ENDOCRINE DISRUPTORS AND THE UNBORN CHILD

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Organophosphate pesticides
Polybrominated diphenyl ether (PDBE) flame retardants
Combustion-related air pollutants
Lead
Mercury
Polychlorinated biphenyls (PCBs)
S.Walker

TOPICS COVERED

- Spontaneous abortion
- Sexual differentiation
- Congenital malformations
- Birth weight and growth
- Testicular dysgenesis syndrome
- Ovarian dysgenesis syndrome
- Genetic and DNA effects
- Neurodevelopment
- Cancer
- Metabolism and obesity
- Thyroid problems
- Other body systems

CAVEAT

I am only showing you studies where there are demonstrable effects of endocrine disruptors.

But there are as many studies showing no effect.

I will discuss some of the possible reasons for this at the end.

THE EXTENT OF MATERNAL TOXINS

- A 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?

- In mother/neonate pairs, maternal urinary phthalate metabolite concentrations were associated with their babies' phthalate concentrations (Sathyanarayana S, Environ Res, 2008).
- In Swedish mother/neonate pairs, maternal hair mercury concentrations were associated with cord blood concentrations (Bjornberg KA, Environ Health Perspect, 2003).
- Cord serum DDE levels correlated with maternal serum levels; in fact, DDT metabolites were detected in 99% of placental tissues, despite DDT being banned for some years (Al-Saleh I, Sci Total Environ, 2012).
- So this means that environmental toxins can cross the placental membrane, which separates the foetal from the maternal blood in the placenta, through a simple mechanism of passive diffusion, even in minimal concentrations.
- Even more worrying, environmental toxins can also pass through the still immature blood-brain barrier of the foetus (Roncati L, Sci Total Environ, 2016)
- And…Evidence shows that foetuses are more affected than adults or children by environmental toxins because of a much higher dose per body weight, the immaturity of the immune and detoxification systems and a longer lifetime over which disease initiated in early life can develop.

SPONTANEOUS ABORTION (MISCARRIAGE) AND STILLBIRTH (1)

A miscarriage is the spontaneous loss of a foetus before the 20th week of pregnancy. Pregnancy losses after the 20th week are called stillbirths. Stillbirths are often due to congenital anomalies.

- **Insecticides**: Increased risk in agricultural areas; increased risk if **male partner** was occupationally exposed during the time of pregnancy, with most 1st trimester losses occurring in the spring, the application season. Particular risk if male partner did not wear protective clothing and equipment.
- Increased risk with OP or carbamate exposure within 8 sq miles of home during 3rd-8th week of pregnancy; greatly increased risk within 1 sq mile.
- **Maternal domestic** exposure during 1st trimester was associated with stillbirths due to congenital anomalies and a >50% increase in stillbirth rate, while **paternal** exposure was associated with c30% increase.
- **Herbicides**: 1st trimester losses associated with preconception herbicide exposures. 3rd trimester losses were associated with glyphosate and carbamates, particularly among women aged >34.

(Garry VF, J Toxicol Environ Health, 2002; Arbuckle TE, Epidemiology, 1999; Bell EM, Epidemiology, 2001; Pastore LM, Occup Environ Med, 1997; Savitz DA, Public Health Rep, 1989; (Arbuckle TE, Environ Health Perspect, 2001)

SPONTANEOUS ABORTION AND STILLBIRTH (2)

- **Air pollution**: Bhopal leak of toxic gas (methyl isocyanate) from pesticide manufacture: risk of spontaneous abortion was 4 times higher
- **Cooking over an open fuel wood stove** resulted in an almost 50% greater chance of stillbirth.
- Spontaneous abortion correlated with urban levels of PM_{10} and ozone, even though the median pollution was **within legal limits**.
- Meta-analysis of effect of indoor solid fuel use vs cleaner fuel found solid fuel use was associated with OR of 1.51 for stillbirth.
- **Smoking**: Meta-analyses found increased risk of stillbirth.
- Increased risk of spontaneous abortion among non-smoking women when **both their parents had smoked while they were children** or in pregnant women whose husbands smoked. Risk also increased in those with higher BMI.

(Meeker JD, Hum Reprod, 2007; Meeker JD, Am J Epidemiol, 2007; Zhang J, Early Hum Dev, 1992; Zhang BY, Int J Gynaecol Obstet, 2012; Bajaj JS, Environ Health Perspect, 1993; Ardayfio-Schandorf E, Health Care Women Int, 1993; Di Ciaula A, Int J Environ Health Res, 2015; Pope DP, Epidemiol Rev, 2010; Leonardi-Bee J, Pediatrics, 2011; Nieuwenhuijsen MJ, Environ Health, 2013)

SPONTANEOUS ABORTION AND STILLBIRTH (3)

- **POPs**: PCBs; phthalates; BPA. *In vitro* studies found that BPA can reduce survival of human fertilised eggs and induce meiotic abnormalities.
- **VOCs**: Solvents (especially toluene and including paternal exposure), tetrachloroethylene in dry cleaner/laundry workers; formaldehyde.
- **Disinfectant byproducts**: Meta-analysis found an association between DBPs in water and stillbirth.
- **Radiation**: Meta-analysis found as association between occupational **preconception** exposure and foetal loss. Can also occur with exposure during pregnancy.
- **Incinerators**: Maternal residence near incinerators associated with foetal losses.
- **Groundwater arsenic**: Associated with spontaneous abortion and stillbirth.

(Gerhard I, Environ Health Perspect, 2000; Tsukimori K, Environ Health Perspect, 2008; Peng F, Environ Res, 2016; Chen X, Int J Environ Res Public Health, 2014; Sugiura-Ogasawara M, Hum Reprod, 2005; Brieno-Enriquez MA, Hum Reprod, 2011; Lenie S, Mutat Res, 2008; Lindbohm ML, J Occup Environ Med, 1995; Lindbohm ML, Am J Ind Med, 1990; Taskinen H, Scand J Work Environ Health; Kyyronen P, J Epidemiol Community Health, 1989; Duong A, Mutat Res, 2011; Lassi ZS, Reprod Health, 2014; Zhang J, Am J Ind Med, 1992; Dummer TJ, J Epidemiol Community Health; Quansah R, Environ Health Perspect, 2015; Guha Mazumder D, Kaohsiung J Med Sci, 2011; Nieuwenhuijsen MJ, Environ Health, 2013)

NEONATAL AND INFANT MORTALITY

Congenital anomalies, pre-term birth and low birth weight (<2,500 g) are the main factors associated with neonatal mortality.

But there may be ethnic differences: black infants had higher mortality rates at all gestational ages.

