Preconception counseling

Children's Health and the Environment

CHEST Training Package for the Health Sector

In the following slides and notes environmental hazards are discussed and advices are given to people that plan a pregnancy.

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Definition of preconception counseling

- Systemic evaluation and identification of risk factors
- Additional screening and consultation
- Adequate information and advice
- Medical intervention

AIMS

- To detect and possibly eliminate environmental risk factors associated with poor pregnancy outcome
- To reduce perinatal mortality and infant mortality and morbidity

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Important environmental hazards based on "voluntary" exposure not addressed here

- Alcohol
- Smoking
- Second-hand smoke
- Drugs, including hard drugs and soft drugs
- Medication, such as anticonvulsant medication, except for diethylstilboestrol (DES)

Not addressed in this module are the danger of **alcohol consumption** before and during pregnancy and lactation. Well known is the reduced fertility in both sexes and the chance that the baby develops the fetal alcohol syndrome, a severe form of mental retardation in combination with malformations like the typical face: (small palpebral fissures,long smooth philtrum with a thin and smooth vermillion border, maxillary hypoplasia, short nose and hirsutism) and intra-uterine growth retardation (IUGR). Neither the exposure to **smoking or second hand smoke**, with the reduced fertility, the intra-uterine growth retardation and the increase in miscarriages and prematurity. Both are important examples of environmental hazards in pregnancy as are **drugs** like heroin (IUGR), cocaine (intracranial bleeding). Separate modules address these problems.

Therapeutics like anticonvulsant medication or other medicaments are also not addressed in this module.

Preconception counseling: environmental exposure

History taking

- **Social background: what are the parents' occupations?**
- **Environmental hazards**
- **Medication: antiepileptic drugs, insulin, steroids, diethylstilboestrol (DES)**
- **Chronic illnesses: type 1 diabetes, type 2 diabetes, epilepsy, inflammatory bowel disease, systemic lupus erythematosus, asthma, hypo- or hyperthyroidism, acne treatment**

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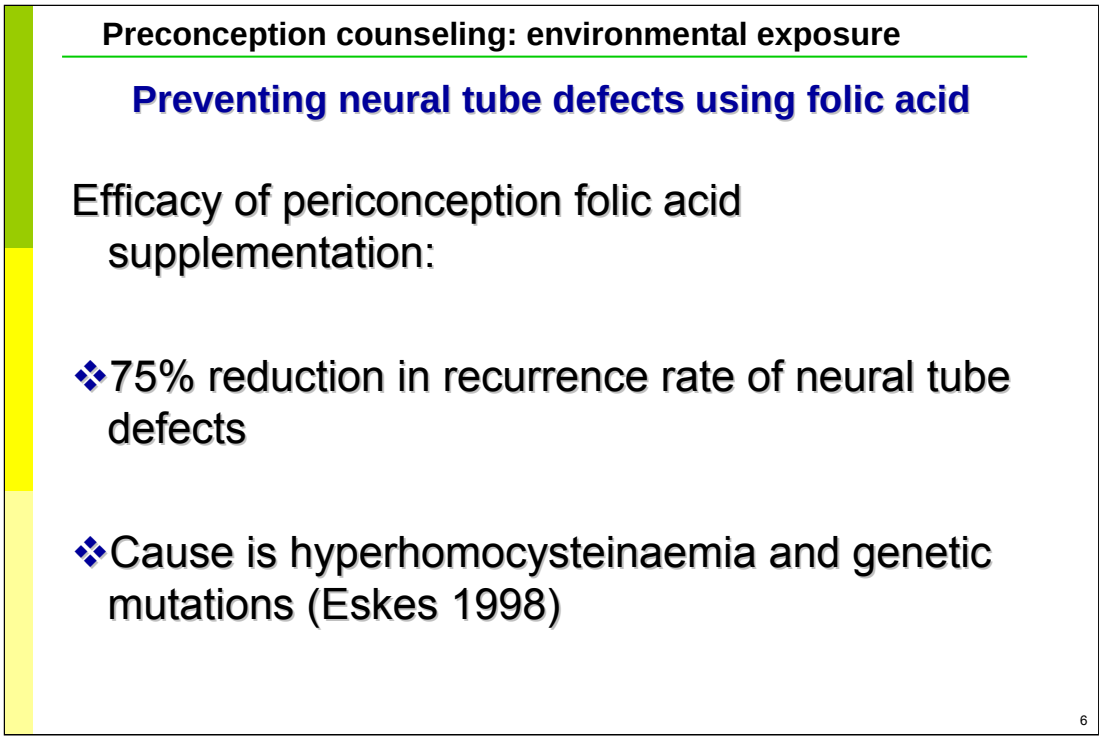
Ref: Cefalo RC and MK Moos: preconceptional health care: a practical guide, Mosby St.Louis 1995

When preconception counselling is given aspects like medication and chronic illnesses must be addressed. For that information we refer to the book of Cefalo and Moos mentioned above.



References

1. Double-blind placebo randomized international study of the vitamin study group of the Medical Research Council (UK). *Lancet* 1991;2:131–137.

2. Eskes TKAB. Open or closed? A world of difference: a history of homocysteine research. *Nutr Rev* 1998;56:236–244.

There are indications that folic acid prevents other congenital malformations: heart defects, cleft lip and palate, limbs, urinary tract malformations. Between 2100 and 5200 congenital malformations per day could be prevented worldwide with the use of a multivitamin containing folic acid.

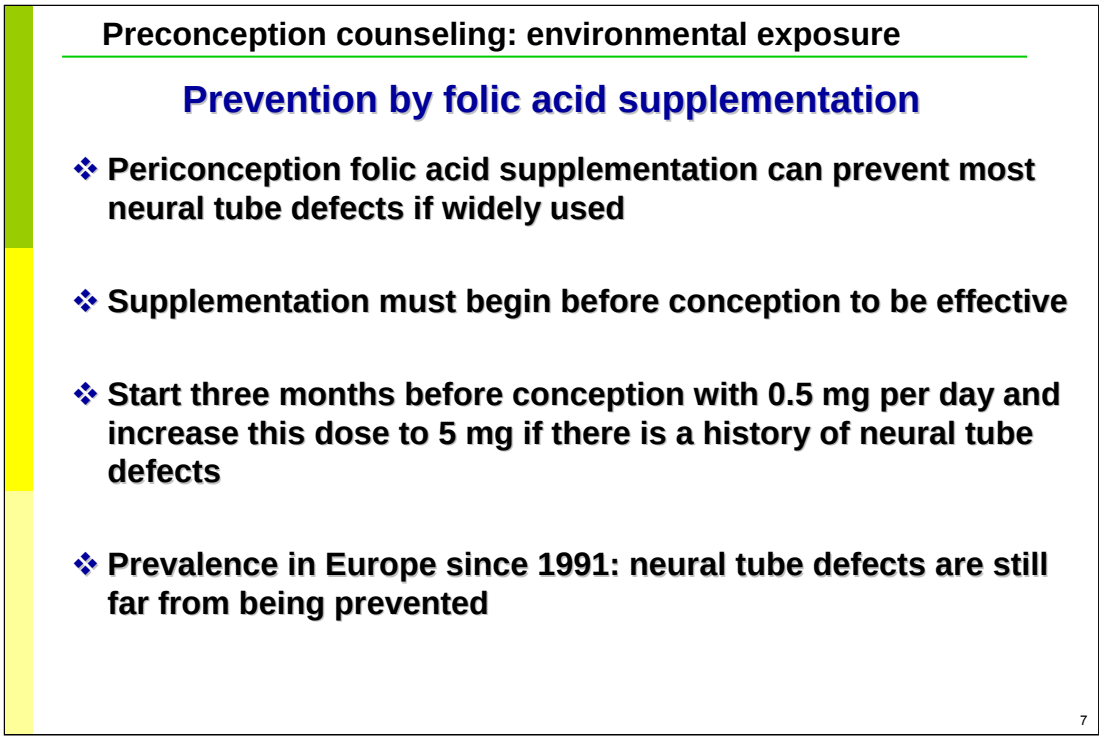
References

Botto LD et al. Vitamin supplements and the risk for congenital anomalies other than neural tube defects. *Am J Med Genet C Semin Med Genet* 2004;125:12–21.

Czeizel AE et al. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;327;1832–1835.

The odds ratios are very hopeful, respectively 0.53 (95% CI 0.35–0.70)and 0,80 (95% CI 0.69–0.93). Even Down syndrome might be prevented.

The question of folic acid alone or in a multivitamin was discussed: so far in the Netherlands, extra **vitamin B_{12}** is recommended to prevent a shortage overshadowed by folic acid together with **folic acid**. A total of 48% of all women planning a pregnancy in the Netherlands have too little **vitamin A in the diet.** So there are strong indications to use these three. No evidence is available for other vitamins or minerals or antioxidants.**Trials to study the others are needed.**



About 80% of neural tube defects can be prevented by supplementation with folic acid: 500 µg a day. However, programmes to recommend this supplementation are still not effective enough.

Ref: Busby A. et al: Preventing neural tube defects in Europe: population based study. BMJ 2005;330:574-5

Fortification of staple foods with folic acid as is done in the US, Canada, Chile and South Africa is highly recommended for Europe as well. However there is a report of preliminary findings that the use of 5 mg/day folic acid as a prevention might increase the risk of breast cancer.

Ref: Botto LD et al. International retrospective cohort study of neural tube defects in relation to folic acid recommendations:are the recommendations working? BMJ doi 10.1136/bmj.38336.664352.82

Honein MA et al. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. JAMA,285;2981-6 (2001).

