ENDOCRINE DISRUPTORS AND THEIR EFFECTS ON CHRONIC DISEASE DEVELOPMENT

Rachel Nicoll PhD

What are endocrine disruptors?

- The Endocrine Society defines an endocrine disrupting chemical (EDC) as an **exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action** (Zoeller RT, Endocrinology, 2012).
- EDCs are synthetic or natural chemicals, which are structurally and behaviourally similar to endogenous natural hormones and can either **mimic natural hormones or interfere either with their interaction with their receptors or between the receptors and their target organs and cells,** thereby transmitting confusing or incorrect signalling.
- **Any toxin can be an endocrine disruptor** if it affects the endocrine system. In practice, studies are showing that this is virtually all of them.
- Toxins tend to be called endocrine disruptors somewhat indiscriminately because it is assumed that the mechanism of action is hormonal. Rather than strictly adhere to a definition of 'affecting the endocrine system', I have taken an endocrine disruptor to be **anything that either affects or is presumed to affect the endocrine system**.

Why are EDCs of particular concern (1)?

- Endocrine disruptors defy everything that is known about toxicology: **minute quantities appear to cause damaging effects, which can be completely different from the effects of the same chemical at higher concentrations**, i.e. they violate the established principles of toxicology.
- Consequently, traditional approaches to determining **safe exposure levels** do not work with EDCs.
- **Mechanisms of action are often unclear**, making them difficult to counteract. And it is not always possible to tell whether a toxin is having an effect through endocrine disruption or some other mechanism.
- Also, an EDC that affects one hormone is likely to affect another so some of its effect may be through the interaction of the two hormone systems.
- The situation is further complicated by the fact that the toxic ingredient may arise from product packaging materials rather than contents, and others may be present as by-products (Dunagan SC, 2011).

Why are EDCs of particular concern (2)?

- There are many periods of vulnerability during which exposure to EDCs can be especially harmful, particularly prenatal and early postnatal development. It is thought that the **effects of toxins on the growing foetus are largely through endocrine disruption**. Effects of early life exposure may be permanent but may not manifest until much later in life.
- EDC exposure in one generation may be transmitted to future generations (**trans-generational effects**) – animal studies have shown effect up to the F4 generation.
- The mechanism of transmission of transgenerational effects involves genomic and nongenomic modifications of the germ line, such as changes in DNA methylation and histone acetylation.
- Causal relationships are inherently difficult to establish in humans. A clear connection between the disorders and specific toxicants has not been established. This does not mean it does not exist but may be indirect rather than direct.

WHO - STATE OF THE SCIENCE OF ENDOCRINE DISRUPTING CHEMICALS 2012: KEY CONCERNS

- Many endocrine-related diseases and disorders are on the rise.
- Close to 800 chemicals are known or suspected to be capable of interfering with hormone receptors, hormone synthesis or hormone conversion. However, only a small fraction of these chemicals have been investigated in tests capable of identifying overt endocrine effects in intact organisms.
- ***The vast majority of chemicals in current commercial use have not been tested at all.***
- The speed with which the increases in disease incidence has occurred in recent decades rules out genetic factors as the sole plausible explanation.
- Worldwide, there has been a failure to adequately address the underlying environmental causes of trends in endocrine diseases and disorders.

But the WHO has no teeth and few governments are taking any notice!

Sources of endocrine disruptors

Not lectured – please see Tables in Handout

Endocrine and other system components which may be affected by EDCs

- Male and female reproductive function (especially fertility)
- Foetal development
- Children's growth and development
- Neuroendocrine function
- Pancreas (insulin secretion, diabetes, obesity)
- Thyroid function
- Adrenal function
- Male and female hormonal cancers

All of these effects can give rise to **chronic disease** and some may have been present from birth. Each organ system has a different developmental trajectory, so the effects of exposures are dependent not only on the type and dose of the chemical, but also when the exposure occurs.

EFFECT OF ENDOCRINE DISRUPTORS IN THE BODY

CAVEAT

For every study showing an association with a particular toxin, there may be another study showing no association.

I am only showing you the studies where there is an association and I don't claim to have them all!

Happily, as study designs and toxin measurements improve, there are fewer studies showing no association.

I have attempted to gather only relatively recent studies, since these are more relevant and carry more weight. I have also tried to gather studies from mainly the 'developed' world.

It is more generally accepted that occupational exposure to chemicals can cause health problems so I have avoided these studies, and also studies of major chemical spills or accidents. By this, I hope to present only the studies of normal day-to-day exposure.

FOETAL HEALTH

The association of foetal toxins with problems evident at birth

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THE EXTENT OF MATERNAL TOXINS

- A 2011 US NHANES study found that >99% of pregnant women had blood or urinary concentrations of:
  - PCBs
  - OC pesticides
  - Perfluorinated compounds (PFOS, PFOA etc)
  - Phenols
  - Polybominated diphenol ethers (PBDEs)
  - Phthalates
  - Polycyclic aromatic hydrocarbons (PAHs)
  - Perchlorate
- The number of detected chemicals ranged from 8 to 50 chemical analytes per female.

(Woodruff TJ, Environ Health Perspect, 2011)

Does maternal exposure = foetal exposure?

- Maternal urinary phthalates associated with babies' urinary phthalates
- Maternal hair mercury associated with cord blood mercury
- Maternal serum DDT associated with cord serum DDT (despite DDT being banned 40 years earlier!)
- This means that environmental toxins can cross the **placental membrane**, which separates the foetal from the maternal blood.
- Even more worrying, environmental toxins can also pass through the still immature **blood-brain barrier** of the foetus.

(Sathyanarayana S, Environ Res, 2008; Bjornberg KA, Environ Health Perspect, 2003; Al-Saleh I, Sci Total Environ, 2012; Ma WL, Environ Res, 2014; Roncati L, Sci Total Environ, 2016; Tsutsumi O, 2005)

SPONTANEOUS ABORTION (MISCARRIAGE) AND STILLBIRTH

- Pesticides: Maternal domestic exposure during 1st trimester associated with >50% increase in stillbirth rate, while **paternal** domestic exposure was associated with 30% increase. 3rd trimester losses associated with glyphosate and carbamates, particularly among women aged >34.
- Air pollution: Spontaneous abortion correlated with urban levels of SO_2, NO_2, CO, PM_{10} and ozone, even though the median pollution was **within legal limits**.
- Disinfectant byproducts: Meta-analysis found an association between DBPs in water and stillbirth.
- VOCs: Solvents (especially toluene and including paternal exposure), tetrachloroethylene in dry cleaner/laundry workers; formaldehyde.
- Incinerators: Maternal residence near incinerators associated with foetal losses.
- Smoking: It is well known that maternal smoking is a risk factor, but…meta-analyses found increased risk of stillbirth and spontaneous abortion among **non-smoking women when both their parents** had smoked while they were children or in pregnant women whose **partner smoked**.

NEONATAL AND INFANT MORTALITY: MATERNAL SMOKING

- Maternal smoking induces foetal hypoxia and morphological changes in the placenta.
- These increase the risks of intrauterine growth retardation and placental abruption, causing late foetal death and neonatal mortality and contributing to SIDS (Cnattingius S, Acta Pediatr 1996).
- The risk is higher even among heavy smokers who **quit for the pregnancy** (Johansson AL, Epidemiology, 2009).

GENDER DIFFERENTIATION

- Virtually all toxin types are associated, but **some are associated with a higher ratio of boys and others with a higher ratio of girls**.

- No hard and fast associations: sometimes the **same toxin has an opposite effect in 2 different populations**.

- **Paternal exposure** also has a bearing on gender of offspring.

PRE-TERM DELIVERY AND LOW BIRTH WEIGHT

- Pesticides:
- Smoking: Note that cigarette smoking, source of several thousand chemicals, is a perfect example of why we shouldn't look at 1 chemical in isolation!
- Air pollution: Domestic and external
- POPs (phthalates, PCBs, BPA, perfluorinated compounds), arsenic, tributyl tin, mercury, phenols.
- Residence near a landfill site.

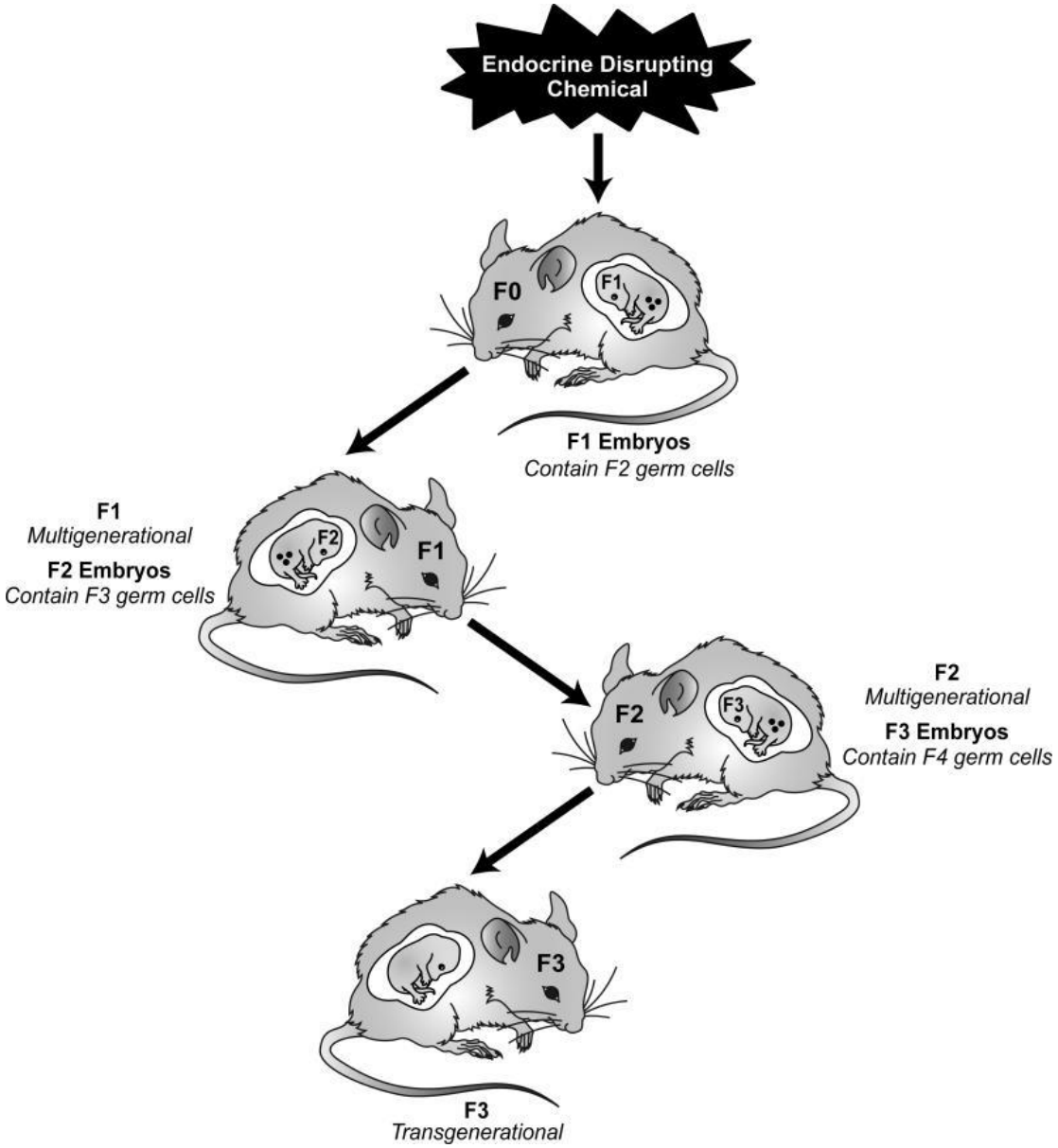
TESTICULAR DYSGENESIS SYNDROME (TSG)

- TSG comprises any male reproductive health issues that originate *in utero* or early life that result from abnormal production of androgens: reduced penile size and ano-genital distance, cryptorchidism, hypospadias, impaired spermatogenesis, reduced semen quality and testicular germ cell cancer.
- Likely mechanism: EDCs inhibit foetal androgen synthesis and conversion of testosterone into dihydrotestosterone, resulting in reduced functioning of Sertoli cells (cells supporting germ cells) and Leydig cells (where androgen synthesis occurs).
- Pesticides, fungicides, PCBs, phthalates
- Smoking: **Maternal and paternal**. Maternal use of **nicotine substitutes** during pregnancy was associated with increased risk of cryptorchidism.
- **Female hairdressers** had a significantly higher risk of hypospadias in male offspring due to hairspray.
- The result of all TSG components is a **demasculinising effect in boys**.