- Maternal residence near **domestic waste landfill sites and incinerators** was associated with neonatal mortality, especially due to spina bifida and heart defects. Maternal residence near **crematoriums**, mortality particularly due to anencephalus, also a **neural tube defect**.
- **Wood fuel use during pregnancy**: A 5-country study showed that use of mainly wood fuel vs cleaner fuel was associated with increased risk for death within 2 days of birth.
- **Bhopal (methyl isocyanate leak)**: increased neonatal mortality.
- **Arsenic**: A meta-analysis found that arsenic in groundwater was associated with increased risk.

Ananth CV, BMC Pregnancy Childbirth, 2004; Joseph KS, BMC Pregnancy Childbirth, 2004; Dummer TJ, J Epidemiol Community Health; Dummer TJ, Arch Environ Health, 2003; Patel AB, Matern Health, Neonatol Perinatol, 2015; Bajaj JS, Environ Health Perspect, 1993; Quansah R, Environ Health Perspect, 2015)

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

Male differentiation is critically dependent on normal androgen action, which in turn depends on normal production of luteinizing hormone.

- Among agricultural pesticide workers, the sex ratio of children with birth defects shows a male predominance (1.75 to 1) for all **pesticides**. But with **fungicide** exposure, normal female births significantly exceed male births (1.25 to 1).
- Males occupationally exposed to the **nematocide** dibromochloropropane fathered a lower proportion of males (16.6% versus 52.9%).
- Proximity to **waste incineration** was associated with lower male:female ratio.
- In the Seveso, Italy, dioxin studies, **paternal**, but not **maternal**, serum TCDD was dose-dependently associated with increased probability of female births, particularly among males exposed when they were age <19 years of age.

(Garry VF, Environ Health Perspect, 2002; Potashnik G, J Occup Environ Med, 1995;(Hu SW, J Air Waste Manag Assoc, 2001; Mocarelli P, Lancet, 2000)

PRE-TERM DELIVERY AND BIRTH WEIGHT

- Preterm birth = birth occurring before 37 weeks gestation.
- Why do these matter? Altered foetal growth, low birth weight and rapid growth in early childhood (catch-up growth) are associated with an increased risk for multiple diseases in adulthood, including hypertension, obesity, cardiovascular diseases, diabetes and cancers. They are also significant contributors to neonatal mortality and morbidity.
- In 13 European countries, 11% of pregnant women were occupationally exposed to EDCs according to job title. Exposure to ≥1 EDC job title group was associated with an increased risk of **low birth weight**; the risk increased with increasing number of EDC groups. But women exposed to BPA or brominated flame retardants were at higher risk for **longer length of gestation**. (Birks L, Environ Health Perspect, 2016)

PRETERM DELIVERY AND LOW BIRTH WEIGHT: Pesticides

- Higher levels of cord blood DDE were associated with lower birth weight in **boys** but higher birth weight in **girls**.
- Exposure to DDT was associated with reduction in foetal head circumference, crown-to-heel length, birth weight and birth height.
- Among **black women**, but not whites or Hispanics, increasing urinary OPs were associated with decreased birth length.
- Cord blood concentrations of hexachlorobenzene (fungicide) were inversely associated with duration of pregnancy and foetal growth.
- Residential exposure to methylbromide during the second trimester was associated with low birth weight, length and head circumference. Curiously, exposure within a **5 or 8km radius of spraying** vs a 1 or 3km radius was more strongly associated. Among a Hispanic agricultural California community, higher maternal urinary OPs were associated with decreased gestation period, particularly for exposure during the **3rd trimester**.

(de Cock M, J Environ Sci Health, 2016; Al-Saleh I, Total Sci Environ, 2012; Harley KG, Environ Health Perspect, 2015; Dallaire R, Environ Int 2013; Gemmill A, Environ Health Perspect, 2013; Eskenazi B, Environ Health Perspect, 2004)

PRE-TERM DELIVERY AND LOW BIRTH WEIGHT

- **Smoking**: Maternal smoking was an independent predictor of pre-term delivery and was associated with lower birth weight. Smoking alone accounted for 33% of the cases of pre-term birth. A meta-analysis found an association between environmental tobacco smoke and low birth weight.
- **Indoor air pollution**: Meta-analyses found that low birth weight was associated with household air pollution, domestic solid fuel use, maternal exposure to carbon monoxide, nitrogen dioxide and particulate matter <PM_{10}.
- **Outdoor air pollution**: Preterm birth and low birth weight were associated with exposure to $PM_{2.5}$, ozone and NO_2, petrol and diesel exhausts and **commercial meat cooking** during pregnancy. A systematic review found that exposure to SO2 was associated with pre-term birth and exposure to ≤$PM_{2.5}$ was associated with low birth weight and pre-term birth. Higher levels of PAHs as DNA adducts in maternal and cord blood WBCs were associated with decreased birth weight, length and head circumference.

(Mei-Dan E, J Perinat Med, 2015; Raisanen S, PLoS One, 2013; Nieuwenhuijsen MJ, Environ Health, 2013; Bruce, BMC Public Health, 2013; Stieb DM, Environ Res, 2012; Laurent O, Environ Health Perspect, 2016; Shah PS, Environ Int, 2011; Perera FP, Environ Health Perspect, 1999)

PRE-TERM DELIVERY AND LOW BIRTH WEIGHT: POPs

- **Phthalates**: Some maternal urinary or cord blood phthalate metabolites were **positively** associated with birth weight among **boys**, while others were **inversely** associated; there was no effect in **girls**. 3rd trimester maternal urinary phthalate metabolite levels were associated with **younger** gestational age (i.e. earlier birth than expected), although another metabolite was associated with **older** gestational age .
- **BPA**: Maternal urinary BPA was higher among those with low birth weight babies, particularly females, and was associated with increased head circumference.
- **PCBs**: Meta-analyses found an association between maternal PCB exposure and cord blood levels and low birth weight and shorter gestation period. The low birth weight was stronger among children of **non-Caucasian** mothers or smoking mothers.
- **Perfluorinated compounds**: A systematic review showed that *in utero* exposure to PFOS and PFOA was associated with **decreased** birth weight, although a later study found that higher cord blood levels of PFOS were associated with **increased** birth weight in boys. Cord PFOS and PFOA were also inversely associated with head circumference.