Charles D et al. BMJ 2004;329:1375-76

Folic acid supplementation is recommended, because the usual daily food doesn't provide enough folic acid (only 200 µg per day).

There are indications that folic acid prevent also **other congenital malformations: heart defects, cleft lip and – palate, limbs, urinary tract malformations, anomalies of great arteries and veins**. Between 2100-5200 congenital malformations a day could be prevented worldwide with the use of a multivitamin containing folic acid.

Ref: Botto LD et al. Vitamin supplements and the risk for congenital anomalies other than neural tube defects.Am.J.Mol.Genet.2004:125 C:12-21

Czeizel AE et al. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. NEJM 327;1832-5 (1992) This is recent information in a Dutch pharmaceutical bulletin of the government about folic acid based on a Hungarian and a case-control study of the US Centers for Disease Control and Prevention, see above. The OR's are very hopeful, respectively 0.53 (95% CI 0.35-0.70) and 0.80 (95% CI 0.69-0.93). Even Down syndrome might be prevented.

Susceptible periods of reproductive toxicity

❖ Preconception

- Directly affecting the maternal or paternal reproductive organs (such as ionizing radiation)
- Stored or accumulated in the mother's body and later mobilized during pregnancy to affect the developing fetus and the offspring (such as polychlorinated biphenyls (PCBs))

❖ Embryonic and fetal period

- Particularly susceptible due to rapid cell growth
- The placenta acts as a barrier (in some cases)
- Many toxic agents can cross the placenta (such as second-hand smoke, carbon monoxide, lead, arsenic and lipophilic compounds such as polycyclic aromatic hydrocarbons)
- Physical agents reach the fetus independently of the placenta (such as ionizing radiation, electromagnetic fields, heat and noise)

PCBs: Poly-Chlorinated Biphenyl's

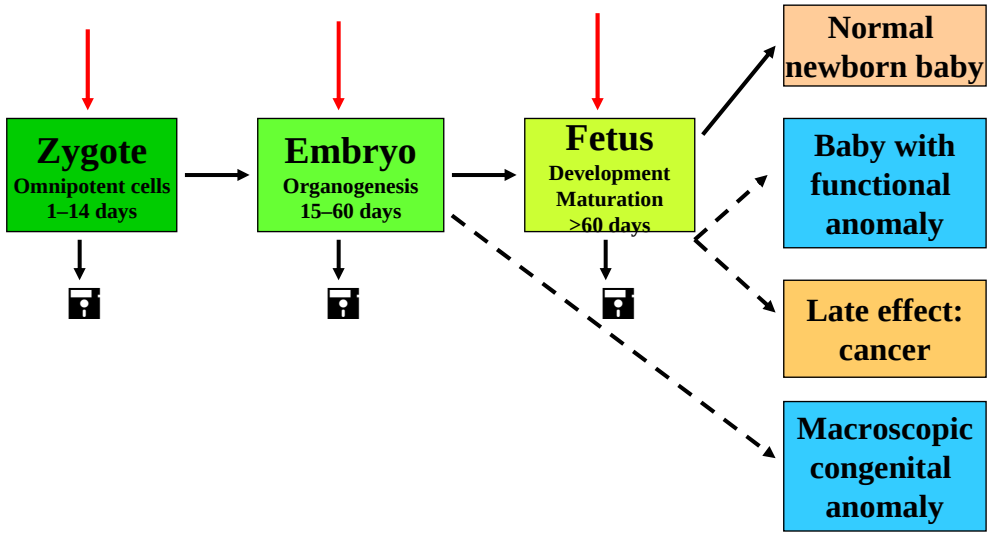
ETS: Environmental Tobacco Smoke.

PAH's :Polycyclic Aromatic Hydrocarbons

CO:Carbon-monoxide.

Preconception counseling: environmental exposure

Various stages of pregnancy and effects of toxic compounds



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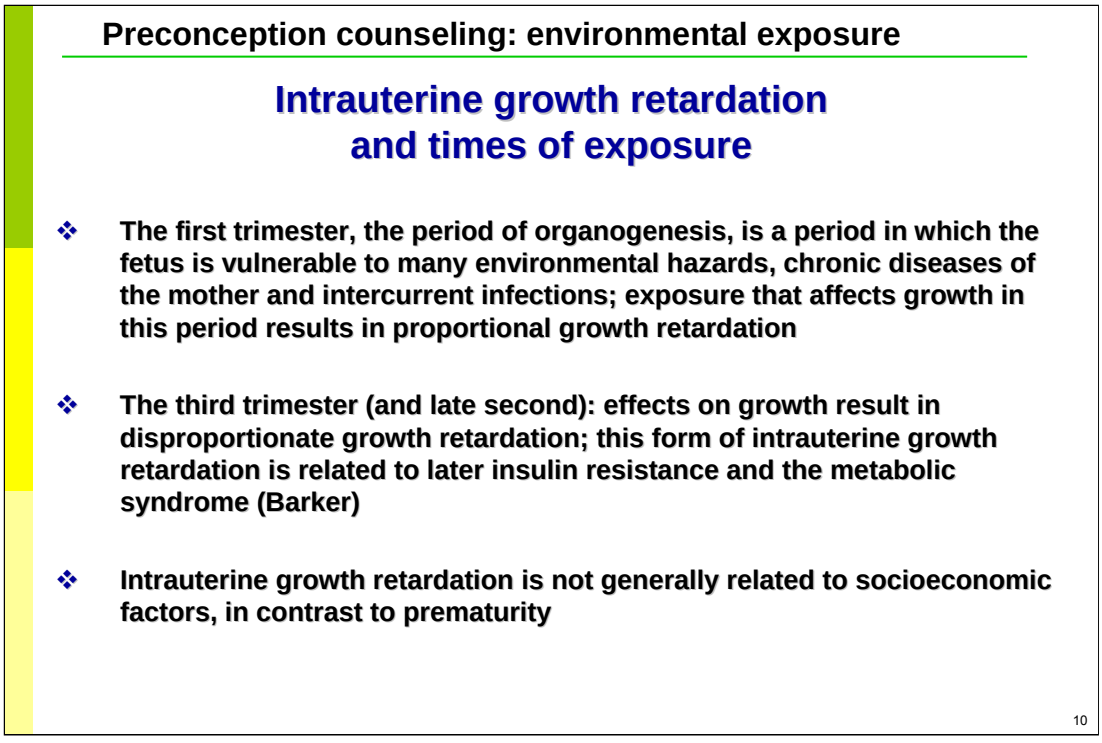
Timing of the environmental attack is crucial from the point of view of the pregnancy's outcome:

If it hits the zygote in the first two weeks of pregnancy, it may result either in an immediate termination of pregnancy or the zygote develops further to an embryo.

If an environmental factor attacks the embryo, it may result either in spontaneous abortion, or may develop into a foetus with some kind of macroscopic congenital anomaly, depending on the phases of organogenesis or develop further to a foetus with functional disturbances or into a healthy foetus.

If the foetus is hit by an environmental attack, it can also terminate the pregnancy (spontaneous abortion or stillbirth) or initiate some genotoxic changes, leading to cancer development later in life, or born either healthy or with some functional anomalies.



There is a misunderstanding about IUGR and effects lateron, because timing is not taken into account. Barker's hypothesis: fetal programming and adult diseases, is related to intra-uterine growth retardation late in the second and in the third trimester, resulting in a dysproportionate growth retardation. Abnormal glucose intolerance tests are found in the cohort of children exposed to the Dutch Hungerwinter in their last three month of pregnancy. Effects of food deprivation and later insulin resistance are also found by Hofman in preterm babies(25-32 weeks) both AGA and SGA. He postulates that this period of pregnancy , late second and early third trimester is a critical window for later insulin resistance and possible cardiovascular disease. *Ref: Hofman et al : New Zealand "Premature birth and Later Insulin Resistance" NEJM 2004 vol 351 page 2179-2186.*

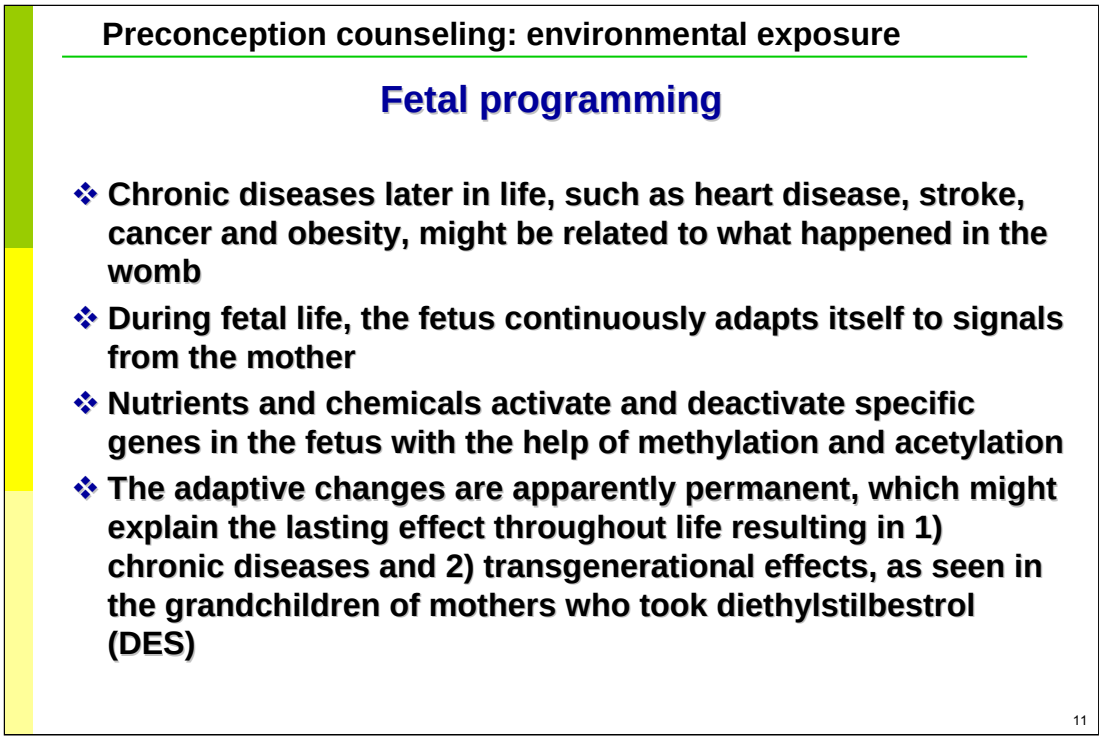
Deprivation of food (mainly a protein deficiency in the first three months after conception) studied in the Dutch Hunger Winter, results in more obesity at the age of 19 as described by Zena Stein.