OVARIAN DYSGENESIS SYNDROME (ODS)

- ODS comprises early puberty (menarche), altered menstruation, anovulation, infertility, oestrogen deficiency, fibroid development, premature ovarian failure.
- POPs, pesticides, smoking, fluoride
- In rats, low dose PCBs were associated with depressed LH and progesterone and smaller uterine and ovarian weights. **Effects were more profound in the F2 than the F1 generation.**

From Schug TT, J Steroid Biochem Mol Biol, 2011



CONGENITAL MALFORMATIONS

- Pesticides
- Smoking
- Air pollution
- Hazardous waste
- Dioxins
- DBPs
- Nitrate
- Chlorophenate wood preservative (paternal exposure)
- Radiation

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Review

Environmental Contaminants and Congenital Heart Defects: A Re-Evaluation of the Evidence

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check for updates

Abstract: Congenital heart defects (CHDs) are a common birth defect of largely unknown etiology, with high fetal and neonatal mortality. A review of CHDs and environmental contaminant exposure found that meta-analyses showed only modest associations for smoking, vehicle exhaust components, disinfectant by-products and proximity to incinerators, with stronger results from the newer, larger and better quality studies masked by the typical absence of effect in older studies. Recent studies

SUMMARY

- A maternal (and sometimes a paternal) toxin = a foetal toxin.
- All toxins mentioned can impair foetal health, particularly maternal smoking and pesticides/herbicides.
- Exposure during the preconception period is critical too, particularly with respect to maternal smoking. Giving up while pregnant or using a nicotine substitute still exposes the foetus to toxins.
- Some ethnicities are more susceptible to certain toxins than others; different toxin metabolites may cause different effects in the foetus; some toxins may be gender-specific. So we can't generalise or make assumptions without testing.
- Effects may be transgenerational.

HEALTH EFFECTS IN CHILDREN:

FROM *IN UTERO*, NEONATAL AND CHILDHOOD EXPOSURE

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TOXIN EXPOSURE: WHY CHILDREN ARE DIFFERENT

It was not until 1993 that it was officially recognised that children were not ‘little adults’, but were much more vulnerable

So how are children different to adults?

- Heavier exposure by body weight or volume through breathing more rapidly, taking in more air, and ingesting more food and liquid per body weight than adults.
- Children's location (close to the floor) and activity (hand to mouth behaviour)
- Different nutrient absorption rates. Lead can be absorbed in place of calcium; an adult absorbs 10% of ingested lead, a toddler 50%.
- Higher metabolic rate
- **Immature systems and pathways**, particularly immune, detoxification, endocrine. Generally cannot efficiently detoxify or excrete toxins.
- **BBB not fully developed**, so toxins can more easily enter the CNS.
- Young children absorb 3x more radiation than adults and have thinner skulls, making brain penetration easier. Furthermore, brain tissue is more conductive
- Long latency diseases

Windows of vulnerability

- Foetuses, infants and young children are particularly vulnerable to environmental toxins.
- Because normal repair mechanisms are not yet established, any damage is likely to be **irreversible and permanent**.
- A 20-30 year follow-up of lead-poisoned children, still found low IQ scores as adults, decreased brain volume and reduction in cortical gray matter, especially in the pre-frontal cortex, responsible for executive functions, mood regulation and decision making. (Mazumdar M, Environ Health, 2011; Cecil KM, PLoS Med, 2008)
- There appears to be **no safe threshold exposure** levels in early development, below which toxic chemicals exert no harmful effects. (Landrigan PJ, Mt Sinai J Med, 2011; Eriksson P, Neurotox Res, 2001; Roosli M, Prog Biophys Mol Biol, 2011)
- Problems are exacerbated where children live in poverty.

BREASTFEEDING or INFANT FORMULA?

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Is breast always best?

- **The mother's personal fat-soluble toxin load can be present in breast milk and is passed on to the infant** owing to the high fat content of breast milk (Sonawane BR, Environ Health Perspect, 1995).
- During 6 months of breast feeding, a mother can transfer up to 50% of her own accumulated burden of PCBs to her child at the most vulnerable period for brain development. (Landrigan PJ, Environ Health Perspect, 2002)
- A mouse study showed that the addition of PCBs to breast milk could increase the lactational transfer of MeHg to the infant (Lee SK, Environ Toxicol Pharmacol, 2009).
- BUT: **Breast milk can mitigate some of the effects of toxins**: air pollution, PCBs and dioxins. Autism was more prevalent where the incidence of breast-feeding was less frequent (Tanoue Y, J Autism Dev Disord, 1989).
- **Where the mother breastfed for longer** (even if breastmilk was a source of PCBs) the damage caused by PCBs was significantly less (Walkowiak J, Lancet 2001).

Adverse effects of breast milk toxins

- PCB-contaminated breast-fed children were lighter and shorter than non-breast fed children, which was attributed to breast milk transfer (Grandjean, FASEB J. 2003).
- Breast milk soy from maternal ingestion was associated with less feminine play in girls (Adgent MA, Environ Health Perspect, 2011).
- PBDEs in breast milk was associated with increased activity and impulsive behaviour in offspring (Hoffman K, Environ Health Perspect, 2012).
- Breast milk phthalate metabolites were associated with elevated SHBG and LH or were inversely correlated with free testosterone (Main KM, Environ Health Perspect, 2006).

Bottle feeding: why is this a problem?

- **BPA and phthalates from plastic bottles.**
- Most commercial infant formulas are very high in processed sugar (often as high fructose corn syrup); infant formula can contain as much sugar as a canned drink. They come with a long list of adverse metabolic effects, raising the child's risk for obesity, T2D and related health problems.
- In addition, formula may contain synthetic vitamins, inorganic minerals, excessive protein and harmful fats.
- Baby milk formulas contain 3–100 times the manganese content of breast milk. Hair manganese levels increase significantly in infants fed formula. Manganese is implicated in aetiology of ADHD and learning disorders.
- There have been infant formula recalls due to contamination with pathogens, heavy metals, perchlorate and foreign substances such as glass or melamine.

Soya-based formula

- With soya-based formula, all the infant's calories are derived from soya, which contains phytoestrogens. These are largely untested in infants. (Strom BL, JAMA 2001)
- Soya formula provides an oestrogen amount equivalent to at least **five birth control pills per day**
- The US CDC have now added phytoestrogens to the list of potential human toxins.
- Concern over the phytoestrogen content of soya and risk of breast cancer in female offspring, caused the UK government to require that soya-based infant formulas be available only on prescription.

NEURODEVELOPMENT

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Autism: the current research

- According to a recent report from the US CDC, approximately one in 40 children suffers from ASD. Much of the cause seems to occur *in utero*, where neurons are being formed at a rate of 250,000 per minute on average over the course of a pregnancy.
- The last 5 or 6 years have seen an explosion in the number of papers concerning environmental causes of autism. These involve both prenatal and postnatal exposure. Many involve genes.
- Interestingly, many studies also show that the microbiome is also modified by environmental toxins in ASD, suggesting that pathways for the toxins to affect neurodevelopment.

NEURODEVELOPMENT: AUTISM SUSCEPTIBILITY GENES

- Many genes have been implicated in autism, known as autism susceptibility genes. Some of these are directly related to **detoxification processes** or **control toxin access across the developing BBB**.

- A review found that a subset of 206 genes, defined as prime autism susceptibility candidates, revealed that most could be related to barrier function at blood/brain, skin, intestinal, placental or other interfaces (Carter CJ, Neurochem Int, 2016)

Toxins associated with ASD

- All types, but note particularly:
- **Copper and low zinc/copper ratio**: There is a high frequency of zinc deficiency, copper toxicity and low zinc/copper ratio in ASD children, possibly indicating dysfunction in metallothionein synthesis.
- **Ultrasound scans**: 1st trimester scans were associated with autism severity in male children with a genetic predisposition to ASD.

Autism: action of glyphosate and aluminium:

(finally, a study examining more than 1 toxin at a time!)

A study by Stephanie Seneff, Agricultural Sciences, 2015 investigated the synergistic effect of aluminium and glyphosate in inducing neurological damage. **Note the agricultural, not medical journal!**

- Glyphosate disrupts gut bacteria, leading to an overgrowth of C. difficile; its toxic product, p-cresol, is linked to autism.
- p-cresol enhances uptake of aluminium via transferrin, resulting in anaemia through aluminium-induced impairment of haem synthesis.
- Anaemia induces hypoxia, promoting neurotoxicity and damaging the pineal gland.
- Both glyphosate and aluminium disrupt cytochrome P450 enzymes, which are involved in detoxification and melatonin metabolism.
- Glyphosate breakdown by microbes leads to the creation of ammonia. Children with autism tend to have significantly higher levels of ammonia in their blood. Ammonia also causes encephalitis (brain inflammation).

Toxins associated with ADHD

- All types, but note particularly:
- 3rd trimester polycyclic aromatic hydrocarbon (PAH) levels were associated with **reduction in left hemisphere white matter,** hence slower information processing speed and more severe ADHD.
- **Water fluoridation**: Each 1% increase in fluoridation prevalence was associated with >100,000 additional ADHD diagnoses. (Malin AJ, Environ Health, 2015)

Toxins associated with other neurodevelopment

- All types, but note particularly:
- **External air pollution:** Early signs of AD (frontal tau hyperphosphorylation and amyloid-β diffuse plaques) detected in exposed children.
- **Toxic metals**: In utero exposure to methyl mercury was associated with lower IQ, impaired fine motor scores and impaired communicative and cognitive skills, particularly in infants with at least one **Apo E4 allele**.
- **Pesticides**: Microcephaly

‘Microcephaly: Brazil Admits It's Not the Virus’ (www.mercola.com)

- Health officials in Brazil say that Zika alone may not be responsible for the rise in birth defects that have plagued parts of the country.
- Although the virus has been spreading throughout Brazil, rates of microcephaly have dramatically increased only in northeastern Brazil.
- This region is a largely poverty-stricken agricultural area with lack of sanitation and nutritional deficiencies. It also uses large amounts of banned pesticides. So maybe it is a combination of pesticides and the Zika virus.
- In response, many areas are ramping up pesticide spraying to combat Zika virus, including Florida in the US.
- This will just compound the problem.