(de Cock M, J Environ Sci Health, 2016; Casas M, Environ Health Perspect, 2016; Whyatt RM, Pediatrics, 2009; Adibi JJ, Am J Epidemiol, 2009; Huo W, Environ Int, 2015; Snijder CA, Environ Health Perspect, 2013; Casas M, Environ Int, 2015; Dallaire R, Environ Int 2013; Nieuwenhuijsen MJ, Environ Health, 2013; Govarts E, Environ Health Perspect, 2012; Bach CC, Crit Rev Toxicol, 2015; Apelberg BJ, Environ Health Perspect, 2007; Philippat C, Environ Health Perspect, 2012)

PRE-TERM DELIVERY AND LOW BIRTH WEIGHT

- **Groundwater arsenic**: A meta-analysis showed that maternal exposure was associated with low birth weight. In a later study, maternal blood arsenic levels were inversely associated with birth weight, gestation period and head circumference.
- **Tributyltin** (found in ships' paint, so exposure through fish): among male babies, placental tributyltin was associated with **weight gain** during 1st three months.
- **Mercury**: cord blood concentrations were inversely associated with duration of pregnancy and foetal growth.
- **Phenols**: Presence of a maternal urinary phenol was associated with **decreased** birth weight but a another phenol was associated with **increased** birth weight and head circumference. A New York study showed that a higher maternal urinary phenol metabolite in the 3rd trimester predicted **lower** birth weight in **boys** but another predicted **lower** birth weight in **girls** but **higher** in **boys**.
- **Landfill sites**: Offspring of mothers living closest to a hazardous waste landfill site had lower birth weight and greater prematurity.

(Quansah R, Environ Health Perspect, 2015; Claus Henn B, Environ Health Perspect, 2016; Rantakokko P, Environ Health, 2014; Dallaire R, Environ Int 2013; Philippat C, Environ Health Perspect, 2012; Wolff MS, Environ Health Perspect, 2008; Berry M, Environ Health Perspect, 1997)

CONGENITAL MALFORMATIONS

It has been estimated that around 20% of all birth defects are due to gene mutations, 5-10% to chromosomal abnormalities and another 5-10% to exposure to a known teratogenic agent or maternal factor. Together, these percentages account for only 30-40%, leaving the aetiology of more than half of all human birth defects unexplained. (Bishop JB, Mutat Res, 1997)

CONGENITAL MALFORMATIONS: Pesticides

- Maternal occupational exposure to pesticides was associated with an elevated risk of **limb defects**, while exposure to herbicides and rodenticides during the 1st trimester was associated with **transposition of the great arteries** in offspring.
- **Congenital anomalies in the CNS** were more frequent among women exposed to pesticides during the first trimester of pregnancy.
- Nevertheless, a California study showed that paternal, but not maternal, occupational pesticide exposure and garden spraying was associated with orofacial clefts, neural tube defects, conotruncal defects and limb defects. Professional domestic spraying was also associated with increased risk of **neural tube and limb defects**. Furthermore, maternal residence within 0.25 miles of an agricultural crop increased risk of neural tube defects.
- A Canadian study suggests that birth defects are more likely in male offspring.
- A California study found that residential proximity to pesticide or herbicide application was associated with **anencephaly and spina bifida (both neural tube defects)**.

(Engel LS, Scand J Work Environ Health, 2000; Loffredo CA, Am J Epdiemiol, 2001; Zhang J, Am J Ind Med, 1992; Shaw GM, Epidemiology, 1999; Weselak M, Reprod Toxicol, 2008; Yang W, Am J Epidemiol, 2014)

‘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.

CONGENITAL MALFORMATIONS continued

- **Smoking**: A meta-analysis and later study found that periconception smoking was associated with a 3-fold increased risk of congenital heart defects.
- **Air pollution**: A meta-analysis found that NO2 concentrations were associated with coarctation of the aorta, while an Israeli study found that PM10 exposure during weeks 3-8 of pregnancy was associated with multiple congenital heart defects. There was an elevated risk of musculoskeletal birth defects associated with living near industrial facilities that emitted solvents or metals into the air.
- **Hazardous waste**: Maternal residential proximity to a site was associated with a higher risk of neural tube defects, particularly anencephaly, malformations of the cardiac septa and anomalies of great arteries and veins, especially among mothers aged ≥35.

(Lassi ZS, Reprod Health, 2014; Mei-Dan E, J Perinat Med, 2015; Chen EK, Int J Environ Res Public Health, 2014; Agay-Shay K, Environ Res, 2013; Marshall EG, Arch Environ Health, 1997; Suarez L, Ann Epidemiol, 2007; Orr M, Int J Hyg Environ Health, 2002; Dolk H, Lancet 1998; Geschwind SA, Am J Epidemiol, 1992)

CONGENITAL MALFORMATIONS continued

- **Dioxins**: A meta-analysis found higher risks of birth defects with maternal dioxin exposure.
- **DBPs**: Chlorine dioxide and other trihalomethanes in maternal drinking water were dose-dependently associated with increased risk of congenital heart defects in offspring.
- **Nitrate**: Nitrate in maternal drinking was associated with increased risk for anencephaly.
- **Chlorophenate wood preservative**: Paternal exposure was associated with congenital malformations in the genital organs and eye, particularly cataracts, anencephaly and spina bifida.
- **Radiation**: A Chinese study showed that maternal occupational exposure to radiation was associated with increased birth defects. The offspring of vets using radiation vs lawyers had a 4-fold higher rate of birth defects among offspring.

(Pan X, Int J Fertil Steril, 2015; Grasty RC, Birth Defects Res B Dev Reprod Toxicol, 2005; Croen LA, Am J Epidemiol, 2001; Dimich-Ward H, Scand J Work Environ Health, 1996; Zhang J, Am J Ind Med, 1992; Schenker MB, Am J Epidemiol, 1990)

NEURODEVELOPMENT

- According to the US CDC, 1 in 10 children has ADHD and 1 in 68 has 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.
- Many genes have been implicated in autism, some of which are directly related to detoxification processes. Many are also expressed prenatally in the frontal cortex where the effects of toxins on neurodevelopment are most relevant. To gain access to the foetal brain, toxins must pass placental and blood/brain barriers, as well as maternal barriers and membranes.
- 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)
- A key role of autism susceptibility genes may thus relate to their ability to facilitate toxin access to the developing foetal brain.

NEURODEVELOPMENT: Pesticides

- **ADHD**: Maternal urinary dialkyl phosphate (OP) during pregnancy was associated with ADHD at age 5, but only among boys.
- **Autism**: Most studies assess maternal residential exposure to agricultural pesticide application. OCs, OPs and pyrethroids were dose- and distance-dependently associated with increased risk for ASD particularly during **2nd and 3rd trimesters**. Some OCs showed a **6-fold increase in risk**.
- Maternal blood and urine transnonochlor (OC) concentrations were also associated with increased autistic behaviour.
- **Mental development and IQ** : Impaired mental development was associated with higher maternal and cord OCs, OPs, carbamates and **pyrethroids** up to 36 months; **Hispanics** may be particularly affected.
- Maternal serum DDT/DDE was inversely associated with processing speed at age 7 years in boys and girls and with IQ in girls. Residence within 1km of use of OPs, was associated with a decrease of 2.2 IQ points and 2.9 points in verbal comprehension for each standard deviation increase in use of organophosphate pesticides, pyrethroids, neonicotinoids, and manganese fungicides.