Ref. Stein Z.A., Susser M.W., Saenger G., Marolla F. Famine and human development: the Dutch Hungerwinter of 1944-45.1975.

There was also an increase in anencephaly, neural tube defects and Schizophrenia.

Ref: Susser E.S., Lin S.P. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944-1945. Arch Gen Psychiatry 49:983-988 (1992).

Chemicals and other toxic influences early in pregnancy may affect the genes (abnormal methylation of DNA) of the fetus causing a proportionate IUGR. This form of IUGR result in chronic diseases later in life like cancer or neurodevelopmental impairments or auto-immune diseases or have transgenerational effects as is found in the offspring of mothers on anticonvulsant drugs. Or proven in the F2 of DES mothers.(see DES, slides 17 and 18) However effects on later development of diabetes, and cardiovascular diseases is never proven in this group of growth retarded (caused by chemicals) babies. The extrapolation of Barker's findings to all forms of IUGR is more related to Sigmund Freud in disguise. In the seventies it were our fathers and mothers and now it is intra-uterine life. See also slide 9 on fetal programming.



In the studies of folic acid and homocystein, epigenetic changes are discussed.

Eskes TKAB: open or closed. Nutrition Reviews 1998;56:236-244

Genetic imprinting by abnormal methylation or acetylation of DNA might be the reason for abnormal fetal programming.This may not be the only reason of later problems originating in fetal life. Also anatomical changes can play a role, like less nefrons in the kidney or a smaller pancreas.

Barker found indications of fetal programming in the cohort of children exposed to food deprivation during the Dutch Hungerwinter in their last (third) trimester. Abnormal glucose tolerance was noted in the group when they were 50 years old exposed to food deprivation in the last three months of pregnancy. That a period of food deprivation during the last trimester of pregnancy or shortly after birth, as in premature babies, results in insulin resistance is demonstrated by Hofman et al.

Hofman et al. "Premature birth and Later Insulin Resistance" NEJM 2004 vol 351 page 2179-2186.

Roseboom TJ, van der Meulen JH, Ravelli AC, Osmond C, Barker DJ, Bleker OP. Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. Mol Cell Endocrinol 185:93-8 (2001).

Another aspect of fetal programming is **Obesity.** In the Dutch Hungerwinter studies Zena Stein found an increase in obese conscripts conceived during the last three months of the Hungerwinter. The hypothesis is that the fetus is programmed for an environment poor in food. When however there is an abundance regulatory systems fail and the person becomes too fat. At the age of fifty again obesity was found.

Ref: Ravelli A.C.J., van der Meulen JH, Osmond C, Barker D.J.P., Bleker O.P. Obesity after prenatal exposure to famine in men and women at the age of 50. International Journal of Obesity 22:S18 (1998).

Ref:Stein Z.A., Susser M.W., Saenger G., Marolla F. Famine and human development: the Dutch Hungerwinter of 1944-45

Environmental hazards 1

- Persistent bioaccumulating toxicants
- Pesticides
- Diethylstilboestrol (DES)
- Mercury
- Lead
- Volatile organic compounds
- Radiation

In these two slides the different compounds or situations are discussed of environmental hazards.

VOC's :Volatile Organic Compounds: The level of VOC's is sometimes used as a measure of air pollution. It are mainly solvents for paint and cleaning products.

Environmental hazards 2

- Household chemical products
- Cosmetics
- Indoor swimming pools
- Drinking-water
- Noise
- Waste landfill sites

Preconception counseling: environmental exposure

Persistent bioaccumulating toxicants 1

- Polychlorinated biphenyls (PCBs) and dioxins
- Polybrominated biphenyls

Viktor Yushchenko, acute dioxin poisoning in 2004

Before **After**

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Developmental effects of background levels as in Europe are described for PCBs and dioxins on brain development (lower IQ and abnormal behaviour),on thyroid hormone status(transient increase in thyroid stimulating hormone:TSH), on bone marrow(less trombocytes) and on lung function (decreased FeV1). The effect of PCBs might be related to the induction of auto-antibodies in the mother against her thyroid, interfering with the thyroid supply in the first six months of pregnancy, PCBs can also directly cause a decrease in T3 levels in the mothers during pregnancy as demonstrated in Canada.

Ref:Takser L., mergler D., Baldwin M., de Grosbois S., Smargiassi A., Lafond J. Thyroid Hormones in Pregnancy in Relation to Environmental Exposure to Organochlorine Compounds and Mercury. Environ Health Perspect 113:1039-1045 (2005).

Ref: Langer P., Tajtakova M., Kocan A., Petrik J., Koska J., Ksinantova L., Radikova Z., Imrich R., Shishiba Y., Trnovec T., Sebekova E.Klimes I. Preliminary fundamental aspects on the thyroid volume and function in the population of long term heavily polluted area in East Slovakia.(PCBRISK EC No.QLK-CT-2000-00488). Organohalogen Compounds 66:3532-3538 (2004).

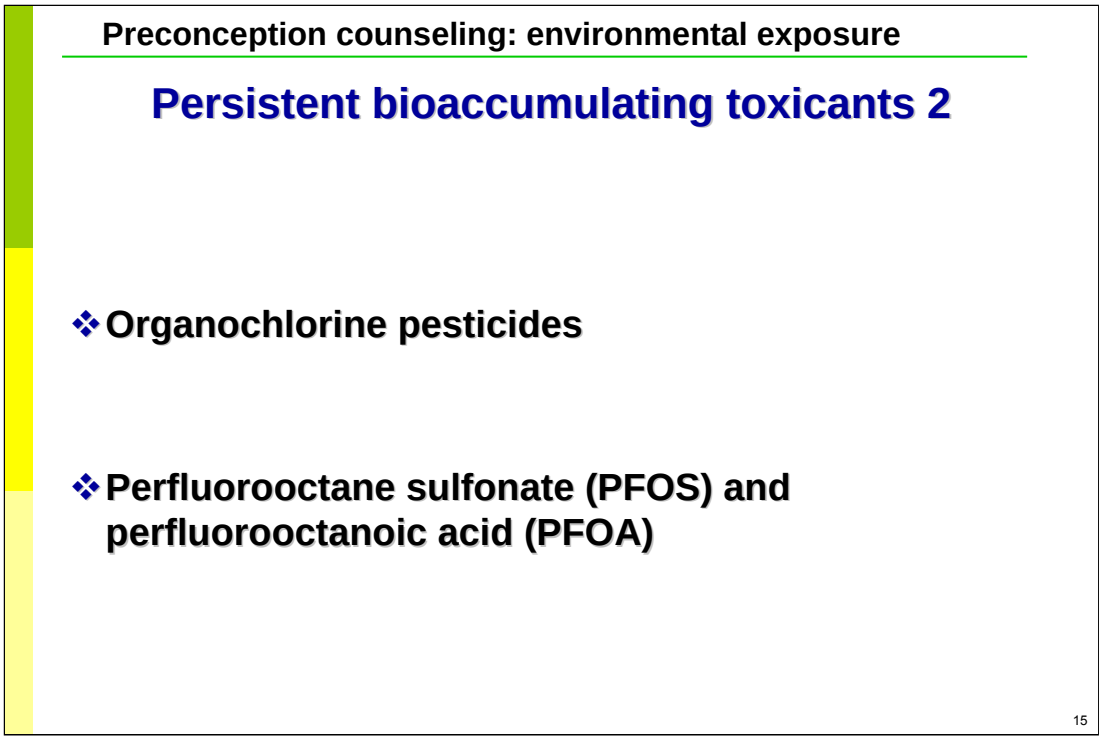
Ref:ten Tusscher G.W., Koppe J.G. Perinatal dioxin exposure and later effects-a review. Chemosphere 54:1329-1336 (2004).

Boersma ER, Lanting CI. Environmental exposure to polychlorinated biphenyls (PCBs) and dioxins. Consequences for longterm neurological and cognitive development of the child lactation. Advances in Experimental Medicine & Biology 478:271-87 (2000).

PCBs are forbidden to produce since 1977, but are still widespread present in the environment. Dioxin levels have decreased with 50 % during the last twenty years (1980-2000) in Western Europe because of redevelopment of incinerators, but **continuous control of levels** is warranted, since the levels in breastmilk are no longer decreasing.