CHILDHOOD CANCER

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Leukaemia

- Mostly vehicle exhaust fumes, domestic dust and VOCs .
- **Recently painted homes.**
- **Domestic incense burning.**

Leukaemia and ionising radiation

- Generally accepted as carcinogenic

- Foetal low dose ionising radiation from diagnostic radiography, particularly in the last trimester, is associated with childhood cancer. There is **no evidence for a threshold dose**, suggesting that all ionising radiation is carcinogenic. (Doll R, Br J Radiol, 1997)

Leukaemia and non-ionising radiation

- In 2001 UK National Radiological Protection Board concluded that there was no proof that EMFs caused cancer. Yet in the body of their report they admitted that current evidence suggests roughly a **doubling of the risk of childhood leukaemia with heavy exposure to very low frequency EMFs**.
- Since then IARC (the International Agency for Research on Cancer) demonstrated consistent epidemiological evidence of an association between childhood leukaemia and exposure to extremely low frequency (ELF) magnetic fields, leading to their classification as a "**possible human carcinogen**".
- IARC has concerns about the potential vulnerability of children because their **brain tissue is more conductive** and RF penetration is greater relative to head size (Kheifets L, Pediatrics, 2005).
- ELFs emitted by all electric power sources, principally domestic wiring, overhead powerlines, transformers, motors, household appliances, video display terminals and various medical devices.

Mobile phones

- The American Academy of Pediatrics has already called for **more protection for children**, citing research showing that living near 4G base stations is associated with headaches, memory problems, dizziness, depression and sleep disturbance.
- The US Adolescent Brain Cognitive Development (ABCD) Study, the largest long term study of brain development:
  - Children who use electronic devices for 7 or more hours per day have **premature thinning of the brain cortex**.
  - Even 2 hours per day of screen time can result in lower scores for thinking and language tests.

5G: the additional risks

- But there is now major concern about the roll-out of 5G, which uses the 'millimeter wave' (MMW) bandwidth, currently used in crowd control weapons in the US.
- In 2017 >180 doctors and scientists from 35 countries signed a petition for a moratorium on 5G roll-out due to potential risks to wildlife and human health, including **altered brain development in children, genetic damage, reproductive problems, cancer and neurological disorders**.
- What is different about 5G? Instead of large antennae on buildings, there will be 'small cell' antennae placed in multiple locations all over every neighbourhood. **There will be no escape!**

Other childhood cancers: highlights

- All classes of toxins
- Ever-use of a **dummy** increased the risk of brain tumour by almost 300%. Dummies contain a number of chemicals including plastics and N-nitroso compounds.
- Prenatal maternal dietary intake of N-nitroso compounds, particularly N-nitrosamides (from cured meat) was associated with risk of childhood brain tumours.

HORMONES:

the effect may be an increase or decrease in a hormone – but any imbalance represents a problem

THE IMPORTANCE OF THYROID HORMONES FOR BRAIN DEVELOPMENT

- Adequate thyroid hormones are **essential for brain development**, during a critical period beginning *in utero* and extending to the first 2 years postpartum.
- They regulate neuronal proliferation, migration, synaptic development, myelin formation and differentiation in the brain. Thyroid hormones are also necessary for normal development of the cytoskeletal system, which is essential for migration and neuronal outgrowth. In addition, they regulate development of cholinergic and dopaminergic systems serving the cerebral cortex and hippocampus.
- **Transient intrauterine thyroid hormone deficiency, even for just 3 days, can result in permanent alterations of cerebral cortical architecture** (similar to those observed in brains of patients with autism), irreversible neurological effects and development of motor and cognitive disorders.

Toxins affecting thyroid hormones

All classes of toxins, but note particularly possible ethnic differences:

- Higher maternal blood mercury was associated with increased TSH in newborns, with an inverse association of cord blood mercury with T3 in **Caucasians** but a positive association in **other ethnic groups**.

Sex hormones and sexual development

All classes of toxins

Early (precocious) puberty – why does it matter?

- Precocious puberty is generally defined as the appearance of secondary sex characteristics before age 8 in girls and before age 9 in boys.
- Children with early or precocious puberty are at a risk for accelerated skeletal maturation and short adult height, early sexual debut, potential sexual abuse and psychosocial difficulties.
- Altered puberty timing is also of concern for the development of reproductive tract cancers later in life. Early female puberty is a risk factor for breast cancer and early male puberty may be a risk factor for testicular cancer.
- Girls, and possibly, boys who exhibit sexual maturation at the age of 10 or 11 are at a higher risk for developing features of metabolic syndrome and later CVD.
- Early maturation is associated with a greater incidence of conduct and behaviour disorders during adolescence.
- Altered timing of puberty is associated with later reproductive toxicity.
- Premature breast development (thelarche) is the growth of mammary tissue in girls younger than age 8 without other manifestations of puberty. Puerto Rico has the highest known incidence of premature breast development ever reported, where it correlates with serum phthalate esters.

Adolescence and puberty

Females

- Premature breast development: Mostly with POPs
- Delayed breast development: POPs, phytoestrogens, lead, incinerators
- Precocious puberty: POPs, OC pesticides, phytoestrogens
- Delayed puberty: Lead, POPs, pesticides (OC and OP)
- Shorter cycles and abnormal menstrual bleeding: PCBs
- Longer cycles: DDE

Males

- Some pesticides, dioxins and PCBs associated with precocious puberty, but others with delayed puberty.
- Serum dioxins at age 9 predicted lower sperm concentration and total sperm count at age 19.

OBESITY, DIABETES AND CARDIOVASCULAR DISEASE

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LOW BIRTH WEIGHT AND LATER OBESITY OR T2D

- Low birth weight babies have significantly increased susceptibility to obesity, type 2 diabetes and cardiovascular disease in later life.
- With inadequate nutrition, the foetus channels its scarce nutrients at essential organs such as the brain, at the expense of other tissues, particularly the pancreas.
- These observations led to the Thrifty Phenotype Hypothesis, which suggested that a suboptimal environment, originally due to poor maternal nutrition, programmed the growing foetus to store food as a child and adult, regardless of its availability.
- This is now known as the 'predictive adaptive response', i.e. the postnatal phenotype is set by foetal expectations that nothing will change. Where the pre- and postnatal environments are matched, such as in parts of Africa, T2D does not develop. But in the developed world food is readily available.
- Something similar seems to be happening with environmental toxins, possibly because essential nutrients are diverted to up-regulate antioxidant enzymes and detoxification capacity.

Obesity

All classes of toxins associated but note particularly:

- Pesticides: Prenatal maternal DDE concentrations associated with increased BMI **in boys only** but cord blood DDE levels were associated with overweight **in girls only**.
- POPs: Urinary phthalates were **inversely** associated with BMI, but BPA **positively** associated with BMI.
- NHANES study found that urinary BPA was associated with **obesity among girls** but **higher lean body mass among boys**
- Urinary BPA was associated with obesity among **whites**, but **not blacks or Hispanics**
- VOCs: Prenatal maternal serum PBDEs were associated with **higher BMI in boys**, but **lower BMI in girls.**

Obesity: more studies investigating more than 1 toxin!

- Air pollution: Although PAHs were significantly associated with obesity in children and adolescents, the **association was much stronger** when exposure to ETS was also considered.
- Air pollution: Neither proximity to road traffic nor environmental tobacco smoke (ETS) were significantly associated with obesity **unless both exposures were analysed together**.

Type 2 diabetes and NAFLD

All types of toxins but note particularly:

- **Prenatal** maternal smoking is associated with **adult** diabetes risk.
- Urinary phthlates were associated with increased insulin secretion and insulin resistance among prepubertal **girls, but not boys**.
- Urinary BPA levels were associated with NAFLD in adolescents. (Verstraete SG, Environ Health, 2018)

HEALTH EFFECTS IN ADULTS:

from *in utero*, childhood and adult exposure

Obesity

- Metals: tributyltin
- VOCs: PBDEs, PAHs
- Pesticides
- POPs: PDBEs, BPA, parabens
- Several studies suggest that these environmental toxins can induce obesity as they are peroxisome proliferator-activated receptor (PPAR) agonists and may alter the methylation of PPAR-γ, the master regulator of adipogenesis, or its target genes. (Stel J, 2015, La Merrill M, 2011; Tang-Peronard JL, Obes Rev, 2011)
- Studies indicated that exposure *in utero* may cause permanent physiological changes which predispose to later weight gain (Tang-Peronard JL, Obes Rev, 2011).
- Adipose tissue BPA content was associated with suppressed adiponectin release (Hugo ER, Environ Health Perspect, 2008).

Diabetes

- POPs, all types
- Pesticides, especially organochlorines
- **Prenatal parental smoking was associated with T2D development in middle age**, particularly in females (La Merrill MA, 2015).
- **Type 1 diabetes**: a review found that higher intake of **nitrates, nitrites and N-nitroso compounds**, as well as higher serum levels of **PCBs** have been associated with increased risk (Longnecker MP, 2001).

Cardiovascular disease (CVD)

- Arsenic: associated with elevated blood pressure
- Pesticides (DDT): hypertension in middle aged females
- Phthalates and BPA: associated with cardiac toxicity, coronary heart disease, and elevated LDL cholesterol and diastolic blood pressure in the elderly
- A Danish study found that reduction in exposure to indoor air particles by filtration was associated with improved microvascular function (Brauner EV, 2008).
- A phthalate was associated with carotid atherosclerotic plaques, with an **inverted U-shaped association** (Lind PM, 2011).

Cancer

- Pesticides:
  - Organochlorine and organophosphate pesticides: associated with breast and prostate cancer
  - Multiple insecticides, particularly acetylcholinesterase inhibitors: more than double the risk of Hodgkin lymphoma in males
  - Adrenal carcinoma cells showed increased atrazine-induced aromatase expression (Fan W, 2007).
- POPs:
  - BPA: associated with prostate cancer incidence
  - Phthalate: promoted human prostate cell proliferation, associated with breast cancer and breast cancer mortality
  - PBDEs: association with thyroid cancer
  - PCBs: associated with prostate cancer
- Frequent use of **skin care and beauty products**: associated with increased risk of breast cancer

Bone and osteoporosis risk

- BPA affects bone cells by binding to the oestrogen related receptor-gamma (ERγ), reducing the bone morphogenic protein-2 (BMP-2) and alkaline phosphatase (ALP) activities. BPA interrupts the bone metabolism via RANKL, apoptosis and Wnt/β-catenin signaling pathways. (Thent ZC, Life Sci, 2018)
- An NHANES study showed that urinary PAHs were associated with decreased BMD and increased risk of osteoporosis, particularly in males (Guo J, Environ Pollut, 2018).