(Marks AR, Environ Health Perspect, 2010; Shelton JF, Environ Health Perspect, 2014; Roberts EM, Environ Health Perspect, 2007; Braun JM, Environ Health Perspect, 2014; Eskenazi B, Basic Clin Pharmacol Toxicol, 2008; Eskenazi B, Environ Health Perspect, 2007; Horton MK, Pediatrics, 2011; Engel SM, Environ Health Perspect, 2011; Shelton JF, Environ Health Perspect, 2014; Gaspar FW, Environ Int, 2015; Gunier RB, Environ Health Perspect, 2016)

NEURODEVELOPMENT: Glyphosate

- In US children born to pesticide/herbicide appliers, adverse neurologic and neurobehavioral developmental effects were noted particularly in offspring of appliers of the herbicide glyphosate (Garry VF, Environ Health Perspect, 2002).
- Glyphosate breakdown by microbes in the body leads to the creation of ammonia.
- Children with autism tend to have significantly higher levels of ammonia in their blood than the general population. Ammonia causes encephalitis (brain inflammation).

NEURODEVELOPMENT: POPs

- **PCBs**: A systematic review found that prenatal exposure was associated with abnormal reflexes, decreased motor skills and cognitive deficits. Maternal 2nd trimester serum PCBs were associated with **increased ASD** risk.
- **Phthalates**: Maternal 2nd and 3rd trimester urinary phthalates were associated with more **feminised play** amongst boys, impaired mental development among girls (not boys), impaired psychomotor development in boys (not girls), impaired social functioning at ages 7-9 and increased conduct problems.
- **BPA**: A systematic review showed that *in utero* exposure to bisphenol A (BPA) was associated with increased aggressive behaviour and ADHD. Maternal urinary BPA was associated with depression and anxiety in girls (not boys) aged 3 and boys (not girls) aged 10-12..
- **PBDE**: Maternal serum PBDEs were associated with impaired attention at age 5, lower IQ at age 7 and poorer attention and executive function age 9 and 12.
- **Dioxins**: Maternal exposure was associated with language delay.

(Ribas-Fito N, J Epidemiol Community Health, 2001; Boersma ER, Adv Exp Med Biol. 2000; Jacobson JL, N Eng J Med, 1996; Percy Z, Environ Health, 2016; Miodovnik A, Neurotoxicology, 2011; Tellez-Rojo MM, Sci Total Environ, 2013; Swan SH, Int J Androl, 2010; Engel SM, Environ Health Perspect, 2010; Mustieles V, Neurotoxicology, 2015; Perera F, Environ Res, 2016; Braun JM, Pediatrics, 2011; Eskenazi B, Environ Health Perspect, 2013; Sagiv SK, Neurotoxicol Teratol, 2015; Caspersen IH, Environ Int, 2016

NEURODEVELOPMENT

- **Air pollution**: 3rd trimester polycyclic aromatic hydrocarbon (PAH) levels or PAH-DNA adducts in Hispanic or African American women were associated with **reduction in left hemisphere white matter**, hence slower information processing speed and more severe behavioural problems, including ADHD. Increased autism was associated with residence near industrial emissions or urban traffic.
- **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**. Maternal exposure to manganese from fungicides was associated with behavioural problems in boys.
- **Fluoride**: Water fluoridation was associated with ADHD and lower IQ.
- **Radiation**: Norwegian adolescents exposed in utero to low dose radiation from Chernobyl had poorer verbal working memory, verbal memory, executive function and verbal IQs.
- **Ultrasound scans**: 1st trimester scans were associated with autism severity in male children with a genetic predisposition to ASD.

(Peterson BS, JAMA Psychiatry, 2015; von Ehrenstein OS, Epidemiology, 2014; Perera FP, PLoS One, 2014; Becerra TA, Environ Health Perspect, 2013; Vejrup K, Environ Int, 2016 Snoj Tratnik J, Environ Res, 2016; Jacobson JL, Environ Health Perspect, 2015; Rahman SM, Environ Health Perspect, 2016; Malin AJ, Environ Health, 2015; Choi AL, Eviron Health Perspect, 2012; Heiervang KS, Scand J Psychol, 2010; Heiervang KS, Dev Neuropsychol, 2010; Webb J, Autism Res, 2016)

TESTICULAR DYSGENESIS SYNDROME (TSG)

- The androgenic effects of testosterone masculinise the male foetus during a critical and narrow programming window early in gestation. If testosterone production or its action via the androgen receptor are disturbed at this early stage, reproductive organs are likely to be smaller and exhibit altered function or even malformation.
- 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.
- The anogenital distance: the distance from the anus to the genitals - used as a marker for reproductive toxicity. Shorter anogenital distance predicts poorer semen quality, impaired testosterone production and reduced fertility in males.
- Cryptorchidism: failure of the testes to descend to the bottom of the scrotum.
- Hypospadias: a congenital malformation of the urethral opening that originates in the first trimester of pregnancy when the urethral folds normally fuse under the influence of androgens from the foetal testis. It is one of the most common urogenital congenital anomalies affecting baby boys. Currently, the only available treatment is surgery.
- The result of TSG components is a demasculinising effect in boys.

TESTICULAR DYSGENESIS SYNDROME

- **Phthalates**: Maternal urinary metabolites, particularly from 1st trimester, were associated with decreased ano-genital distance, penile width and length, cryptorchidism and hypospadias.
- **BPA**: Placenta BPA concentrations or occupational exposure predicted chryptorchidism and hypospadias and were associated with reduced ano-genital distance; an *in vitro* study showed that BPA inhibits testosterone production.
- **Toxic metals**: Placenta dibutyltin concentrations were associated with cryptorchidism in Finnish boys.

(Martino-Andrade AJ, Andrology, 2016; Swan SH, Hum Reprod, 2015; Bornehag CG, Environ Health Perspect, 2015; Sathyanarayana S, Environ Res, 2016; Bustamante-Montes LP, J Orig Health Dis, 2013; Suzuki Y, Int J Androl, 2012; (Fernandez MF, Reprod Toxicol, 2016; Miao M, Birth Defects Res Clin Mol Teratol, 2011; Ben Maamar M, PLoS One, 2015; Rantakokko P, Hum Reprod, 2013)

TESTICULAR DYSGENESIS SYNDROME

- **Pesticides**: **Maternal** occupational exposure was dose-dependently associated with reduced genital size and abnormal serum hormone concentrations at age 3 months. At age 6-11, boys had reduced testicular volume and penile length and genital malformations, indicating that in utero exposure has long term effects. **Paternal** exposure was associated with cryptorchidism, hypospadias or penile size. Placenta OCs (DDT, lindane, endosulfan, mirex) as well as maternal occupational exposure were associated with increased cryptorchidism or hypospadias.
- **Smoking**: Maternal smoking during pregnancy was associated with bilateral cryptorchidism, decreased number of gonocytes, earlier onset of puberty, smaller testicles and reduced semen quality and sperm count, while paternal smoking was associated with hypospadias. Maternal use of **nicotine substitutes** during pregnancy was associated with increased risk of cryptorchidism.
- **Hair spray**: Maternal occupational exposure to hair spray had a significantly higher risk of hypospadias in male offspring.