PBBs or brominated flame retardants are newly produced and their levels in breastmilk are increasing. In high concentration they are known to induce an early puberty in girls, accidentally exposed. *REF:Blanck H.M.et al: Age at menarche and Tanner Stage in Girls Exposed In Utero and Postnatally to Polybrominated Biphenyl. Epidemiology 11nr6:641-647 (2000).*

Brominated flame retardants can also interfere with thyroid hormone metabolism.



Levels of DDE the persistent metabolite of DDT, are related to reduced mental and psychomotor development at age 13 months in a study in Spain heavily polluted by organochlorines.

Ref:Ribas-Fito et al: Breastfeeding, exposure to organochlorine compounds, and neurodevelopment in infants. Pediatrics:2003;111e580-e585

DDT or its metabolite is probably also involved in an increase in hypospadias and polythelia.

PFOS and PFOA are synthetic chemicals used in the production of advanced plastics including Teflon for which there is some evidence that it may be linked to birth defects and other health hazards. Teflon was invented in the US in the 1930s and first marketed by Dupont as Teflon in 1946. It is famous as the non-stick chemical on cookware, but is also used as coating for carpets and clothes. There are considerable scientific uncertainties of the substance. And there is some evidence that it might be linked to birth defects. In rat studies during pregnancy effects on the thyroid are described and growth retardation in the offspring. This was not found in a human study in Japan in 15 mother-baby pairs. There was a good correlation in levels of PFOS in maternal and cord blood.

Ref:Inoue et al: Perfluorooctane Sulfonate (PFOS) and related Perfluorinated Compounds in Human Maternal and Cord Blood Sample's: Assessment of PFOS Exposure in a Susceptible Population during Pregnancy.Env. Health Perspectives vol 112, nr 11:1204-1207

Preconception counseling: environmental exposure

Secondary prevention of the effects of persistent bioaccumulating toxicants

- **Control the thyroid hormone status of the woman who wants to become pregnant: all persistent bioaccumulating toxicants can interfere with thyroid hormone status and may promote the development of autoantibodies against the thyroid**
- **Recommend breastfeeding and loving care to mitigate and cure the effects of persistent bioaccumulating toxicants**
- **Avoid second-hand smoke, stop smoking, no alcohol**
- **Use a multivitamin with carotene (vitamin A), vitamin B_{12} and folic acid and eat food high in antioxidants such as carrots, beetroots, grapes, broccoli, olive oil, tea and berries**

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The thyroid status of the mother in early pregnancy is crucial for her baby. Low free Thyroxin in the mother lowers the baby's IQ.

Ref: Pop et al: Clin. Endocrin. 50:149-55 (1999)

Pop et al:J.Clin.Endocrin. And Met.80 3561-66 (1995)

Haddow etal: NEJM 341 546-602

There are many environmental synthetic chemicals that have effects on Thyroid function: 42 pesticides, 29 industrial chemicals, 21 additional chemicals as published by Francis Brucker.

Ref:Brucker-Davis F. Effects of environmental synthetic chemicals on thyroid function. Thyroid 8:827-856 (1998).

A multivitamin containing folic acid, vitamin B 12 and vitamin A is recommended, together with food high in anti-oxidants, for instance: carrots, beats, grapes, broccoli, olive oil, tea, berries.

An effect of the anti-oxidants Vitamin C and E is not proven. Small amounts may do some good, but Vitamin E in higher doses might have negative effects.

Preconception counseling: environmental exposure

Pesticides 1
Insecticides

Four categories of insecticides most commonly used in Europe currently or in the past

- **Organochlorines such as DDT** (now banned, persistent organic pollutant, but might be present on imported food)
- **Organophosphates such as malathion, chlorpyrifos and diazinon** (inhibit acetylcholinesterase)
- **Carbamates such as aldicarb and maneb** (inhibit acetylcholinesterase)
- **Pyrethroids such as permethrin and fenvalerate** (used for the treatment of scabies and lice)

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Organochlorine insecticides like DDT, aldrin, chlordane, dieldrin, endrin, heptachlor,mirex and toxaphene belong to the group of persistent organic pollutants (POPs), are very longlasting in nature and are polluting food. Prenatal exposure to p,p'DDE, a metabolite of DDT is related to a delay in mental and psychomotor development in a Spanish study.

Ref: Ribas-Fito et al: Breastfeeding, Exposure to Organochlorine Compounds, and neurodevelopment in Infants. Pediatrics 111, e580-e585 (2003)

Organophosphates are known to cause a hypercholinergic syndrome in acute toxicity similar to wartime nerve gases.

Chlorpyrifos is related with IUGR (intra-uterine growth retardation)

Ref: *Perera F.P. et al. Effects of transplacental Exposure to Environmental Pollutants on Birth Outcomes in a Multiethnic Population. Environ Health Perspect 111:201-205 (2003).*

and with smaller head circumference when the mother's paraoxonase activity is low; this enzyme activity is necessary to metabolize chlorpyrifos. In general the paraoxonase activity in all infants is low and activated later in life.

Ref:Berkowitz G.S. In utero Pesticide Exposure, Maternal Paraoxonase Activity, and Head Circumference. Environ Health Perspect 112:388-391 (2004).

Both **carbamates and pyrethroids** are known to disrupt thyroid hormone status.

Pesticides 2
Effects on reproduction

- **Reproduction is affected in farming households and after occupational exposure: decreased fecundity, infertility, poor sperm quality, an abnormal sex ratio (more girls born than boys) and cancer (Ewing sarcoma)**
- **Women in agricultural occupations have an increased risk of spontaneous abortion**
- **Intrauterine growth retardation may be associated with exposure to pyrethroids**
- **More stillbirths were observed among women who lived near an application site of carbamates during the second trimester of pregnancy**

During occupational exposure negative reproductive effects of pesticides are described in both man and women. Stillbirths, more spontaneous abortions, poor sperm quality,increased congenital malformations and Ewing sarcoma.

Ref: Bell E.M., Hertz-Picciotto, I., Beaumont J.J. Case-control analysis of agricultural pesticide applicators near maternal residence and selected causes of death. Am J Epidemiol 154 (8):702-710 (2001).and Hanke W., Romitti P., Fuortes L., Sobala W., Mikulski M. The use of pesticides in Polish rural population and its effect on birth weight. Int Arch Occup Environ Health 76:614-620 (2003).

Preconception counseling: environmental exposure

Pesticides 3
What should be done?

- **When future parents of reproductive age are employed as farmers or in other agricultural occupations where chemicals are being used, precautions must be taken such as extra protection with clothes and extra showering**
- **In a general household, Philip Landrigan (photograph) recommends prudent avoidance before, during and after pregnancy; organically grown vegetables can be recommended, also because they contain more healthy nutrients**

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In a profile of Philip Landrigan, the children's health crusader, his work on pesticides is praised. "Children are uniquely susceptible to the effects of pesticides". And when asked what he did himself his answer is that he raised his own three children using ***"prudent avoidance".***

Ref: Lancet vol 365;1301(2005)

Most pesticides now in use in Europe are "transient", they are quickly metabolized and don't accumulate and avoid them in pregnancy is easy. This in contrary to the PBT's, see above!

Organic food can be recommended and has the advantage of containing more minerals due to a slower growth process. But one must be cautious. For instance because of certain lifestyle rules for chickens the level of dioxins are allowed to be higher.

A major change in regulatory approaches to pesticides occurred when the US Congress passed the Food Quality protection Act in 1996. Residue levels for food must be set that protect the most vulnerable (fetus and children) of the population. In the US because of this law **chlorpyrifos and diazinon** , previously widely used , are voluntarily taken from the market.

Preconception counseling: environmental exposure

Diethylstilboestrol (DES): example of a xeno-oestrogen 1

- **DES was used from 1950 to 1970 for preventing miscarriages and preterm delivery; it increases the level of progesterone in the placenta**
- **Adenosis and adenocarcinoma of the vagina and congenital malformations of the uterus in the DES daughters (the first generation: F1). The incidence of adenocarcinoma of the vagina or cervix is bimodal: at the end of puberty (age 20 years) or after the menopause (age 70 years)**
- **Increase in the risk of preterm delivery, related to an abnormally short cervix, a disturbed neuroendocrine axis (lack of progesterone) or another cause**
- **Increase in the risk of hypospadias in the male F2 generation is a transgenerational effect of the grandmother through the mother on her son**
- **Increase in autoimmune diseases in F1 through immunotoxic effects**

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Besides the wellknown effects of DES on the development of an **adenocarcinoma** in the vagina or cervix and congenital malformations in the female genitalia also a transgenerational effect is described : hypospadias and prematurity in the grandchildren of exposed mothers. Prematurity might be explained by a persistent effect of DES on the neuro-endocrine axis of the F1 generation. DES is known to produce progesterone in the placenta. It is known that a shortness of progesterone is causing a preterm delivery and this might be based on a disturbed neuro-endocrine axis in the F1 generation as is demonstrated in animal experiments. .

Ref:Klip H.et al: Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. Lancet 359:1102-1107 (2002).and Gupta C.H et al: Decreased neonatal testosteron in plasma and brain with subsequent reproductive dysfunction of the offspring exposed to phenobarbital prenatally. Pediatric Research 14:467 (1980).