Thyroid function

- POPs: PCBs, phthalates, BPA, PBDEs, PFOS/PFOA
- Pesticides: DDE associated with TSH
- Hexachlorobiphenyls: associated with low T3 in females
- Cigarette smoke: stimulated increased thyroid hormone, may reinforce hormone binding to the thyroid receptors
- Soy: goitrogenic (has anti-thyroid effects)

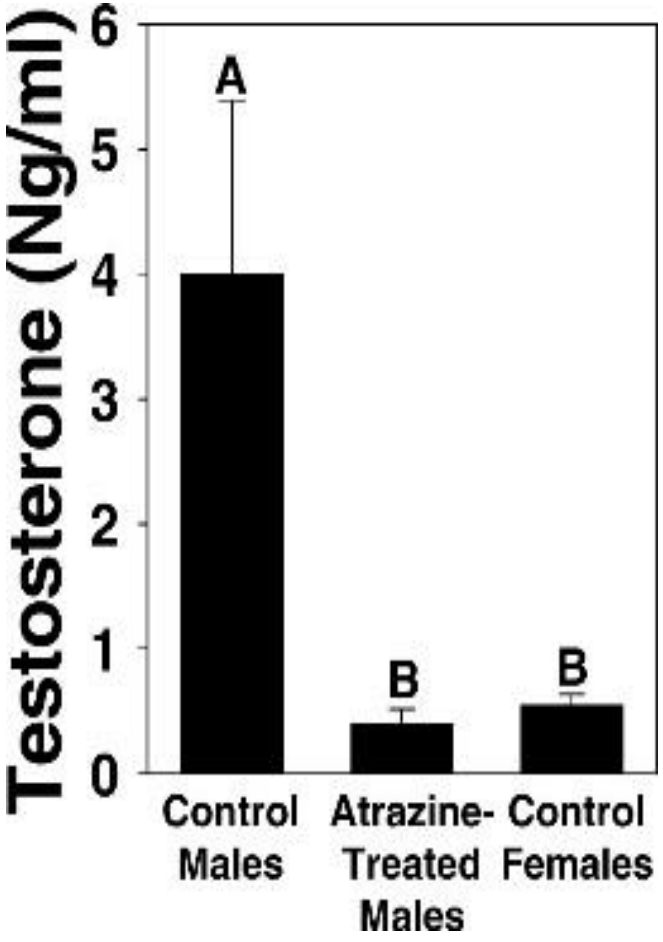
MALE REPRODUCTIVE HEALTH

- Semen quality is declining throughout the world, putting male fertility at risk. Animal studies suggest that EDCs may be the culprit. (Nordkap L, Mol Cell Endocrinol, 2012; Giwercman A, Reprod Biomed Online, 2007)
- There is a high incidence of **low sperm counts in European men** over recent decades. '**Spermatogenesis….is poorly organized and inefficient** so that men are poorly placed to cope with environmental insults'. (Sharpe RM, Philos Trans R Soc Lond B Biol Sci, 2010).
- 50 years ago the principal exposures for males were occupational. Industrial exposures in the developed world are now much reduced but the chemicals have become ubiquitous in our daily lives.
- These exposures have largely oestrogenic and anti-androgenic effects on males, resulting in **reduced fertility and more feminine characteristics** among males.

Male reproductive function

- All classes of toxins may be associated with low testosterone, SHBG, LH, semen volume and total sperm count, testis weight, degraded sperm quality, motility and volume, higher oestradiol concentrations and sperm DNA fragmentation index, structural damage to testis vasculature and blood-testis barrier, cytotoxicity in Sertoli and Leydig cells, chromosome aberration frequency (genomic instability), increased oxidative stress.
- Some phthalates associated with **lower** sperm concentration and SHBG; others were associated with **higher** sperm concentration and SHBG.
- Pesticides: **occupational exposure studies** showed a positive association with oestradiol and testosterone and an inverse association with FSH. But **non-occupational studies** showed an inverse association with oestradiol, testosterone and FSH.
- The combination of higher PCB and phthalate metabolites had a **greater than additive effect** on decreased sperm motility.
- Phthalate exposure can disrupt testosterone, LH and FSH in exposed males but only those with **no prior exposure**, suggesting an **adaptive effect.**
- Among Swedish men, PCBs were **positively** associated with higher Y-chromosome-bearing spermatozoa (i.e. higher proportion of males) but in Polish males there was an **inverse** association.

Examples of feminised male frogs



Effect of 46-day exposure to low dose atrazine on plasma testosterone levels in sexually mature male frogs. The dose was equivalent to normal human exposure.

Note that atrazine-treated males have less testosterone than females!

The low testosterone induced feminine qualities in the male frogs.

(Hayes TB, Proc Natl Acad Sci USA, 2002)

And it certainly fooled some!

A healthy male frog attempting (but failing!) to mate with a male frog exposed to atrazine.

The exposed frog had become fully feminised, tricking the healthy male into thinking it was a female.

FEMALE REPRODUCTIVE FUNCTION

- Female reproductive function depends upon the exquisite control of ovarian steroid production, which enables follicle production, ovulation and pregnancy.
- Ovarian development and function are collectively regulated by a host of endogenous growth factors, cytokines, gonadotropins and steroid hormones as well as exogenous factors such as nutrients and environmental agents.
- EDCs can disrupt ovarian processes, leading to anovulation, infertility, oestrogen deficiency and premature ovarian failure, principally by altering the availability of ovarian hormones or by altering the binding and activity of the hormone at the receptor level (Craig ZR, Reproduction, 2011).
- The impaired fertility rate in the U.S. increased from 11 to 15% between 1982 and 2002 (Guzick and Swan, 2006). Although various other confounding factors such as lifestyle changes can contribute to this decline, the role of EDCs is strongly implicated.

Female reproductive function

- All classes of toxins can impact menopause timing, abnormal menstrual cycles, uterine fibroids, reduced fertility, reduced oestrogen and progesterone levels, increased FSH, LH and testosterone, time to pregnancy, *in vitro* fertilisation failure, shorter pregnancy duration and pregnancy complications (anaemia, toxaemia and preeclampsia).
- PCB exposure was associated with **shorter** cycles and abnormal menstrual bleeding, DDE was associated with **longer** cycles.
- In particular, a systematic review showed that **cigarette smoking dose-dependently affected each stage of reproductive function**: folliculogenesis, steroidogenesis, embryo transport, endometrial receptivity, endometrial angiogenesis, uterine blood flow and uterine myometrium (Caserta D, Hum Reprod Update, 2011).
- BPA: the prime suspect BPA was originally developed as a **synthetic oestrogen**; its oestrogenic effect was used to induce rapid growth in cattle and poultry. It was also used for a few years as **oestrogen replacement** for women (Singh S, 2012). It appears to be the key chemical involved in infertility.
- And for **gynaecological conditions hindering pregnancy**: Polycystic ovary syndrome (PCOS), endometriosis and uterine fibroids: mostly associated with BPA, phthalates and perfluorinated compounds.

And another factor hindering pregnancy

Rubber ducks can kill your sex drive, research finds (Guardian, 2014)

Women with the highest levels of phthalates - chemicals used to make plastics bendy – were far more likely to suffer low libido, study reveals.

(Barrett E, Horm Behav, 2014)

Glucocorticoids (mostly animal studies)

- The glucocorticoid receptor pathway is integral for proper fetal and placental development; perturbations in this pathway may lead to adverse birth outcomes.
- Metals: mercury, arsenic
- POPs: PFOS/PFOA, BPA, dioxins
- Fungicides

2 glyphosate studies

Journal of Organic Systems, 9(2), 2014

ORIGINAL PAPER

Genetically engineered crops, glyphosate and the deterioration of health in the United States of America

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Abstract

A huge increase in the incidence and prevalence of chronic diseases has been reported in the United States (US) over the last 20 years. Similar increases have been seen globally. The herbicide glyphosate was introduced in 1974 and its use is accelerating with the advent of herbicide-tolerant genetically engineered (GE) crops. Evidence is mounting that glyphosate interferes with many metabolic processes in plants and animals and glyphosate residues have been detected in both. Glyphosate disrupts the endocrine system and the balance of gut bacteria, it damages DNA and is a driver of mutations that lead to cancer.

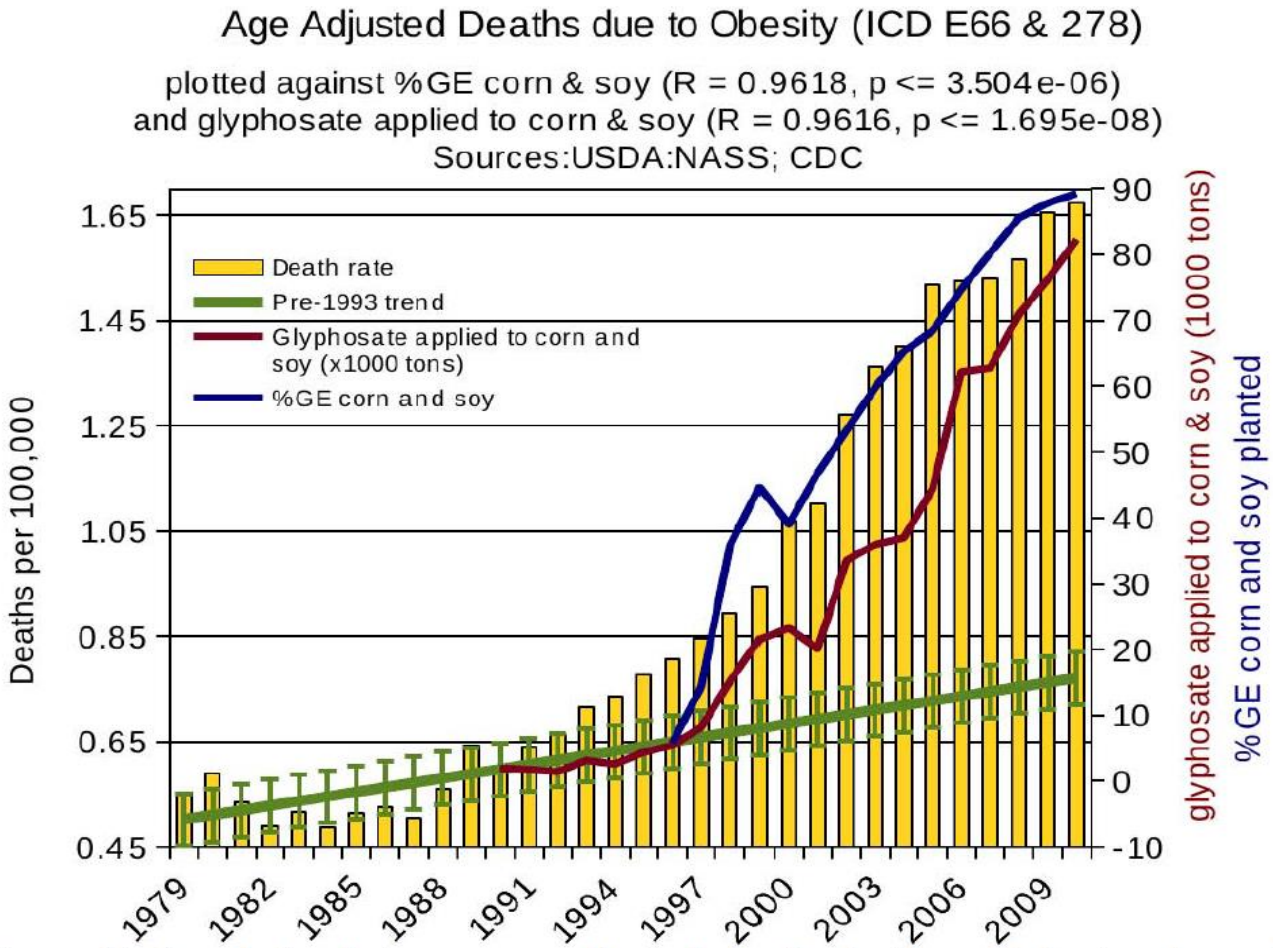


Figure 13. Correlation between age-adjusted obesity deaths and glyphosate applications and percentage of US corn and soy crops that are GE.