(Fernandez MF, Environ Health Perspect, 2007; Wohlfahrt-Veje C, Int J Androl, 2012; Pierik FH, Environ Health Perspect, 2004; Gaspari L, Hum Reprod, 2011; Damgaard IN, PloS One, 2008; Pierik FH, Environ Health Perspect, 2004; Hart RJ, J Clin Endocrinol Metab, 2016; Ravnborg TL, Hum Reprod, 2011; Thorup J, J Urol, 2006; Jensen TK, Am J Epidemiol, 2004; (Ormond G, Environ Health Perspect, 2009)

OVARIAN DYSGENESIS SYNDROME

Ovarian dysgenesis syndrome can include:

- early puberty (menarche),
- altered menstruation,
- anovulation,
- infertility,
- oestrogen deficiency,
- fibroid development
- premature ovarian failure.

OVARIAN DYSGENESIS SYNDROME

- **POPs**: Offspring of women exposed to phthalates or PBDEs had early breast and pubic hair development and increased testosterone and DHEA-S, indicative of **early puberty**. Maternal serum PCBs from eating sport fish were associated with **decreased fertility** of female children. In rats, the effects of low dose PCBs (depressed LH and progesterone and smaller uterine and ovarian weights) were **more profound in the F2 than the F1 generation**.
- **Pesticides**: Maternal serum DDT/DDE was associated with earlier puberty and decreased fertility in female children
- **Smoking**: Maternal exposure to smoking during pregnancy was associated with decreased fertility in female children.
- **Fluoride**: Sodium fluoride administered to mouse embryos showed increased embryo apoptosis in the blastocyst stage at **lower, but not higher, doses**.

(Watkins DJ, Environ Res, 2014; Blanck HM, Epidemiology, 2000; Han L, Environ Health, 2016; Steinberg RM, Biol Reprod, 2008; Cohn BA, Lancet, 2003; Vasiliu O, Hum Reprod, 2004; Jensen TK, Int J Androl, 2006; Fu M, Environ Sci Technol, 2014)

CANCER DEVELOPMENT FROM *IN UTERO* EXPOSURE

- **Pesticides**: Maternal serum DDT levels predicted a 5-fold increased risk of breast cancer in female offspring. Residential use of insecticides was associated with childhood lymphoma and a 10-fold increase in infant acute leukaemia. A meta-analysis showed an association between parental occupational pesticide exposure and brain tumour development in offspring.
- **POPs**: Animal studies show that *in utero* exposure to **low dose** BPA or phthalates was associated with accelerated mammary gland growth, increased mammary tumours and decreased tumour latency; **high dose** BPA exposure was protective. In males, BPA exposure was associated with increased prostatic epithelial cell proliferation and increased prostate size in males.
- **Solvents**: Parental occupational exposure or employment in the automotive industry was associated with childhood leukaemia. Maternal residence in homes painted extensively in the year before birth was associated with increased risk of acute lymphoblastic leukaemia.
- **Smoking**: Maternal smoking during pregnancy was dose-dependently associated with increased risk for any childhood cancer but the risk was doubled for non-Hodgkin lymphoma, acute lymphoblastic leukaemia and Wilms' tumour.
- **Cured meats**: Maternal consumption of cured meats containing N-nitroso compounds (nitrosamines and nitrosamides) was associated with increased risk of childhood brain tumour
- **Ionising radiation**: Radiation was associated with increased risk for childhood cancer, particularly leukaemia. Maternal proximity to, and paternal employment at, **Sellafield nuclear power station** was associated with increased risk of leukaemia and non-Hodgkin's lymphoma.

(Meinert R, Am J Epidemiol, 2000; Alexander FE, Cancer Res, 2001; Cohn BA, Environ Health Perspect, 2007; van Maele-Fabry G, Environ Int, 2013;(Timms BG, Proc Natl Acad Sci USA, 2005; Macon MB, J Mammary Gland Biol Neoplasia, 2013; Freedman DM, Am J Public Health, 2001; Colt JS, Environ Health Perspect, 1998; Shu XO, Cancer Epidemiol Biomarkers Prev, 1999; Vianna NJ, J Occup Med, 1984; Sternfjeldt M, Lancet, 1986; Dietrich M, Cancer Causes Control, 2005; Gardner MJ, BMJ, 1990; Doll R, Br J Radiol, 1997)

DIABETES, METABOLIC DISORDERS AND OBESITY

- Low birth weight babies have significantly increased susceptibility to 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.

DIABETES, METABOLIC DISORDERS AND OBESITY

- **Pesticides**: Maternal serum DDT/DDE during pregnancy was associated with a BMI growth pattern in boys, but not girls, that is stable until about age five but then displays increased growth to age nine. The fungicide hexachlorobenzene was associated with overweight by age 18 months and 6½ years.
- **Air pollution**: Maternal exposure to PM2.5 in the 3 months prior to conception and at any time during pregnancy was associated with childhood overweight or obesity between the ages of 2 and 9. Maternal PAH levels were associated with higher BMI and higher risk of obesity in offspring at ages 5 and 7.
- **Smoking**: Maternal smoking during pregnancy was associated with **decreased weight at birth** but at age 11 in females and age 16 in males there was **increased risk** of being in the highest decile of BMI. Obesity risk increased with age, with increased T2D among middle-aged daughters.
- **POPs**: Maternal urinary BPA concentrations were associated with increased BMI and waist circumference aged 4, but not at earlier ages. Cord blood PCBs were associated with overweight in girls, but not boys, but high maternal exposure was associated higher BMI at all childhood ages. Maternal serum PBDEs were associated with higher BMI in boys at age 7 but a lower BMI in girls, while maternal serum PFOS and PFOA were associated with overweight at ae 18 months in all offspring. In pregnant rats given BPA, the **lowest**, but **not higher** doses, were associated with increased body weight late in life in female (but not male) offspring.
- **Metals**: In pregnant mice given inorganic arsenic, offspring had significantly greater body weight gain. Females had increased body fat content and glucose intolerance, while males had increased insulin resistance, hyperglycaemia and plasma triglycerides and increased the expression of genes involved in fatty acid synthesis, lipogenesis and inflammation.