That progesterone is important for the prevention of prematurity is demonstrated in a clinical trial revealing the success of the use of progesterone. *Ref: Meis et al: Prevention of Recurrent Preterm Delivery by 17 Alpha-hydroxyprogesterone Caproate. NEJM 348:2379-85*

Preconception counseling: environmental exposure

Diethylstilboestrol (DES): example of a xeno-oestrogen 2

- **DES was also used as a growth-promoting hormone in cattle, sheep and poultry in the European Union until 1980**
- **Gynaecomasty is described in people consuming many chicken necks, the place where the hormone was injected**
- **The whole (meat-eating) population in Europe was exposed to low levels of DES until 1980 because it was used in livestock production**
- **It is not known whether this low-level exposure has caused any harm, because no studies were done**
- **DES for use in humans was banned in the 1970s based on the precautionary principle**

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How the **carcinogenicity of DES** in humans is caused is not completely understood, both local influences on the genes and hormonal effects or both are hypothesized. One can speculate that the trans-generational effect of hypospadias might be related to the shortness of progesterone in the mother, but this cannot be the explanation why in animal- experiments through both the female and the male F1 a carcinogenic effect is found in the offspring.

Transgenerational effects on both the ovum and the sperm resulting in tumours of the F2 generation are found in animal experiments.

Ref: J.L.Bernheim: The DES-syndrome In: Endocrine Disrupters. Eds.P.Nicolopoulou-Stamati, L.Hens,C.V.Howard. Environmental Science and technology Library. Vol18 Kluwer Academic publishers.(2001) ISBN)-7923-7056-2

Effects on **gender behaviour**, the boys more feminine and the girls more tomboys, severe depression and more anorexia nervosa are found in the DES cohorts. This might be based on disturbance in the neuroendocrine-immune system. This system is most sensitive during the perinatal period. This might explain the increased incidence in DES-daughters of anorexia nervosa, a primary hypothalamic disease probably based on an auto-immune process.

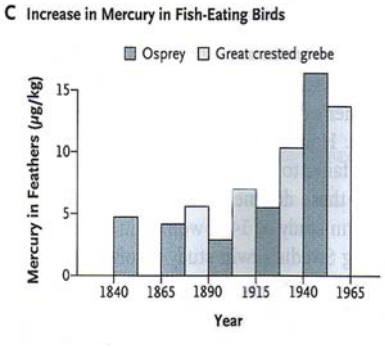
Ref:J.G.Vos.Immunotoxicity of hexachlorobenzene. In: Morris CR & Cabral JR. eds. Hexachlorobenzene:Proceedings of an international Symposium. Lyon:IARC Scientific Publications, pp 347-356

The problems in stock raising and the use of DES are well discussed in the article of J.L.Bernheim. See reference above.

Preconception counseling: environmental exposure

Mercury

- Mercury is released by several industries but also by volcanoes and by burning coal
- During the past 50 years, mercury levels in fish-eating birds have increased sharply because the fish have become more polluted with mercury due to industrialization



Clarkson et al. *N Engl J Med* 2003;349:1734. Reproduced with permission

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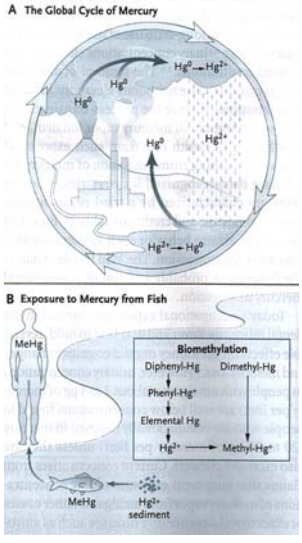
Preconception counseling: environmental exposure

The global cycle of mercury



Clarkson et al. *N Engl J Med* 2003;349:1734. Reproduced with permission

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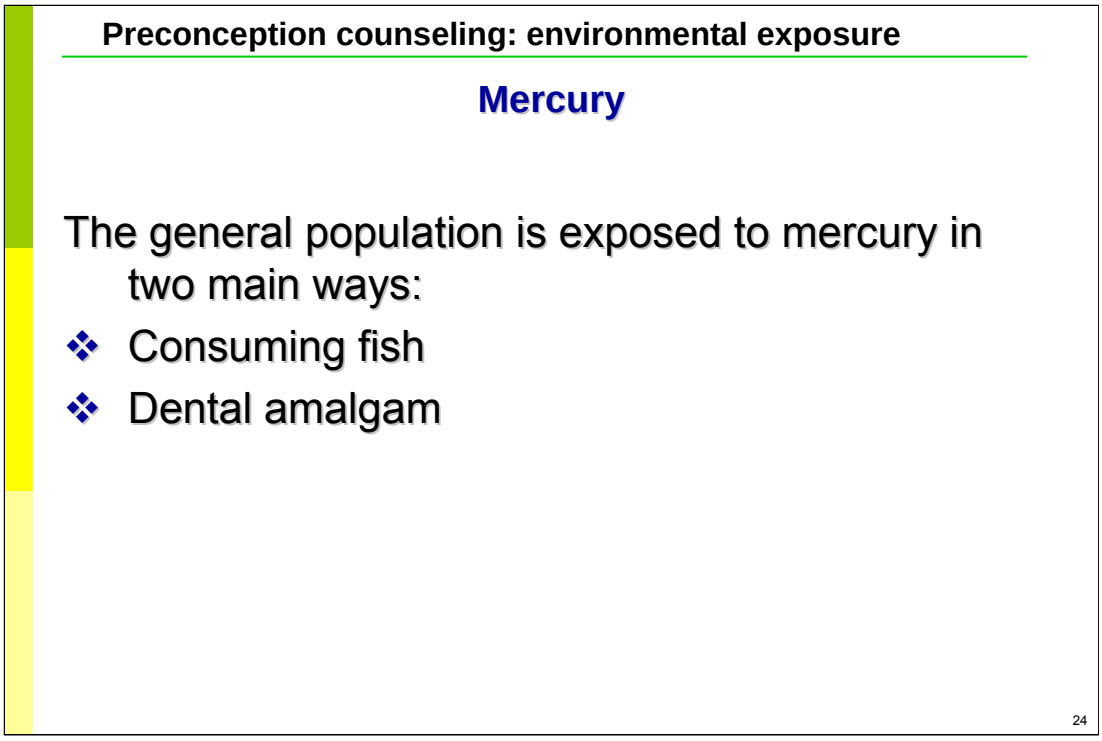
A.The global cycle of mercury starts in nature with mercury vapor Hg , a stable monatomic gas, from both soil and water and is emitted by volcanoes. Anthropogenic sources include emissions from coal-burning power stations and municipal incinerators. After approximately one year, mercury vapor is converted to a soluble form (Hg^2) and returned to the earth in rainwater. It may be converted back to the vapor form both in soil and in water by micro-organisms and reëmitted into the atmosphere. Thus mercury may circulate for long periods. Mercury attached to aquatic sediments is subject to microbial conversion to methyl mercury (MeHg), whereupon it enters the aquatic food chain. It reaches its highest concentrations in long-lived predatory fish, such as sharks.

B. In this panel the routes of transformation to methyl mercury are indicated as orginally suggested by Jernelöv.

Ref:A.Jernelöv Conversion of mercury compounds. In: Miller et al: Chemical fallout:current research on persistent pesticides. Springfield,Ill.:Charles C.Thomas, 1969:68-74



In Europe about 25 % of the mercury exposure is related to fish eating, 30 % comes from fruits and vegetables, 20 % from meat and 16 % from cereals. In Germany, where data are available, levels of exposure come close to the EPA recommended level of 0,1 µg/kg/d.

SCOOP Report of Experts participating in TASK 3.2.11, March 2004: Assessment of dietary exposure to Arsenic, Cadmium, Lead and mercury of the population of the EU member States.

Wellknown is the intoxication in Japan in the 1950's of pregnant mothers eating fish highly polluted with mercury. Levels are not known. The babies were spastic, growth retarded and severely mentally retarded: the Minamata Disease.

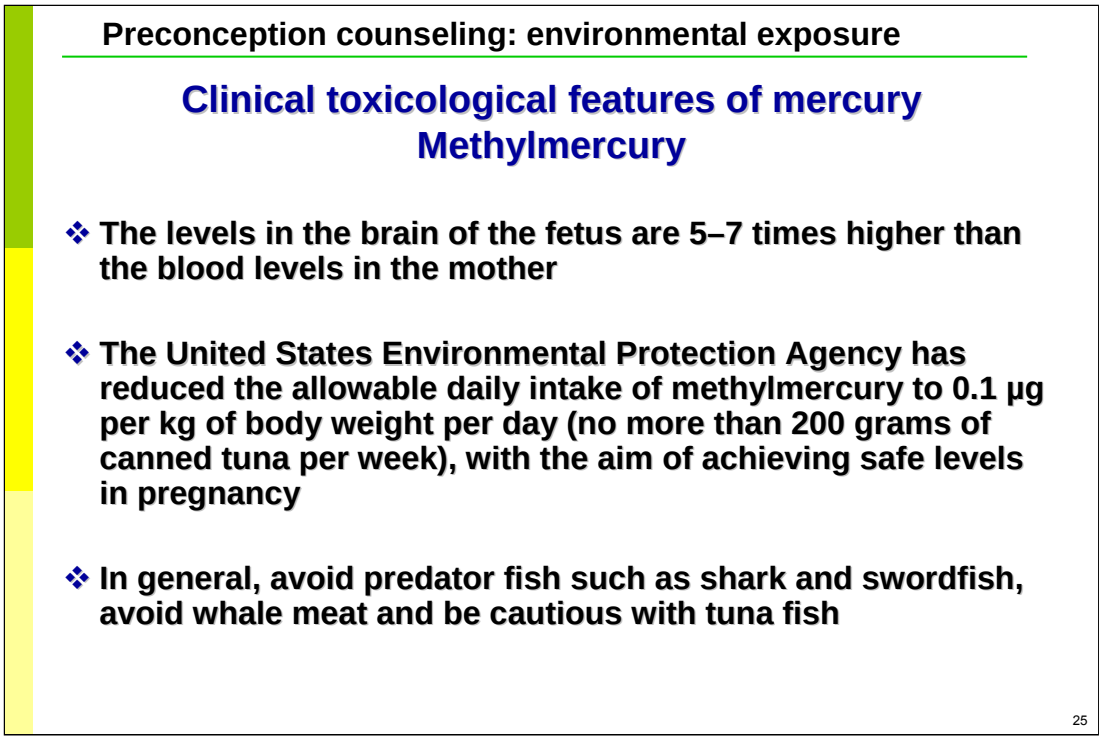
In Iraq in winter 1971-1972 grain seeds treated with a fungicide containing mercury to use as plant seed were used for making bread. Hundreds of children died. Research done revealed that at levels of 10 ppm peak mercury in hair of the mother growing during pregnancy might be associated with adverse fetal consequences.