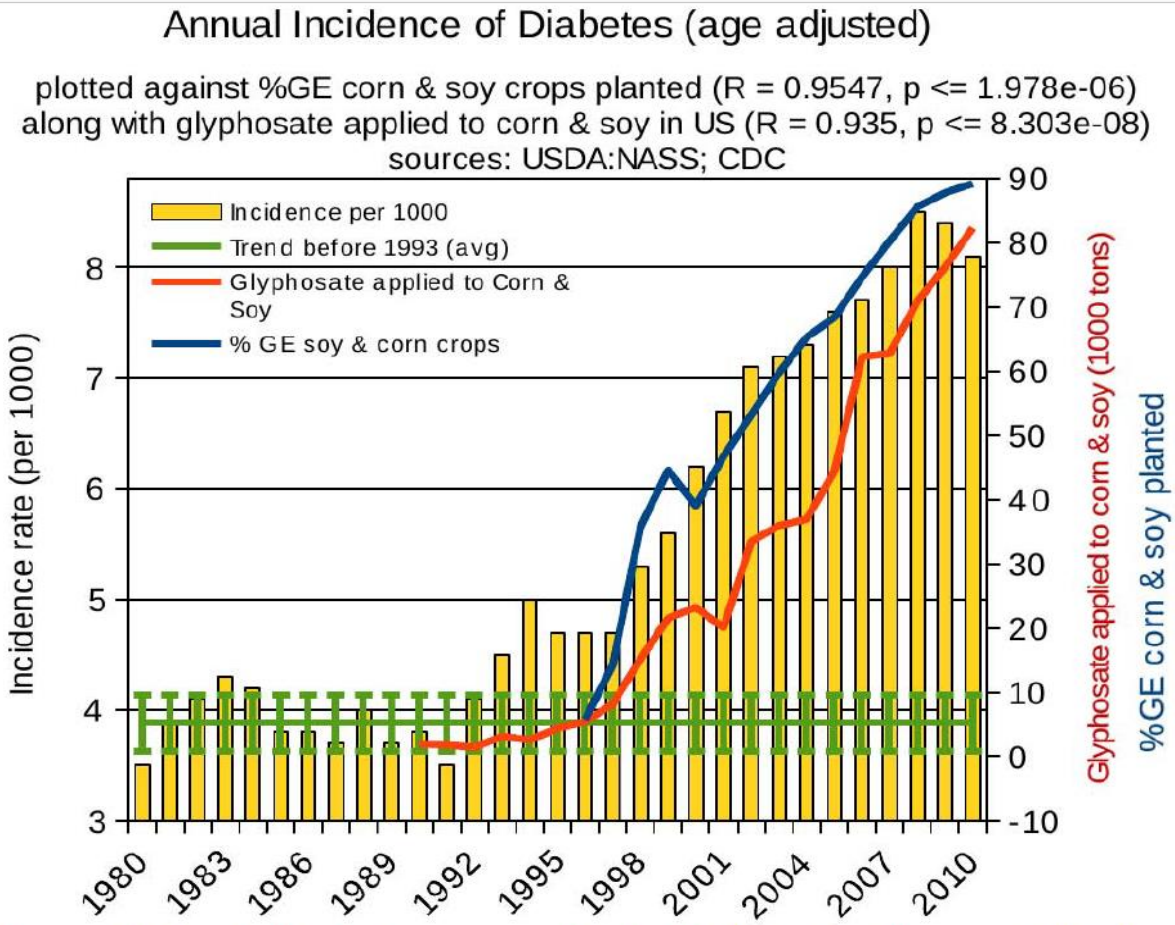
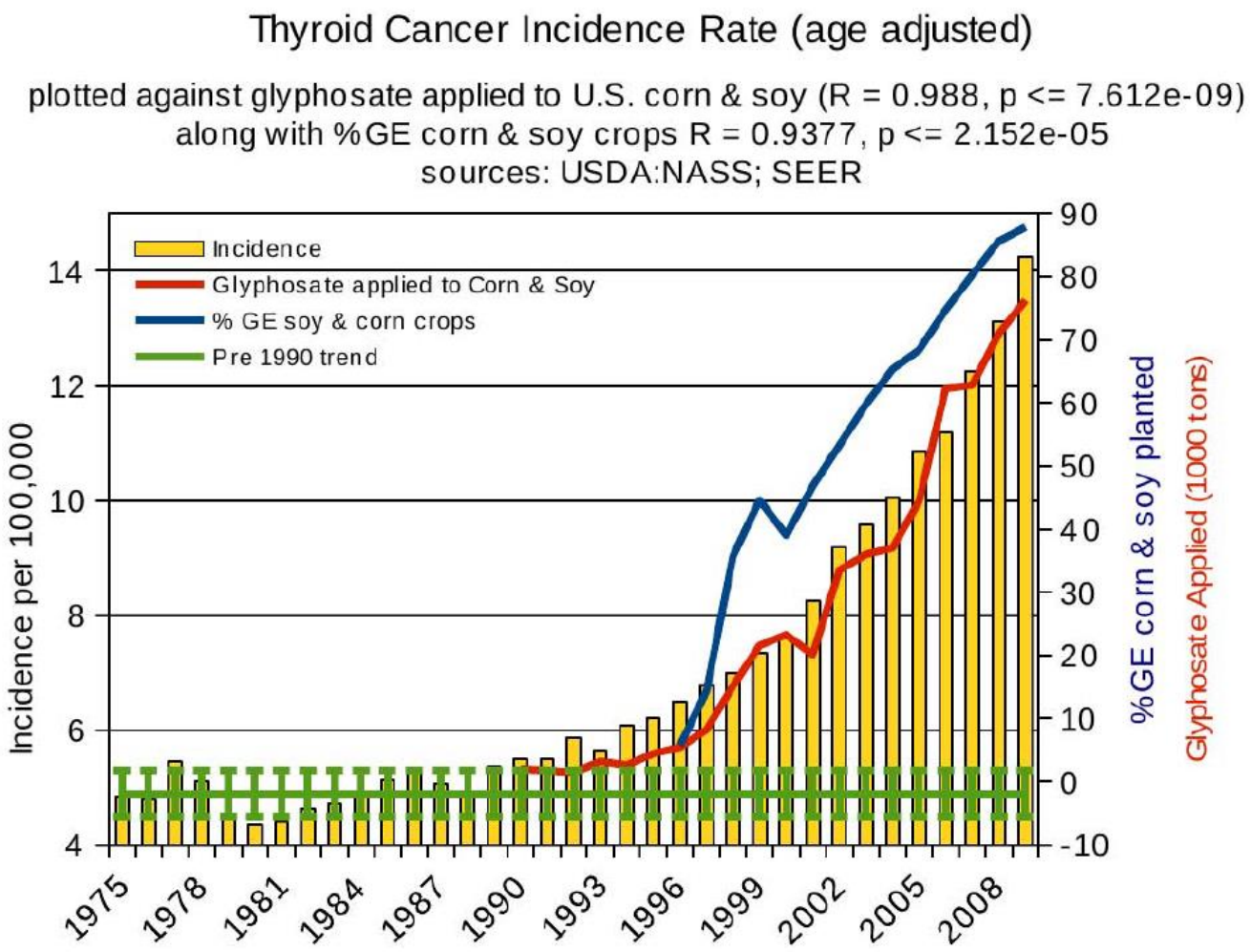


Figure 14. Correlation between age-adjusted diabetes incidence and glyphosate applications and percentage of US corn and soy crops that are GE.


Thyroid Cancer Incidence Rate (age adjusted)
plotted against glyphosate applied to U.S. corn & soy (R = 0.988, p <= 7.612e-09)
along with %GE corn & soy crops R = 0.9377, p <= 2.152e-05
sources: USDA:NASS; SEER
Incidence
Glyphosate applied to Corn & Soy
% GE soy & corn crops
Pre 1990 trend
Incidence per 100,000
%GE corn & soy planted
Glyphosate Applied (1000 tons)
4
6
8
10
12
14
-10
0
10
20
30
40
50
60
70
80
90
1975
1978
1981
1984
1987
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1996
1999
2002
2005
2008