(Heggeseth B, PLoS One, 2015; Warner M, Am J Epidemiol, 2014; Valvi D, Obesity, 2014; Smink A, Acta Pediatr, 2008; Karlsen M, Reprod Toxicol, 2016; Mao G, Environ Health Perspect, 2016; La Merrill MA, J Dev Orig Health Dis, 2015; Power C, Int J Epidemiol, 2002; Rundle A, Am J Epidemiol, 2012; Hass U, Andrology, 2016; Valvi D, Epidemiology, 2013; Ditzel EJ, Environ Health Perspect, 2016; Rodriguez KF, Environ Health Perspect, 2016; Valvi D, Environ Health Perspect, 2012; Verhulst SL, Environ Health Perspect, 2009; Erkin-Cakmak A, Environ Health Perspect, 2015; Karlsen M, Reprod Toxicol, 2016)

THYROID AND THE BRAIN

- 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.
- Thyroid hormones cross the placenta and enter the brain primarily as thyroxine (T4); therefore any toxins lowering serum T4 levels alter brain hormone availability.
- A lower cord blood FT4 concentration was associated with lower birth weight (Janssen BG, Environ Health Perspect, 2016).

EDCs AND THYROID

- **POPs**: In newborns, cord blood perfluorinated compounds were positively associated with cord blood T4 and T3 and inversely associated with cord blood TSH in girls but not boys. Maternal urinary BPA was associated with reduced TSH in boys, but not girls, and was stronger when measured in the 3rd trimester. Higher placental PCBs was an independent predictor of decreased free T4.
- **Metals**: 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**. Cord blood cadmium concentrations were inversely associated with neonatal TSH levels.
- **Air pollution**: Maternal 3rd trimester exposure to PM2.5 was inversely associated with foetal TSH and the FT4/FT3 ratio.

(Shah-Kulkani S, Environ Int, 2016; de Cock M, Environ Health, 2014; Chevrier J, Environ Health Perspect, 2013; Wang SL, Environ Health Perspect, 2005; Ursinova M, Biol Trace Elem Res, 2012; Iijima K, Biol Trace Elem Res, 2007; Janssen BG, Environ Health Perspect, 2016)

OTHER BODY SYSTEMS

- **Liver**: Offspring of pregnant rats fed BPA exhibited decreased liver mitochondrial respiratory activity, alterations in gene expression involved in mitochondrial fatty acid metabolism, development of micro-vesicular steatosis, up-regulated genes involved in lipogenesis pathways and increased ROS generation. At older age, extensive fatty accumulation in liver and elevated serum ALT were observed, with impaired hepatic mitochondrial function and ATP production, increased ROS generation and altered mitochondrial membrane potential.
- **Respiratory problems**: A 2014 meta-analysis found that prenatal exposure to DDE and PCBs was associated with bronchitis prior to 18 months of age, while maternal urinary OPs in **later, but not earlier**, pregnancy were associated with respiratory symptoms at age 5 and 7. Newborns of women who smoked during pregnancy were more likely to suffer respiratory distress syndrome.
- **Cardiovascular problems**: Meta-analyses of maternal air pollution found that NO2 concentrations were associated with coarctation of the aorta, while a review showed that maternal smoking as well as high concentrations of NO2, SO2 and PM10 were associated with congenital heart defects. Maternal exposure to herbicides and rodenticides during the 1st trimester was associated with transposition of the great arteries in offspring, while maternal serum DDT was associated with hypertension in middle age. Prenatal exposure to BPA impaired cardiac mitochondria.

(Jiang Y, Toxicol Let, 2014; Mei-Dan E, J Perinat Med, 2015; Gascon M, Epidemiology, 2014; Raanan R, Environ Health Perspect, 2015; (Baldacci S, Epidemiol Prev, 2016; Chen EK, Int J Environ Res Public Health, 2014; Lassi ZS, Reprod Health, 2014; Agay-Shay K, Environ Res, 2013; La Merrill M, Environ Health Perspect, 2013; Loffredo CA, Am J Epidemiol, 2001; Jiang Y, J Appl Toxicol, 2014)

PARENTING PROBLEMS

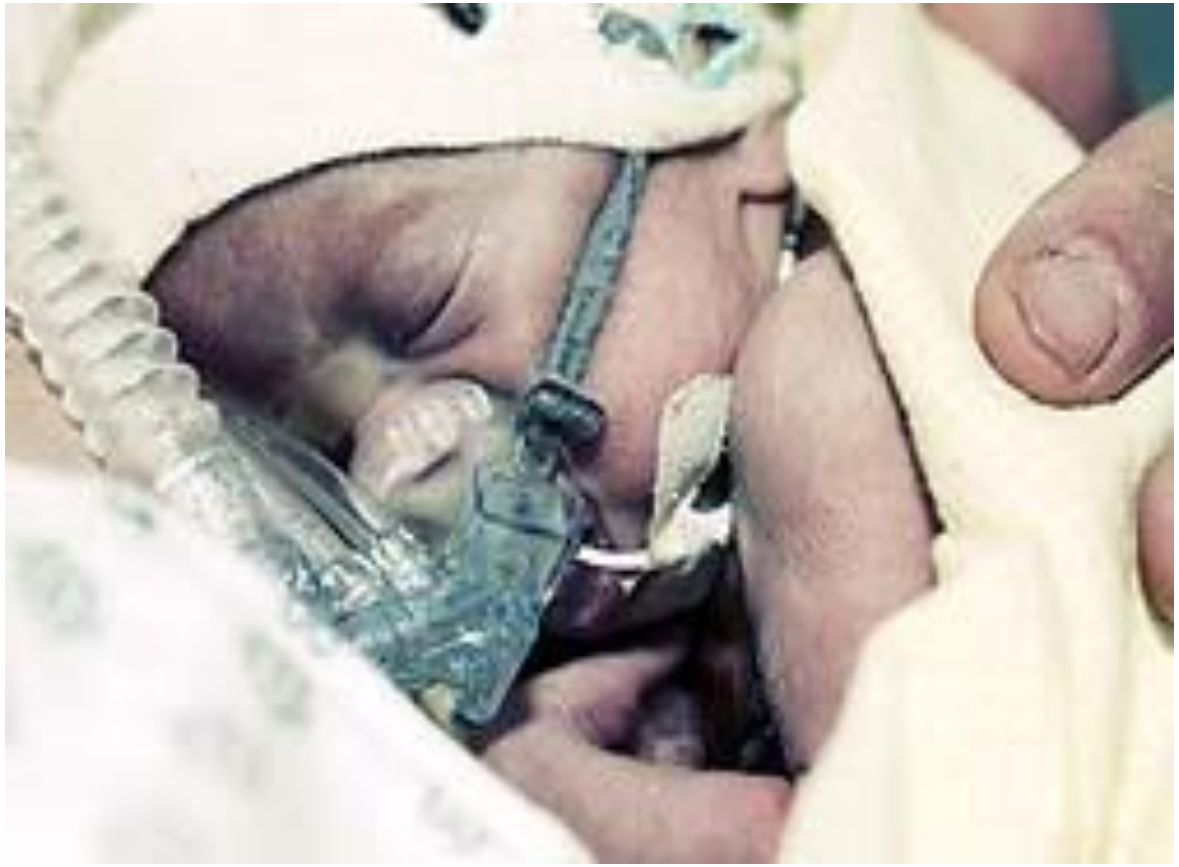
- Female mice exposed to BPA spent less time breast feeding, grooming and associating with their pups.
- Interestingly, non-exposed females appeared able to ‘sense’ a male partner previously exposed to BPA and consequently reduced their own parental investment in offspring from mating (i.e. poorer parenting if mothers or their partners exposed to BPA).

