and earlier sexual maturity** (Guo YL, Lancet 2000).
- **Phthalates:**
  - **Endocrine disruptors** (Cho SC, 2010; Engel SM, 2010), **early puberty in girls** (Colon I, Environ Health Perspect, 2000)
  - **Increased risk of breast cancer** (Lopez-Carrillo 2010 Environmental Health Perspectives)
  - **Increased diabetes risk** (Svensson 2011 Environmental Research)