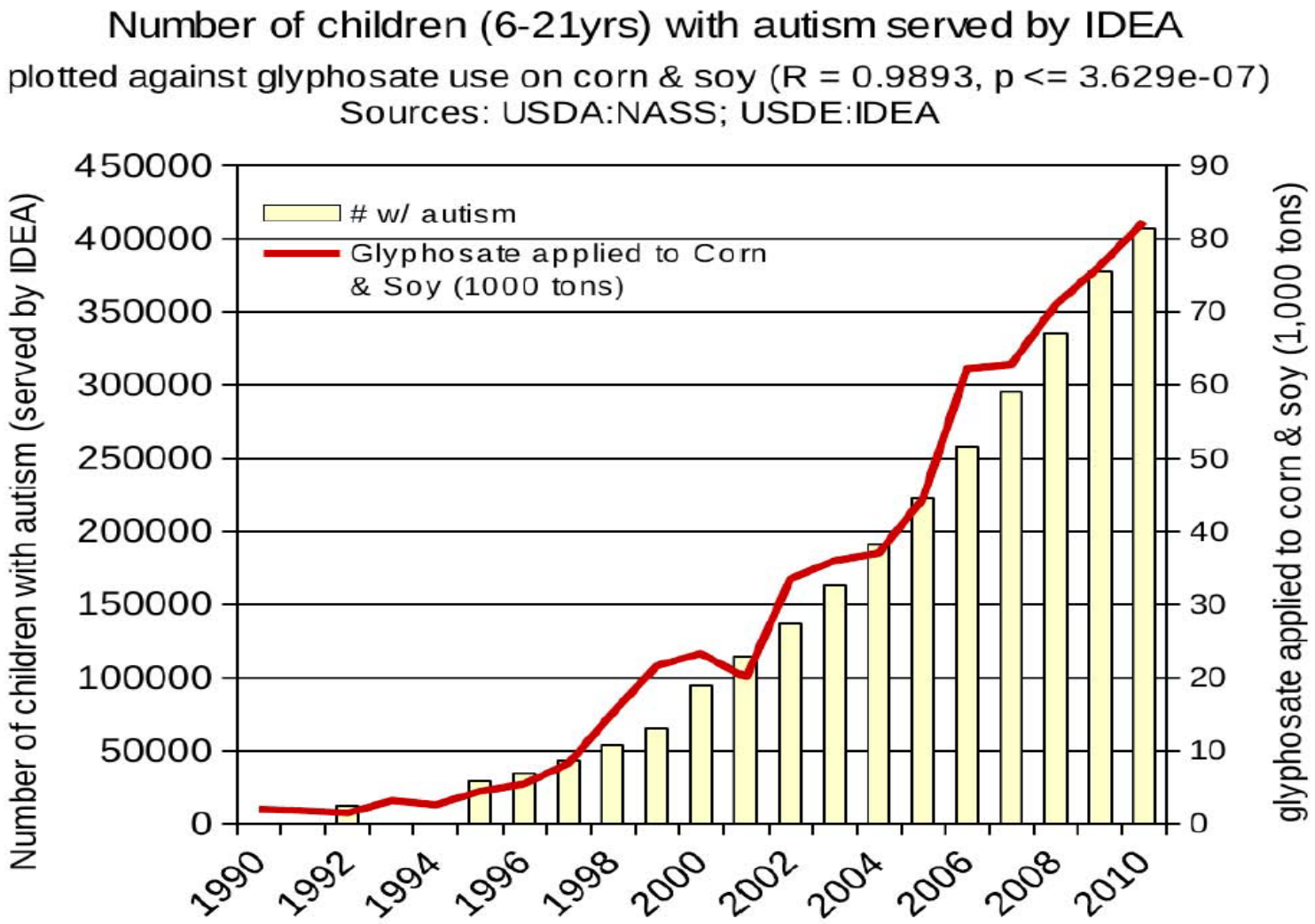


Figure 23. Correlation between children with autism and glyphosate applications.

Séralini et al. Environmental Sciences Europe 2014, 26:14
http://www.enveurope.com/content/26/1/14

Environmental Sciences Europe
a SpringerOpen Journal

RESEARCH Open Access

Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize

Gilles-Eric Séralini[1*], Emilie Clair[1], Robin Mesnage[1], Steeve Gress[1], Nicolas Defarge[1], Manuela Malatesta[2], Didier Hennequin[3] and Joël Spiroux de Vendômois[1]

Abstract

Background: The health effects of a Roundup-tolerant NK603 genetically modified (GM) maize (from 11% in the diet), cultivated with or without Roundup application and Roundup alone (from 0.1 ppb of the full pesticide containing glyphosate and adjuvants) in drinking water, were evaluated for 2 years in rats. This study constitutes a follow-up investigation of a 90-day feeding study conducted by Monsanto in order to obtain commercial release of this GMO, employing the same rat strain and analyzing biochemical parameters on the same number of animals per group as our investigation. Our research represents the first chronic study on these substances, in which all observations including tumors are reported chronologically. Thus, it was not designed as a carcinogenicity study.

Summary of Seralini et al paper

- The health effects of a Roundup-tolerant genetically modified maize (from 11% in the diet), cultivated with or without Roundup, and Roundup alone (from 0.1 ppb in water), were studied 2 years in rats.
- In female rats, there was **200-300% higher mortality** in all glyphosate treated groups compared to controls.
- Females developed large mammary tumors almost always more often than and before controls; the pituitary was the second most disabled organ. The sex hormonal balance was modified by GMO and Roundup treatments.

HEALTH EFFECTS SUMMARY

Rachel Nicoll PhD, 2019

Health effects from the studies

- External air pollution is particularly associated with neurological, respiratory and cardiovascular conditions. But other than this, almost any toxin type can cause any adverse condition in humans.
- But not every toxin type has been studied in connection with a specific condition, so the absence of a study does not mean no effect.
- There is likely to be an effect of toxin mixtures, but there are hardly any studies on this.

Observations

- With most body systems, it matters not if a toxin is associated with lower levels of e.g. a hormone, or higher levels. Any deviation from normal range represents a potential problem.
- Not all associations are linear. EDCs may show a non-linear but monotonic effect, a non-linear, non-monotonic effect or a threshold effect. *(More of this later)*
- Toxins have been found to vary in effect between genders, between ethnicities and at different foetal or childhood ages of exposure.
- They can also have the complete opposite effect between 2 studies of similar populations.
- So clearly there is some factor unique to the individual or group which determines the effect, if any, of a toxin.
- Genetics may play a role. But other factors (probably individual biochemistry) appear to be equally or more important.
- Scientists have not yet begun to consider individual factors, other than genetics.

ENDOCRINE DISRUPTORS: FEW MECHANISM STUDIES

- Relatively **few studies** have investigated the mechanism of effect of endocrine disruptors, or indeed of toxins in general.
- Most of the studies investigating mechanisms are *in vitro* or animal studies….principally because it is **unethical to give toxins to humans** for the purpose of investigation.
- Problems in finding funding. Which industry-funded university would risk taking it on?

ENDOCRINE DISRUPTOR MECHANISMS: Genetics

- Of those studies investigating genetics, only 1 line of enquiry has proved fruitful: the **paraoxonase1 (PON1) gene**. PON1 **detoxifies** oxidative derivatives of some OP pesticides and reduce oxidative stress.
- PON1's genetic polymorphisms influence enzyme activity and quantity. (Eskenazi B, Environ Health Perspect, 2010; Engle SM, Environ Health Perspect, 2015)
- **The PON1 gene does not become fully functional until the age of 9.**
- Among Hispanics in an agricultural region, lower maternal PON1 enzyme levels during pregnancy increased susceptibility of their offspring to neurotoxicity from organophosphate pesticide exposure (Eskenazi B, Environ Res, 2014).

ENDOCRINE DISRUPTOR MECHANISMS: Oxidant and antioxidant effects

- Offspring of pregnant mice given sodium fluoride showed significantly **increased liver malondialdehyde levels** (indicating lipid peroxidation) and **reduced catalase** (antioxidant) activity, which was more affected by low than high doses (Niu R, Biol Trace Elem Res, 2016).
- Rat maternal mercury exposure induced significantly **disturbed glutathione level** in the foetal brain (Watanabe C, Tohoku J Exp Med, 1999).
- Offspring of pregnant mice exposed to methylmercury showed dose-dependent **suppression of cerebral glutathione** and related enzymes, with a marked increase in **cerebral F(2)-isoprostanes** levels (indicating lipid peroxidation in the brain) (Stringari J, Toxicol Appl Pharmacol, 2008).
- Cellular toxin damage in semen is a result of an **imbalance between ROS generation and endogenous antioxidant activity**, which explains why numerous antioxidants, such as vitamin C, vitamin E, glutathione and co Q10, have proven beneficial effects in treating male infertility (Sheweita SA, Curr Drug Metab, 2005).

ENDOCRINE DISRUPTOR MECHANISMS: DNA methylation

- **DNA methylation is an epigenetic marker of genome instability** and adequate levels are essential for foetal development. Animal studies show that **alteration of DNA methylation** in the germ line **can transmit transgenerational adult onset disease, including cancer**.
- EDCs can demethylate the DNA sequence of an oestrogen-responsive gene during development. In adult animals, this is associated with persistent abnormal gene expression.

A few human studies

- A meta-analysis found that maternal residential NO2 exposure (as a marker for air pollution) during pregnancy was inversely associated with cord blood DNA methylation (Gruzieva O, Environ Health Perspect, 2016). Maternal PAHs was associated with impaired methylation of DNA in cord white blood cells in offspring with asthma prior to age 5 (Perera F, PLoS One, 2009).
- Placenta arsenic levels were associated with altered gene DNA methylation in 163 placental locations (Green BB, Environ Health Perspect, 2016).
- Maternal urinary phthalate metabolites and serum DDT and PBDEs were associated with DNA hypomethylation in offspring aged 9 (Huen K, Environ Res, 2016).

ENDOCRINE DISRUPTOR MECHANISMS: Metallothionein

- Metallothionein is involved in the protection of human trophoblastic cells from heavy metal-induced and severe oxidative stress-induced apoptosis.
- Metallothionein can both bind essential metal ions, but these are preferentially **displaced by toxic metal ions or free radicals**. (McAleer MF, Birth Defects Res C Embryo Today, 2004)

PREVENTION

PREVENTION: Avoidance

- Buy organic food, avoid all processed foods, forget ‘5-a-day’, eat ‘7-a-day’.
- Invest in a ‘whole house’ water filter, buy low chemical cosmetics, toothpaste, cleaning products, paints etc, find a ‘mercury-free’ dentist and don’t accept any metal in the mouth. Do not use metal or plastic cookware; glass is safest. Avoid using a microwave.
- Avoid vaccination unless absolutely necessary and detox afterwards.
- Avoid air conditioned buildings where the windows cannot be opened. In a house with new building work, decoration, furniture or furnishings, ensure off-gassing is complete before closing windows.
- Use wired broadband instead of wifi; protect bedrooms with anti-radiation paint. Don’t use a modern baby monitor as they use microwave technology.
- Ensure immune and detoxification systems are optimised.
- Ensure microbiota are optimised and the gut contains nothing pathogenic; treat intestinal permeability.

PREVENTION: Food and supplements (1)

- B vitamins can reduce the adverse effects of $PM_{2.5}$ on heart rate, heart rate variability and total white blood and lymphocyte count in humans (Zhong J, Sci Rep 2017) and increase urinary arsenic excretion (Argos M, Eur J Nutr, 2010)
- Folic acid helped protect against effects of PAHs on human placenta DNA (Dodd-Butera T, Environ Res, 2016).
- 1st trimester folic acid supplementation helped protect against risk of hypospadias among male offspring of pregnant women occupationally exposed to hair spray or phthalates (Ormond G, Environ Health Perspect, 2009)
- Folic acid supplementation helped protect against the reduced DNA methylation in offspring of pregnant mice fed BPA (Dolinoy DC, Proc Natl Acad Sci USA, 2007).
- Methyl donors given to pregnant rats prevented BPA-induced DNA hypomethylation in offspring (Dolinoy DC, Proc Natl Acad Sci USA, 2007)
- Vitamins C and E reduce phthalate-induced spermatogenic disturbance (Ablake M, Int J Androl, 2004); Vitamin C improved the lead- and chlorpyrifos-induced alteration in thyroid hormones and increase in malondialdehyde (Ambali SF, J Thyroid Res, 2011)
- Zinc supplementation helped protect against the reduced intrauterine growth from maternal cadmium and the foetal death induced by maternal smoking in humans (McAleer MF, Birth Defects Res C Embryo Today, 2004).
- Selenium helped protect against the neurobehavioural deficits in mouse offspring fed mercury (Watanabe C, Neurotoxicol Teratol, 1999).
- Antioxidants improved sperm quality and function in males after EMF exposure (Houston B, Reproduction, 2016)
- Proanthocyanidins protected human embryo hepatocytes from fluoride exposure by regulating iron metabolism (Niu Q, Biol Trace Elem Res, 2016)

PREVENTION: Food and supplements (2)