(Johnson SA, PLoS One, 2015)

FRACKING AND WAR

- Offspring of pregnant mice exposed to a mixture of commonly used oil and gas fracking chemicals had suppressed pituitary hormone concentrations (prolactin, LH, FSH and others), increased body weights, altered uterine and ovary weights, increased heart weights and collagen deposition and disrupted folliculogenesis, even in the lowest dose group (Kassotis CD, Endocrinology, 2016).
- War-created pollution is a major cause of rising birth defects and cancers in Iraq. Analysis of trace elements in deciduous teeth of these children with birth defects found very high levels of lead from children from Basra, Iraq. Two Iraqi children with birth defects had four times more tooth lead, and one had 50 times more tooth lead than samples from non-exposed areas. (Savabieasfahani M, Environ Monit Assess, 2016)

Toxic legacy of the US assault on Fallujah 'worse than Hiroshima‘ (Independent, 2010)



‘The shocking rates of infant mortality and cancer in the Iraqi city raise new questions about battle’.

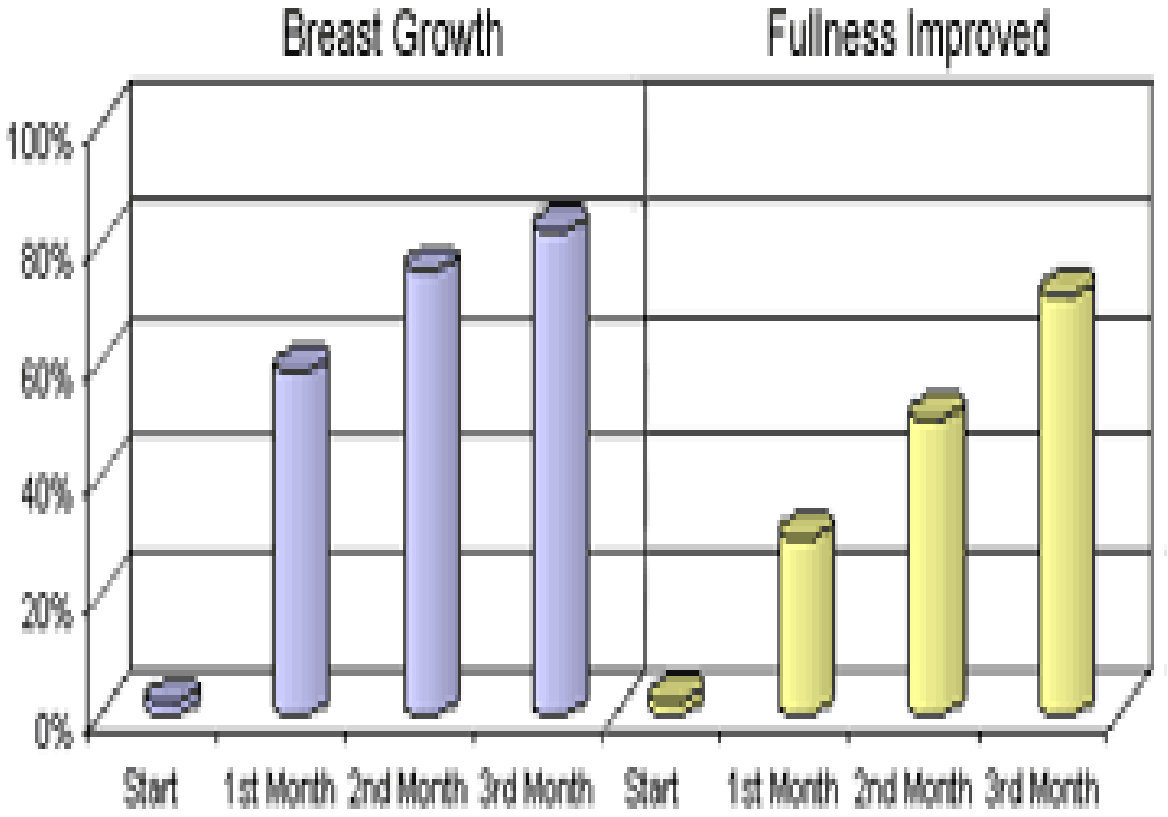
PHYTOESTROGENS AND ISOFLAVONES

- Isoflavones first drew attention as a possible health hazard in the 1940s, when Australian ewes grazing on clover were found to have reduced fertility [Clover contains the isoflavone coumestan]
- Isoflavones comprise mainly genistein, daidzein and coumestan, found predominantly in legumes, particularly soyabean.
- When taken as food, they may have beneficial effects and may be protective against breast, uterus and prostate cancer in Asian women. These women do not take large amounts or supplement isoflavones.
- In larger amounts, phytoestrogens become endocrine disruptors, evoking all the same hormonal responses as physiological oestrogens. The US CDC have now added phytoestrogens to the list of potential human toxins.
- High levels of soya during pregnancy increased the risk of breast cancer in female offspring, causing the UK government to require that soya-based infant formulas be available only on prescription. (Hilakivi-Clarke L, Oncol Rep 1999; Bennetts H, J Dept Agric West Aust 1946; (Boulet MJ, Maturitas 1994; (Strauss L, Toxicol Lett, 1998; (Kuiper GG, Endocrinology 1998).

Another use for phytoestrogens?

- A high intake of dietary soya for just 14 days significantly stimulated the proliferation rate of healthy breast cells (McMichael-Phillips DF, Am J Clin Nutr 1998).
- Consequently, phytoestrogen supplements are now being marketed as a form of natural breast enhancement.

www.herbalove.com



TAKE HOME MESSAGES

- A maternal (and sometimes a paternal) toxin = a foetal toxin.
- Toxins damaging foetal health include particularly maternal smoking and pesticides/herbicides, but also all POPs, outdoor and indoor air pollution, solvents, formaldehyde, phenols, radiation, nuclear power stations, cured meats, DBPs, fluoride, nitrates, landfill sites, incinerators, metals, phytoestrogens.
- 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.