Marsh et al: Fetal methyl-mercury poisoning. Relationship between concentration in single strands of maternal hair and child effects.Arch Neurol (1987\) 44 (10):1017-1022

This is in accordance with the dose in the Faroese study: 12 µg/g hair and the Seychelles study: 15.3 µg/g hair.

Grandjean P. Cognitive deficit in 7 year old children with prenatal exposure to methyl mercury born in 1986 and 1987. Neurotoxicology Teratology 19:417-428 (1997).

Myers G.J., Davidson P.W., Cox C., Cernichiari E., Shamlaye C.F., Palumbo D., Cernichiari E., Sloane-Reeves J., Wilding G.E., Kost J., Huang L-S., Clarkson T.W. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet 361:1686-1692 (2003).



Mercury poisoning in adults can result in Erethism. This is a bizarre behavior such as excessive shyness and even aggression. The proverb “As mad as a hatter” reminds of an occupational exposure in the production of hats, where mercury containing dye was used. Mercury vapor is a way of exposure. >1000 µg/m³ of air gives stomatitis, metallic taste, gingivitis, increased salivation.

> 500 µg/m³ of air gives proteïnuria (kidney),peripheral neuropathy, erethism (tremor). In the general population most exposure to **mercury vapor** is from **dental amalgams**. Brain, blood, and urinary concentrations correlate with the number of amalgam surfaces present. 10 amalgams surfaces will roughly double the background concentrations. Removal of dental amalgam fillings can temporarily raise the blood concentrations. Occupational exposure in dental offices can lead to mild reversible effects on the kidney or cognitive changes and memory loss.

Dental amalgams are supposed to be not toxic if excessive chewing is avoided. **It is not recommended to remove dental amalgam fillings shortly before or during pregnancy. Girls should not be treated with amalgam.**

Clarkson et al:The toxicology of mercury-current Exposure and Clinical Manifestations.2003.NEJM 349;18 pp1731-1737

In urban areas levels of mercury are 10 nanograms/m³ versus 2-4 nanograms/m³ in rural areas remote from industry, these levels are much lower than the exposure to dental amalgams.(WHO Air quality guidelines) In Europe a limit of 0.05 µg/m³ is proposed, a level rarely exceeded in the ambient air.

Blood concentration above 200µg/l gives paraesthesia, ataxia, visual and hearing loss.

Clinical toxicological features of mercury
Thiomersal in vaccines

- **Thiomersal was used as a preservative in vaccines**
- **It contains ethylmercury, resembling methylmercury**
- **The half-life of ethylmercury is much longer in the brain than in the blood, so the danger of accumulation in the baby's brain is real**
- **In most countries, single-dose vaccines without thiomersal are used**
- **Multiple-dose vaccines need a preservative such as thiomersal to prevent contamination**

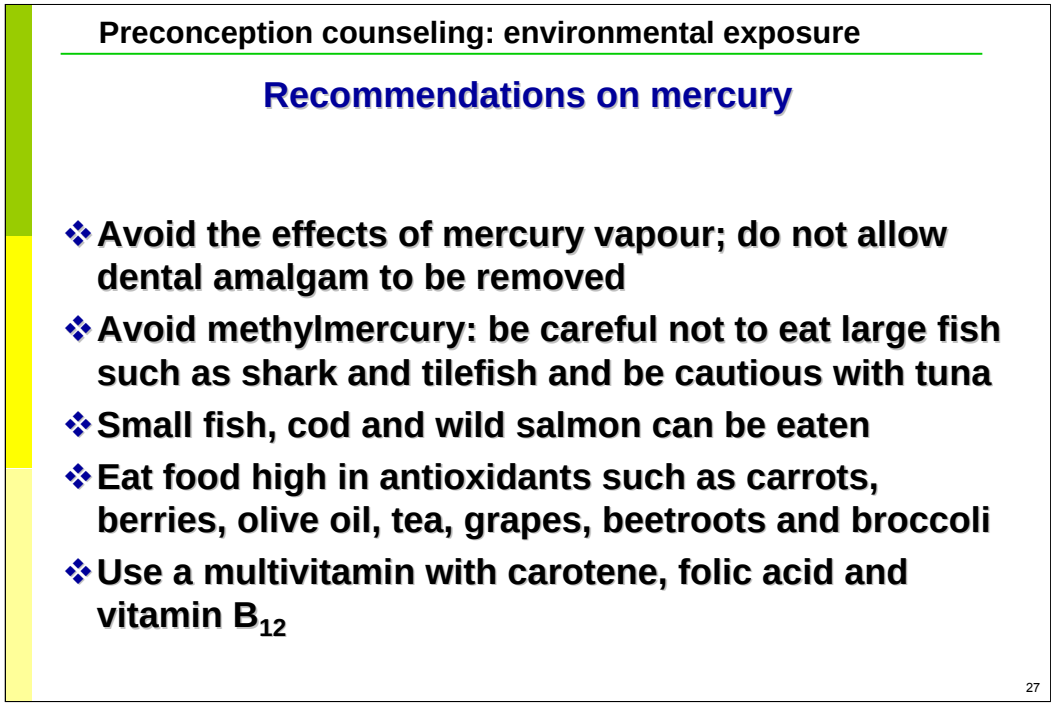
A recent publication demonstrates a longer half life in brain, 24 days versus blood 6.9 days of ethyl-mercury. This makes the use of mercury containing vaccines **dangerous because of accumulation in the baby's brain.** (Only when multiple dose vaccins are in use as in underdeveloped countries than the preservative is necessary and has a higher priority to prevent contamination with fungi or bacteria.)

In Europe thiomersal containing vaccines are contraindicated in pregnancy or in the baby.

Ref:Burbacher T.M. et al:

http://ehp.niehs.nih.gov/members/2005/7712/7712.pdf

In the US the mercury-laced preservative is phased out.



To lower the intake of methyl mercury by fish one has to start at least three months before conception. *Ref:Clarkson et al:The toxicology of mercury-current Exposure and Clinical Manifestations.NEJM 349;18 pp1731-1737*

In Europe the situation of fish might be different regionally. If there are special concerns about mercury resulting from the environmental history a level in blood of the woman might be controlled. However there is no therapy to remove methyl mercury from the body, besides chelation that can be of some help.

Clarkson T.W. 1987. Mercury. In: Trace elements in Human and Animal Nutrition. 5th Ed. Ed. Walter mertz Viol1. Pp 417-428 New York Academic Press.

The debate about mercury and fish is ongoing. Especially big fish like tuna fish are more polluted than small fish, because the tuna is higher up in the food chain.This is underlined by a study in Italy were subclinical neurobehavioural effects are found of the consumption of tuna fish, while the consumption of small fish had positive effects due to other (long chain fatty acids?) contents in this fish.

Ref Carta et al:Subclinical neurobehavioural abnormalities associated with low level of mercury exposure through fish consumption.Neurotoxicoly.24:617-623(2003) and Lucchini et al:Application of a latent variable model for a multocentered study on early effects due to mercury exposure.Neurotoxicology.24:605-16(2003).

Whale meat as consumed incidentally by the population of the Faroe-islands contains 2mg/kg Hg together with high levels of PCBs. It is plausible that the combination of these two pollutants cause the neurobehavioural abnormalities described in the offspring of Faroese mothers. *Ref: Grandjean et al:Cognitive deficits in 7-year old children with prenatal exposure to methyl-mercury born in 1986 and 1987.Neurotoxicology Teratology 20:417-28* In Europe the mean intake of MeHg from fish and seafood per week is about 30 µg, 25 % of the provisional tolerable weekly intake (PTWI) as recommended by the JECFA= 2.1µg/kg/week three times more than EPA recommends (0,1mg/kg/day).

In Portugal exposure by fish alone is already quite high. (0,2 µg /kg/day). And also in Germany. (0,13 µg/kg/day). In the UK: 0,04 µg/kg/day.

Levels in food must be reduced.

SCOOP Report of Experts participating in TASK 3.2.11, March 2004: Assessment of dietary exposure to Arsenic, Cadmium,Lead and mercury of the population of the EU member States.