- Melatonin helped protect against effects in offspring of mobile phone radiation exposure in pregnant rats (Erdem Koc G, Int J Radiat Biol, 2016) and against TCDD-induced cardiac injury (Sarihan ME, Eur J Pharmacol, 2015)
- Melatonin reduced TCDD-induced hypertension by improving glutathione levels (Ilhan S, Toxicol Ind Health, 2015)
- Melatonin protected against mercury-induced oxidative stress in the thyroid (Rao MV, Food Chem Toxicol, 2010)
- Omega-3 fats helped protect against effects in offspring of mobile phone radiation exposure in pregnant rats and maternal PCBs, mercury and hexachlorobenzene exposure in pregnant rats (Erdem Koc G, Int J Radiat Biol, 2016; Dallaire R, Environ Int 2013).
- Phospholipid supplementation can attenuate vaccine-induced depressive behaviour in mice (Kivity S, Immunol Res 2016)
- Panax ginseng given to young females decreased urinary BPA and malondialdehyde levels and alleviated self-reported menstrual irregularity, menstrual pain and constipation (Yang M, BMC Complement Altern Med, 2014) and reversed the effect of phthalates and BPA on reprotoxicity in pregnant female rats (Saadeldin IM, Environ Sci Pollut Res Int, 2018)
- Spirulina reduced the effect of sodium fluoride in pregnant rats on offspring thyroid hormone, behaviour and antioxidant production (Banji D, Food Chem, 2013)
- Resveratrol reduced the growth effects of several EDCs on ovarian cancer cells (Kang NH, Mol Med Rep, 2012)
- Dark chocolate can provide neuroprotection from the damaging effects of traffic pollution in mice (Villarreal-Calderon R, Int J Toxicol, 2010).
- Pectin can reduce lead-induced thyroid injury (Khotimchenko M, Environ Toxicol Pharmacol, 2004)

Organic food – it really does make a difference

- Buy only organic wholefood i.e. real food, nothing with a label.
- A 2019 study showed that:
  - **After just 6 days of eating an all-organic diet, pesticide levels had dropped by >60%.**
  - This was particularly so for organo-phosphates, linked to neurodevelopment in infants.
  - Regular organic food eaters had an **80% lower level of glyphosate**. (Hyland C, Env Res, 2019)
- A 2006 study showed that children given only organic food for 5 days showed **reduced urinary malathion and chlorpyrifos** (organophospates) to **non-detectable levels** and remained nondetectable until conventional diets were reintroduced (Lu C, Environ Health Perspect, 2006).
- Organic farmers had significantly **higher sperm concentration** (Larsen SB, Occup Environ Med, 1999) and **lower levels of damaged or dead spermatozoa** (Juhler RK, Arch Environ Contam Toxicol, 1999)

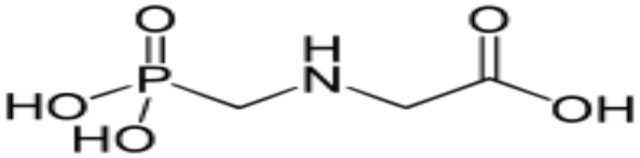
Testing for toxic overload

- Blood and urine testing
- Hair analysis
- These can be carried out at Biolab in Weymouth St, London W1 http://www.biolab.co.uk/
- Biolab are also the UK agents for the most comprehensive toxin tests currently available, from the US Great Plains Laboratory: GPLTox, is a urine test for toxic organic chemical exposure.
- Also Genova Diagnostics
  https://www.gdx.net/uk/

Treatment for glyphosate

- Glyphosate is an analogue of the amino acid **glycine**, which attaches to receptors and processes that need glycine.
- **Glycine is used up in the detoxification of glyphosate**, suggesting that we will be deficient if we are trying to detox glyphosate.

Glyphosate = glycine + phosphate



- Dr Dietrich Klinghardt has a protocol which involves saturating the body with **4g of glycine powder twice a day** for a few weeks and then lowering to a maintenance dose of 1g twice a day.
- This forces the glyphosate out in the urine.

Fasting: academic studies

- Response to toxins: DNA damage and blood malondialdehyde were significantly reduced.
- Toxin excretion: Increases urinary arsenic excretion 9-fold; increases total plasma organochlorine concentration.
- Side effects: Because the body is breaking down fat, it is also **releasing a lot of fat-soluble toxins into the bloodstream**. This may generate headaches and other symptoms.

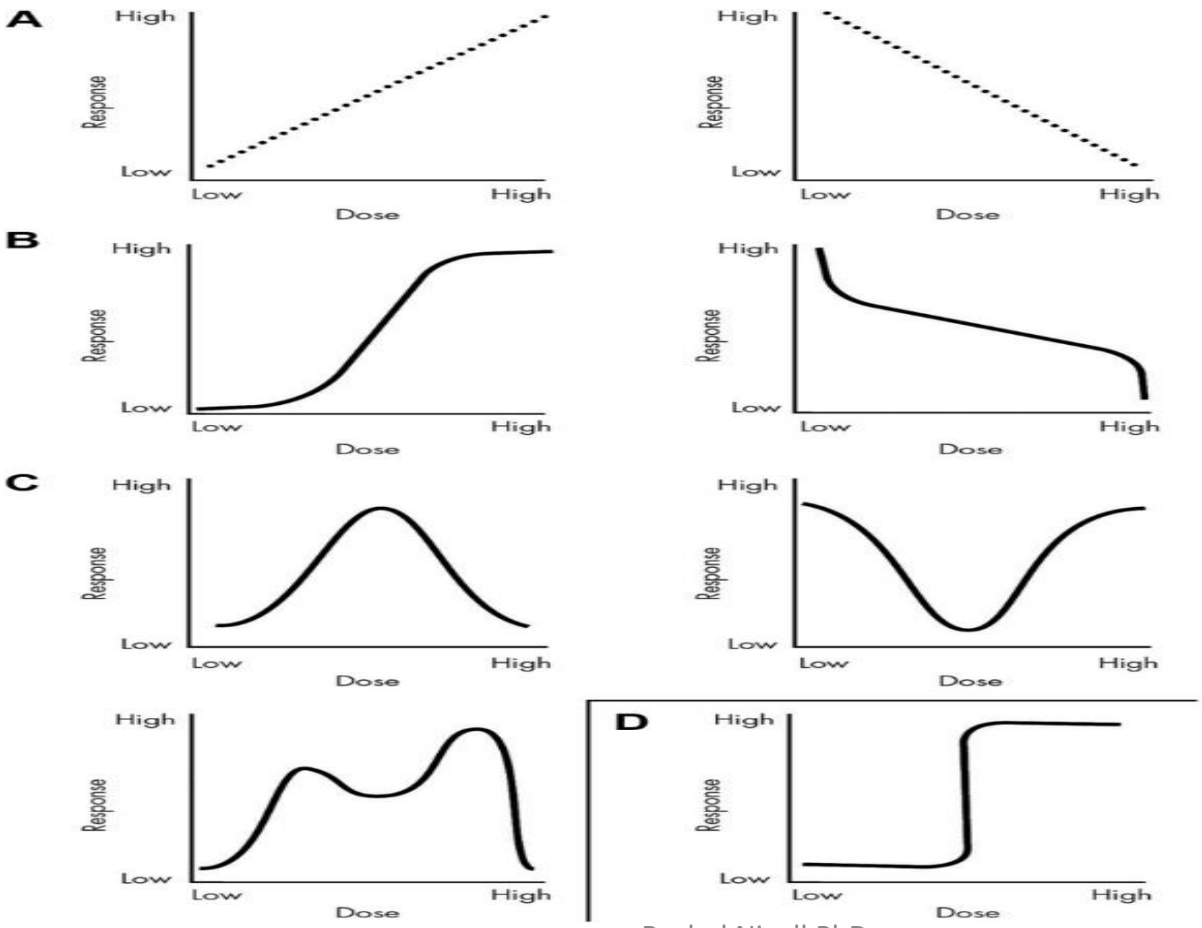
Craig C, Med Hypotheses, 2015; Li C, Forsch Komplement Med, 2013; Teng NI, Aging Male, 2013; Brima EI, J Environ Monit, 2007; Hue O, Obes Surg, 2006

ENDOCRINE DISRUPTORS: LOW DOSE EXPOSURE

- In recent years, scientists have now begun to consider the concept of **low dose exposure being stronger than high dose exposure** - although there is little consensus over what constitutes 'low dose'.
- 'Low dose' is generally taken to mean doses that are in the range of human exposure or doses below those traditionally tested in toxicological studies.
- Our natural endogenous hormones act at extremely low serum concentrations, typically in the picomolar to nanomolar range. So it makes sense that EDCs will have an effect in the same range.
- If we are prepared to investigate low dose exposure in combinations of toxins, then we find that when several EDCs at levels below their 'No observed effect concentrations' (NOEC) were added together and their effects tested *in vitro*, there was a significant additive effect even though individually they had no effect (Silva E, 2002; Rajapakse N, 2002).
- This is a truer reflection of real life, where we are exposed to many chemicals simultaneously, and suggests that it is body burden that causes the problem, not one exposure.

EDCs: NON-MONOTONIC DOSE RESPONSE CURVES

- Discussion of 'low dose' often goes hand-in-hand with discussion of non-monotonic dose response curves (NMDRCs). These are non-linear dose response curves that change sign. These are often U-shaped or inverted U-shaped, showing a bi- or multi-phasic response.
- Many scientists did not accept that a non-monotonic dose response existed because they could not envisage a mechanism for it (Vandenberg L, Endocr Rev, 2012).
- Also it meant that scientists and policy makers could continue making the assumption that one can extrapolate from high dose exposure effects to determine low dose effects.
- It makes sense that the dose response curve should be U-shaped because this is often the relationship between natural hormone concentrations and the number of bound receptors. (Vandenberg L, Endocr Rev, 2012).
- Many phyto-oestrogens are aromatase inhibitors at low concentration but oestrogenic at higher concentrations, resulting in a U-shaped dose–response curve (Almstrup et al., 2002; vom Saal et al., 2007).
- Experimental data indicate that EDCs and hormones do not have 'No observed adverse effect levels' (NOAELs) or threshold doses and therefore no dose can ever be considered safe.



Rachel Nicoll PhD, 2019

A. Linear responses, positive or inverse associations, allow for extrapolations from one dose to another.
B. Monotonic, nonlinear responses. The slope of the curve never changes sign, but it does change in value. Extrapolation only within the linear range.
C. Three different types of NMDRC: an inverted U-shaped, a U-shaped and a multiphasic curve. The slope of the curve changes sign one or more times. Extrapolation not possible.
D. Binary response, where one range of doses has no effect, then a threshold is met and all higher doses have the same effect.

Vandenberg L, Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev. 2012; 33(3):378-455

EXAMPLES OF A TYPICAL REACTION TO A FINDING A NON-MONOTONIC DOSE RESPONSE

1. 'Although we found associations between (phthalate) urinary concentrations and altered levels of FSH,

***the hormone concentrations did not change in the expected patterns*.**

Therefore, it is unclear whether these associations represent physiologically relevant alterations in these hormones.' (Duty SM, Hum Reprod, 2005).

2. Faced with a non-linear dose response relationship, the US EPA concluded that '**lack of a (*linear*) dose-dependent response negated the importance of the effect'.** (Hayes TB. 2002).

HORMESIS:

‘What doesn’t kill you makes you stronger!’