ENDOCRINE DISRUPTORS: MECHANISMS

- Relatively few studies have investigated the mechanism of effect of endocrine disruptors, or indeed of toxins in general. Probably this is partly why governments do not yet accept that they exist.
- Most of the studies investigating mechanisms are *in vitro* or animal studies, which are easier to dismiss – what we need is studies translating this research to humans but there are many reasons why this probably won't happen any time soon!
- ….principally because it is unethical to give toxins to humans for the purpose of investigation. Also there is no clear hypothesis to test and who would fund it? (certainly not 'big pharma). Which industry-funded university would risk taking it on?

ENDOCRINE DISRUPTORS: POTENTIAL MECHANISMS - GENETICS

- Of those studies investigating genetics, only 1 line of enquiry has proved fruitful: the paraoxonase1 (PON1) gene. PON1 detoxifies oxon derivatives of some OP pesticides and its genetic polymorphisms influence enzyme activity and quantity. (Eskenazi B, Environ Health Perspect, 2010; Engle SM, Environ Health Perspect, 2015)
- Among Hispanics in an agricultural region, lower maternal PON1 enzyme levels during pregnancy increased susceptibility of their offspring to neurotoxicity from OP pesticide exposure (Eskenazi B, Environ Res, 2014).

ENDOCRINE DISRUPTORS: POTENTIAL 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).
- A similar rat study showed increased glutathione, GPx and vitamin C levels in red blood cells but these decreased at higher dose (Shivarajashankara YM, Ind J Exp Biol, 2003), possibly indicating up-regulation at low dose but depletion following up-regulation at high dose.
- Pregnant mice were injected with methylmercury, which inhibited the activity of glutathione peroxidase in the foetal brain and placenta, but not in the maternal brain (Watanabe C, Environ Res, 1999).
- Offspring of pregnant mice exposed to methylmercury showed dose-dependent suppression of the normal increase 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).

ENDOCRINE DISRUPTORS: POTENTIAL 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.
- The example of diethylstilbestrol (DES) showed that 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 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).
- Offspring of pregnant mice exposed to BPA showed hypomethylation of DNA (Dolinoy DC, Proc Natl Acad Sci USA, 2007).

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. 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.
- Ensure immune and detoxification systems are optimised.
- Ensure microbiota are optimised and the gut contains nothing pathogenic; treat intestinal permeability.

PREVENTION: FOOD AND SUPPLEMENTS

- 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).
- Melatonin helped protect against effects in offspring of mobile phone radiation exposure in pregnant rats (Erdem Koc G, Int J Radiat Biol, 2016).
- 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).
- The proanthocyanidins in grapeseed extract helped protect against effects of maternal sodium fluoride in human embryo hepactocytes (Niu Q, Biol Trace Elem Res, 2016).
- Spirulina helped protect against the effects of maternal sodium fluoride on thyroid hormones and behaviour in offspring of pregnant rats (Banji D, Food Chem, 2013)
- Zinc supplementation helped protect against the reduced intrauterine growth from cadmium given to pregnant animals 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 offspring of pregnant mice fed mercury (Watanabe C, Neurotoxicol Teratol, 1999).

HOW HAVE WE COME TO THIS?

- We are surrounded by toxins all the time, regardless of our avoidance measures. Why aren't the risks spelled out more effectively?
- Firstly, there is a large gap between scientific research and integration of new knowledge into clinical practice, particularly in the area of complex chronic disease. This is true of all research, not just EM.
- 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 and they only seem to care about cancer!
- 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).

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.
- 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 Caucsasians. When results are pooled they will show no effect.

BUT DOESN'T EU LEGISLATION PROTECT US?

- Up to a point: it is the strictest in the world. And the Precautionary Principle in enshrined into the 1994 Maastricht Agreement, which 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.
- i.e. *a chemical should be guilty until proven innocent*
- Does this make a difference in practice? Not really. Policing chemicals and their effects and distribution takes a lot of manpower and hence money.
- Also, no-one has yet found a mechanism to assign a monetary value to life, health or quality of life.
- But attempts have been made to assign monetary value to disease:
  - US NRC report in 2000: the monetary cost of chemically induced neurobehavioural disorders were estimated at $9.2 billion p.a. based on 1997 costs (Landrigan P, 2002).
  - From Trasande L, Andrology, 2016: 'We conclude that endocrine disrupting chemical exposures in the EU are likely to contribute substantially to disease and dysfunction across the life course with annual costs amounting to €163 billion (1.28% of EU Gross Domestic Product).

OTHER PROBLEMS

- 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.
- Brexit: Unless we enshrine current and future EU environmental legislation into UK law, we will have no legal protection from toxins.
- The Health and Environment Alliance (HEAL) http://www.env-health.org/policies/environment-health/ newsletter on environmental health issues in Europe.
- HEAL is currently agitating that the European Parliament not yet signed up to the Minamata convention to phase out dental amalgam.
- But there are complaints even about Europe….

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

The European Court of Justice has ruled that the European Commission has not been quick enough in identifying and banning potentially harmful '*endocrine disruptor*' chemicals.

- Sweden brought case against the European Commission in 2014, complaining that their efforts had come to a "complete standstill" and that illnesses caused by EDCs could be costing hundreds of millions of euros every year.
- There are now complaints that the previously strict level of proof is being watered down in the June 2016 EDC bill.
- There is also concern that the Transatlantic Trade and Investment Partnership (TTIP) will force the EU to adopt US legislation on toxic chemicals

IN FACT WE ARE LAB RATS IN A MASSIVE TOXOLOGICAL CLINICAL TRIAL

- In a drug clinical trial, each subject must give written, informed consent. Even when a licensed drug is prescribed, the patient still has a choice whether or not to take the prescription to a chemist and then to take the drug.

- But we are usually unaware of eating, drinking, touching or inhaling toxic chemicals.

- The long term results for this clinical trial are unknown but there have been many casualties along the way.

BECOME THE CATALYST FOR CHANGE?

- 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: 'Surely they wouldn't let us be poisoned?' **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 need to shift the burden of proof. Instead of requiring government and the public to demonstrate a chemical's harm, we shoud require independent tests for safety. This is only what should happen anyway under the Precautionary Principal.
- We need to promote the public's 'right-to-know' by campaigning for increased transparency about product ingredients through labelling requirements.
- Finally, policy change will only come about through 'people power', so become activists yourselves and encourage your patients to become activists as well.

A new scientific truth does not triumph by convincing its opponents but rather because its opponents die and a new generation grows up that is familiar with it.’

Max Plank, German physicist, 1949 Nobel prize winner.