Preconception counseling: environmental exposure

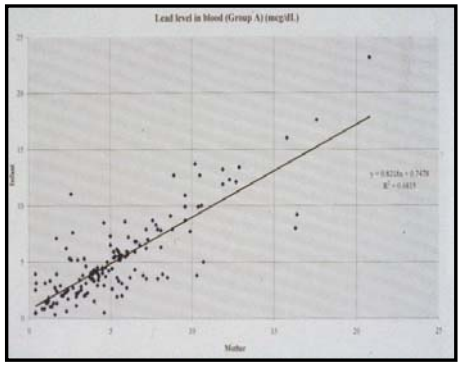
Lead

Lead Poisoning in Children

PAEDIATRIC ROUTES OF EXPOSURE (1)

Prenatal

- Lead crosses the placenta
- Fetal/placental ratio: 0.9
- Graph with data of maternal-newborn (cord blood) blood lead-level pairs



Adapted by Dr. Amitai from: Amitai, IMAJ (1999) 1: 250

14/05/05

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The following 5 slides are copied from the training module on Lead.This slide demonstrates the prenatal exposure to lead with data of mother-baby pairs. The prenatal exposure is determined by maternal body burden of lead. In general the newborn's blood levels are about 90 % of that of their mother's.

Ref: Amitai, Prenatal lead exposure in Israel: an international comparison, Israel medical Association Journal (1999) 1:250

During pregnancy lead can cause miscarriage, premature birth or low birth- weight. It interferes with neurodevelopment for instance in the hippocampus, disturbing memory and learning. Lead also affects the dopamine receptors and there is a clear association with Attention Deficit Hyperactivity Disorder. Lead accumulates in astrocytes and this intially protects neurons from toxic effects: but glial stored lead may thereafter continuously be released into the neurons.

Ref: Lidsky T.I. And Schneider J.S. Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain (2003); 126: 5-19

Gilbert M.E. and Lasley S.M. Longterm consequences of devlopmental exposure to lead or polychlorinated biphenyls: Synaptic transmission and plasticity in the rodent CNS. Environmental Toxicology and Pharmacology 2002; 12:105-17

In mineralizing tissues like bones and teeth the half-life is 25 years, in children 73 % and in adults 94 % of the total body burden is in these compartments. During pregnancy and lactation out of these compartments lead comes free, when Calcium is mobilized for the baby. A maternal diet poor in Calcium, Phosphate, Iron and Zinc can increase the mobilization during pregnancy and lactation.So prevention in pregnancy is to provide **extra Calcium and Iron.**

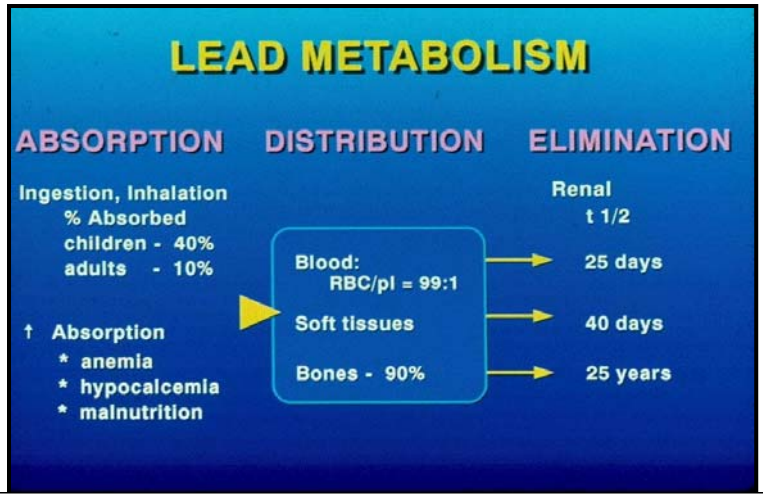
Sargent J.D.: The role of nutrition in the prevention of lead poisoning in children. Pediatr Ann 1994;23: 636-42

Lagerkvist B.J. et al: Increased blood lead and decreased Calcium levels during pregnancy: A prospective study of Swedish Women living near a smelter. Am. J. Public Health (1996) 86(9):1247-52

Preconception counseling: environmental exposure

Lead Poisoning in Children

TOXICOKINETICS



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In this slide the lead metabolism is demonstrated. Striking is the long half-life in bones and teeth versus soft tissues and blood.

Preconception counseling: environmental exposure

Lead: a wide spectrum of symptoms and signs

❖ **Central nervous system:**

- **Hyperactivity, restlessness**
- **Behavioural disturbances**
- **Learning disabilities (low scores in cognitive tests; scores decline by 0.25–0.50 points for each increase of 1 µg/dl in blood concentration)**
- **Blood concentration >70 µg/dl (rare): headache, lethargy, coma, seizures**

❖ **Peripheral nervous system**

- **Neuropathy (in adults!)**

❖ **Gastrointestinal**

- **Anorexia, vomiting, constipation, abdominal pain (colicky, >45 µg/dl)**

❖ **Blood**

- **Anaemia, basophilic stippling**

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<<READ SLIDE>>

This slide demonstrates problems that are partly originating from prenatal exposure and partly from exposure after birth on the developing brain:effects on the IQ and behaviour, more ADHD (Attention Deficit Hyperactivity Disorder), more aggression and delinquent behaviour.

For each 1 microgram/dL elevation in BLL (blood lead level), there is a reduction of about 0.25–0.5 point in cognitive score.

Abdominal pain occurs with BLL > 45 micrograms/dL: pains are colicky (porphyria like).

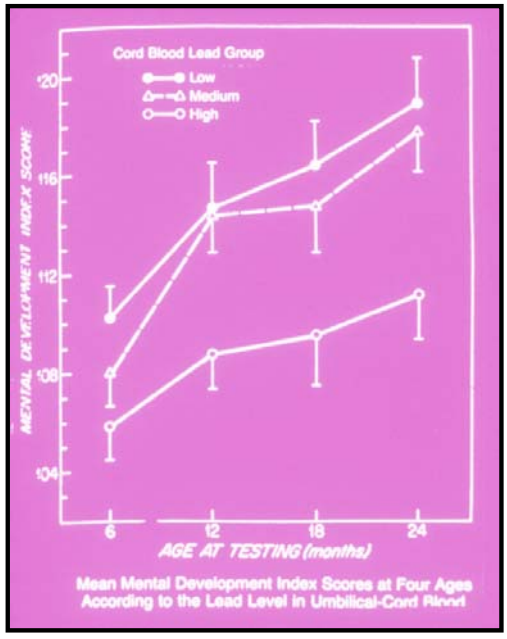
The neurotoxicity of lead might be related with the effect on haem synthesis.

Lead induces accumulation of protoporphyrin in chick dorsal root ganglions in tissue culture, especially in glial elements. Lead results in demyelination. δ- Amino Laevulinic Acid (δ –ALAD) increases due to inhibition of the dehydratase enzyme and this increase is associated with pharmacologic ,biochemical and behavioral effects. δ –ALA is known to concentrate in the hypothalamus and is neurotoxic.

Ref: Sergio Piomelli chapter " Lead Poisoning" in Hematology in infancy and childhood edited by David G.Nathan and Frank A.Oski 4th edition (1993) W.B.Saunders Company ISBN 0-7216-4603-472-494

Preconception counseling: environmental exposure

CORD BLOOD LEAD LEVEL AND MENTAL DEVELOPMENT INDEX



Bellinger D et al. *N Engl J Med* 1987;316:1037–1043.

When lead poisoning begins in the womb, the most critical system is the central nervous system of the fetus. **There is no safe lead level.**

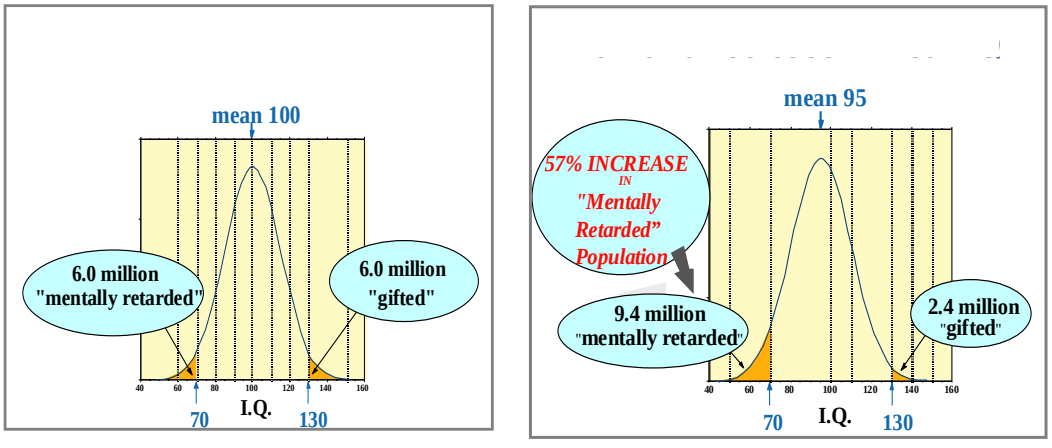
This article on the slide, published in 1987, was essential in increasing understanding of the potential for lead to cause damage at levels much lower than those that cause overt symptoms. It shows a high correlation between blood lead level in the umbilical cord and mental development index at 2 years of age.

Ref:

•Bellinger D et al. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development, N Engl J Med (1987) 316 (17):1037–1043.