- Hormesis is a non-monotonic dose response, where a low dose generates a beneficial effect and a higher dose generates a pathogenic effect. This may also be called the adaptive response.
- Typically the substance will display a J-shaped dose response curve.
- Many chemicals, as well as radiation, are known to demonstrate hormesis.
- But the concept of a beneficial low dose but a harmful higher dose has failed to gain widespread acceptance because it is counter-intuitive and ‘sounds suspiciously like homeopathy’.
- Chemicals that induce a hormetic dose response may not be recognized as such because of the difficulties in detecting the low dose response when there is no harmful effect at high dose.

LEGISLATION AND ACTIVISM

Why isn't EU legislation protecting us better?

- Despite being the strictest environmental legislation in the world, EU legislation has many failings.
- Principal failing: the EU is **not adhering to the Precautionary Principle.**
- The Precautionary Principle is enshrined into the 1994 Maastricht Agreement. This shifts the presumption that specific chemicals are safe until proven dangerous, to a presumption that a chemical is unsafe unless proven otherwise.
- **i.e. *a chemical is guilty until proven innocent.***
- At present the EU claims that **a substance must demonstrate an adverse effect in order that it is banned**, whereas the Precautionary Principle requires that to be licensed, **a substance must demonstrate no adverse effect.**
- Furthermore, even where the legislation is adequately protective, the sale, distribution and use of banned chemicals is rarely policed as it takes a lot of manpower, and hence money.
- The most effective policing is carried out **by the public and by activists.**

Endocrine disruptors: European Commission 'breached law' (Independent, December 2015)

Following a legal challenge from Sweden, the European Court of Justice ruled that the European Commission had failed to:

- produce a legislative definition of an EDC and
- identify and ban potentially harmful EDCs.

The problem revolves around the precise burden of proof required, i.e. should the Precautionary Principle be applied.

Successes? EDCs

- February 2017: The EU finally recognised **four phthalates** as human endocrine disruptors.
- Meanwhile **Madrid has unilaterally voted to become EDC-free**. This includes limiting the use of pesticides in public spaces and buildings, promoting organic meals in schools and informing the public of the dangers of EDCs.
- The **state of California** has brought in similar legislation.
- **Where is the legislation for London…..or Dublin?**

Successes? Vaccines

- A June 2017 European Court of Justice (ECJ) ruling could make vaccine manufacturers more liable to compensate individuals damaged by vaccines. This case was originally brought in the French courts by a man who was vaccinated against hepatitis B, then developed MS and died.
- The ECJ ruled that **plaintiffs bringing vaccine injury lawsuits against drug companies do not have to prove causation but, instead, can provide clinical and circumstantial evidence to demonstrate that a vaccine more likely than not caused a person's injury or death.**

Successes? Mercury

- August 2017: **the Minamata Treaty came into force**. This is a global treaty that will **phase out mercury-based medical devices by 2020**. This includes mercury thermometers and blood pressure devices.
- Minamata disease was caused by the release of methylmercury in industrial wastewater from a Japanese chemical company - first reported in 1956. Locals who ate the contaminated fish in the Bay of Minamata became sick and their children suffered devastating neurodevelopmental injuries. It has taken over 60 years to achieve this very tentative step towards removing mercury from our environment.
- From 1 Jan 2018 the EU is required to **phase down (NOT phase out) dental amalgam**. It has already banned amalgam for children under 15 and for pregnant and breast-feeding women.
- Yet coal-fired power plants remain one of the greatest source of mercury emissions worldwide.

Glyphosate: carcinogenic or not?

- The International Agency for Research on Cancer (IARC) classified **glyphosate as a 'probable carcinogen'** in 2015.
- Glyphosate was listed as a carcinogen in March 2017 in the **State of California.** Monsanto challenged the listing but was unsuccessful.
- The **European Chemicals Agency (ECHA) ruled that glyphosate is not a carcinogen.**
- A joint letter to the European Commission by Greenpeace, HEAL and many other groups pointed out that the ECHA committee was using "**unpublished scientific evidence provided by industry**, in formulating its opinions".
- Similarly, the German Federal Institute for Risk Assessment has been found guilty of copy and pasting large chunks of its risk assessment of glyphosate from published and unpublished industry-sponsored studies as part of its own assessment process.

In the US

- The German company Bayer took over Monsanto in June 2018 at a price of $63 billion….
- and has been regretting it ever since!
- Bayer now faces **thousands of U.S. lawsuits by people who say its Roundup and Ranger Pro products caused their cancer**. A US federal judge overseeing the lawsuits has ruled that the **plaintiffs could introduce evidence of Monsanto's alleged attempts to ghostwrite studies and influence the findings of scientists and regulators** during the upcoming trials. Obviously Bayer had hoped to exclude this!
- In the US, a report found that the **Environmental Protection Agency (EPA),** in reaching its conclusion that glyphosate was not carcinogenic, had relied on results from **unpublished industry studies**, rather than peer reviewed published studies, which mostly found that glyphosate was genotoxic.
- Monsanto did not just give us glyphosate – it is also responsible for the first PCBs.

As well as GM foods and Round-Up, we can also blame Monsanto for PCBs

BREAKING NEWS

MONSANTO LOSES PCB LAWSUIT

Ordered to pay $46.5 million by St. Louis jury in a suit alleging negligence in the production of PCBs. Three plaintiffs claimed PCBs caused their cancer.

"... justice is going to be served whether it's a year after the products are put out, or in this case, 80 years." - Juror Ashley Enochs

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Success: French Court Cancels Monsanto Roundup Permit on Safety Grounds

- A court in Lyon has effectively brought in a **France-wide ban on Roundup** by ruling that the approval granted by **French environment agency** ANSES in 2017 had **failed to take into account potential health risks**, citing the WHO 2015 opinion that glyphosate was 'probably carcinogenic', and…
- That ANSES had **not respected the 'precautionary principle**', by not conducting a specific evaluation of health risks for Roundup Pro 360.
- This led the former French Environment Minister to describe Monsanto as "the worst firm in the world" (Le Journal du Dimanche 2 February 2019).
- Evidence of the harm to health from glyphosate continues to grow.

Why aren't the effects of environmental toxins more widely recognised?

- The science itself is not clear and a number of studies show no effect of a specific toxin.
- This may be because studies have not investigated:
  - The interaction between toxins in the body. Scientists are only just now beginning to investigate the effect of 2 toxins at a time – yet we are exposed to hundreds concurrently on a daily basis!
  - The effect of biochemical individuality is not studied. Only genetics is studied, detoxification, antioxidant and methylation status are ignored.
- There is a large gap between scientific research and integration of new knowledge into clinical practice, particularly in the area of complex chronic disease. We see this all the time in nutrition!
- Many of the companies that make toxic chemicals also manufacture the pharmaceuticals that are prescribed to treat the health damage symptoms.
- The outcome: Orthodox medicine's denial of environmental illness results in misdiagnosis, improper treatment and huge cost (because successive treatments fail).

The cost of health and disease

- No-one has yet found a mechanism to assign a **monetary value to life, health or quality of life.** And since everything comes down to money, this is a serious drawback.
- But attempts have been made to assign **monetary value to disease**:
  - The Royal College of Physicians estimated that UK air pollution costs the economy £20 billion per year, with 6 million working days lost from pollution-related illnesses.
  - US NRC report in 2000: the monetary cost of chemically induced neurobehavioural disorders in children were estimated at $9.2 billion p.a. based on 1997 costs.
  - The cost of Special Services due to prenatal PAH-induced developmental delay in New York City exceeded $13.7 million p.a. for Medicaid births (Weiland K, 2011).
  - From a **2016 European Expert Panel report**: '(there is) a probable (>20%) endocrine disrupting chemical causation for IQ loss and associated intellectual disability; autism; attention deficit hyperactivity disorder; endometriosis; fibroids; childhood obesity; adult obesity; adult diabetes; cryptorchidism; male infertility, and mortality associated with reduced testosterone….with annual costs amounting to **€163 billion**. (Trasande L, Andrology, 2016)

GENERAL 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.
- Because humans are surrounded by toxins every day, there can be no true non-exposed control group, although most researchers do not recognise this fact. Current exposures may be confounded by previous exposures, which may be largely unmeasurable; the concentrations of these chemicals may vary substantially between individuals and mask effects of current exposures (Krysiak-Baltyn et al., 2010).
- Toxins rarely occur in isolation and the combinations of toxins may have additive or antagonistic effects.
- Studies tend to focus on 1 chemical and 1 endpoint. But very few diseases are toxin specific (asbestosis is an exception).
- Researchers tend to look for effects in specific organs. This ignores effects on other organs, DNA, mitochondria, the immune system etc.

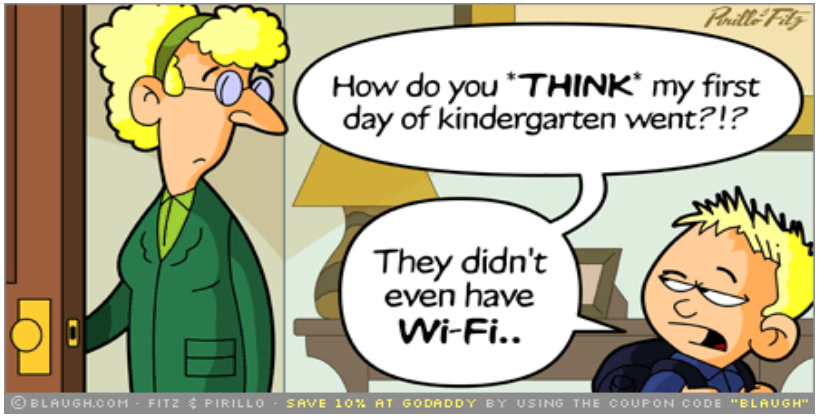
ADDITIONAL PROBLEMS WITH RESEARCH INTO EDCs AND LOW DOSE EXPOSURE

- Non-linearity of the dose/response relationship in low dose range.
- 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.
- In the low dose range, 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, 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.
- Many studies of EDCs show one result with one EDC metabolite and the opposite result with another, or one result in girls and the opposite in boys, one result in Hispanics and the opposite in Caucasians. When results are pooled in an study or a meta-analysis, they will show no effect.

So what can we do?

- The general public wants to believe that every substance on the market has been tested for toxicity, is safe and 'approved' for use, so that they are only minimally exposed to toxins. **This is not the case.**
- It's not just conventional doctors who adhere to the 'magic bullet' concept of treatment – most patients do too.
- So education of the public, particularly young people, with some hard evidence comprising facts and figures is imperative.
- We should require our governments to adhere to the Precautionary Principle, and require independent tests on all substances for safety.
- We need to promote the public's 'right-to-know' by campaigning for increased transparency about product ingredients and packaging through labelling requirements.
- Finally, policy change will only come about through 'people power', so do **become activists** yourselves and encourage your patients to become activists as well.

Parent Power



- **WIFI too Dangerous for German Schools.**
- German parents have demanded a WIFI ban in schools.
- https://www.youtube.com/watch?v=iQzJTJ1l3po

Quote from the late Professor Irving J Selikoff,

responsible for establishing the link between lung disease and asbestos fibres:

“The numbers in the tables represent human destinies, although the tears have been wiped away”.