In a prospective cohort study of 249 children from birth to two years of age, we assessed the relation between prenatal and postnatal lead exposure and early cognitive development. On the basis of lead levels in umbilical-cord blood, children were assigned to one of three prenatal-exposure groups: low (less than 3 micrograms per deciliter), medium (6 to 7 micrograms per deciliter), or high (greater than or equal to 10 micrograms per deciliter). Development was assessed semiannually, beginning at the age of six months, with use of the Mental Development Index of the Bayley Scales of Infant Development (mean +/- SD, 100 +/- 16). Capillary-blood samples obtained at the same times provided measures of postnatal lead exposure. At all ages, infants in the high-prenatal-exposure group scored lower than infants in the other two groups. The estimated difference between the overall performance of the low-exposure and high-exposure groups was 4.8 points (95 percent confidence interval, 2.3 to 7.3). Between the medium- and high-exposure groups, the estimated difference was 3.8 points (95 percent confidence interval, 1.3 to 6.3). Scores were not related to infants' postnatal blood lead levels. It appears that the fetus may be adversely affected at blood lead concentrations well below 25 micrograms per deciliter, the level currently defined by the Centers for Disease Control as the highest acceptable level for young children. Picture: Copyright (1987) Massachussets Medical Society, All rights reserved. Used with permission.

SIGNIFICANCE OF FIVE-POINT REDUCTION IN IQ: THE WEISS EFFECT



Adapted with permission from Schettler T. *In harm's way*. Boston: Greater Boston Physicians for Social Responsibility, 2000.

A 5 point loss in IQ might not affect the ability of an individual to live a productive life. But if that loss is experienced by an entire population, the implications for that society could be profound.
Bernard Weiss, a behavioural toxicologist at the University of Rochester, USA, examined the societal impact of seemingly small losses of intelligence. Imagine an unaffected population numbering 260 million people (such as that of the USA) with an average IQ of 100 and a standard deviation of 15 (left-hand graph). In that population there would be 6 million people with IQs above 130 and 6 million below 70.

A decrease in average IQ of 5 points would shift the distribution to the left (right-hand graph). The number of people scoring above 130 would decline by 3.6 million while the number below 70 would increase by 3.4 million.

Adapted with permission from Schettler T. *In harm's way*. Boston: Greater Boston Physicians for Social Responsibility, 2000.

Preventing lead toxicity in pregnancy

- **The lead levels in the mother can be measured and might be indicated if she lives close to a smelter**
- **In general, good calcium and phosphorous supply is important to prevent mobilization from the bones of the mother during pregnancy**
- **Iron and zinc are important to reduce effects on the haem synthesis pathway**

Lead toxic effects are based on the ability of lead to substitute for Calcium and Zinc. Lead disrupts Calcium homeostasis causing intracellular Ca++ accumulation leading to mitochondrial dysfunction with consequent activation of the apoptotic cascade and cell death. Lead may also disrupt thyroid hormone transport into the brain by decreasing the transporter protein levels.

The activity of ALAD (δ-amino laevulinic acid dehydratase) is a sensitive biomarker of a lead toxic effect .Lead inhibits this activity.This enzyme is important for haem synthesis. Polymorphism in the genes coding for this enzyme makes a person more susceptible to lead intoxication. ALA 2-2 phenotypes are less susceptible than ALA 1-1 or 1-2.

Ref: Bellinger D. Lead. Pediatrics (2004); 113:1016-22

Preconception counseling: environmental exposure

Volatile organic compounds

- **Solvents for paints: benzene, toluene, xylene, ethylbenzene, ortho-, meta- and paraxylene**
- **Effects: odour annoyance, irritation of eyes, nose and throat and inflammatory effects, fatigue and perception of confusion in general**
- **Prenatal use of chemical household products: among young children, more wheezing (ALSPAC study)**
- **Prevention: ventilation, especially after decorating the home – that is, painting and varnishing – since children have more obstructive bronchitis after their home is decorated**

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Concentrations of VOCs are about ten times higher indoors than outdoors. Children spend 85% of their time indoors and babies even 95%. VOCs are often measured as BTX (benzene, toluene, ethylbenzene, ortho-meta-para-xylene). The BTX concentration is higher in winter than in summer. BTX levels indoors measured in Italy and Germany were in the range of 2–10 µg/m³ for benzene and xylenes and 7–60 µg/m³ for toluene. In cars these levels are ten times higher. But in buses and trains these levels are lower than outdoors.There are about 900 different VOCs, but formaldehyde is an important one indoors; concentrations are much higher indoors and smoking is an important source. Benzene concentrations in cars and garages are often higher than the ambient air quality standard of 16.25 mg/m³.

In the Leipzig Allergy Risk Children study a significant increase in obstructive bronchitis is found in children two years old when the house was renovated or redecorated in the first year. Ventilation is very important!!

Ref: Mann HS, Crump D, Brown V. Personal exposure to benzene and the influence of attached and integral garages. J R Soc Health 2001;121:38–46.

Ref: Diez U et al. Redecoration of apartments promotes obstructive bronchitis in atopy risk infants – results of the LARS study. Int J Hyg Environ Health 2003;206: 173–179.

ALSPAC study: indoor VOC levels mainly influenced by **aerosol and air freshener use**. Daily use of air freshener elevated the risk of earache in babies, diarrhoea and vomiting. In mothers: headache and depression.

Ref: Farrow A et al. Symptoms of mothers and infants to total volatile organic compounds in household products. Arch. Environ. Health 2003;58(10):633–641. Children whose mothers often used chemical household products prenatally were twice as likely to wheeze persistently through early childhood. :

Ref: Sheriff A et al. and the ALSPAC study team. Frequent use of chemical household products is associated with persistent wheezing in pre-school age children. Thorax 2005;60:45–49.

See also slides 35–37 in the module on allergy and environment.

Formaldehyde

- Colourless, highly inflammable gas present in construction materials and used in carpets
- Animal studies: embryotoxicity and teratogenicity
- Humans: carcinogenicity (nasopharyngeal cancer and leukaemia)
- Avoid this chemical!

Formaldehyde is increased indoor with smoking. It is present in carpets and plywood and urea-formaldehyde foam insulation and floorings and wallcoverings.

There are about 900 different Volatile Organic Compounds but formaldehyde is an important one indoors.Cconcentrations are much higher indoors and smoking is an important source.

Formaldehyde is used in anatomo-pathologic laboratories and embalment (occupational exposure, risk for cancer of the nasal cavity)

Odour and eye irritation is detected at levels of 0.6 mg/m^3.

Indoor concentration > 60µg/m^3 = elevated risk of asthma.

It is used as a preservative in cosmetics and household cleaning agents, but in Europe in many countries formaldehyde is phased out in these products, but still plenty of products still contains preservatives, which gradually release low levels of formaldehyde of the product. Decorating the home in the first year of life is related to a higher prevalence of bronchitis in the second year if life, might be because of formaldehyde. See also ppt on VOC above.

Ref: WHO Concise International Chemical Assessment Document 40,2002

Total chemical burden of household products in pregnancy (ALSPAC study)

Percentage of pregnant women using the following chemicals:

- Disinfectant: 85%
- Bleach: 85%
- Carpet cleaner: 36%
- Window cleaner: 60%
- Dry-cleaning fluid: 5%
- Aerosols: 72%
- Turpentine or white spirit: 23%
- Air fresheners: 68%
- Paint stripper or varnish: 5%
- Pesticides or insect killers: 21%

The total chemical burden score is based on the frequency of use of each product (0=not at all,1=less than once aweek,2=about once a week,3=most days,4=every day)

Alspac study : Sheriff A et al, the ALSPAC STUDYTEAM: Frequent use of chemical household products is associated with persistent wheezing in pre-school age children. Thorax 2005:60:45-49

The ALSPAC study is a prospective study of 14541 pregnancies that resulted in 13971 live births surviving to 1 year between 1 April 1991 and Dec 1992 and place of residence within the three Bristol based health districts of the former county of Avon,UK.

Effects of household chemicals (total chemical burden) prenatally

- **In the top decile, the prenatal total chemical burden score above the persistent wheeze in children was twice as high as in the lowest decile**
- **No single product was implicated in the association with infant wheezing but the chemicals altogether**

These results are described in the Alspac study.

Alspac study : Sheriff A et al, the ALSPAC STUDYTEAM: Frequent use of chemical household products is associated with persistent wheezing in pre-school age children. Thorax 2005:60:45-49

Hypothesis: The combination of these chemicals result in a final common pathway, causing abnormal lung growth during pregnancy, predisposing the lungs to abnormal function in later life. The combination of several products and not one special means that there must be a common final pathway where these compounds enhance / or (maybe inhibit) each other.

Dysgenesis of the lung in intra-uterine growth is the most likely explanation for the later complaints. The same sort of effects were found in a follow-up study to perinatal dioxin exposure.

Ref:tenTusscher G.W., Weerdt J.de, Roos C.M., Griffioen R.W., De Jongh F.H., Westra M., Slikke J.W.van der, Oosting J., Olie K., Koppe J.G. Decreased lung function associated with perinatal exposure to Dutch background levels of dioxins. Acta Paediatr 90:1292-1298 (2001).

Indoor swimming pools

- **Chlorination can result in by-products after reacting with the organic substances produced by swimmers. The most dangerous by-products are:**
  1. **Trihalomethanes such as chloroform**
  2. **Chloramines: strong oxidant, toxic deeply in the lung**
- **In pregnancy, avoid crowded and shallow warm polluted pools**

NCL^3 (chloramine) is a chlorination by-product that can be a risk factor for developing permanent bronchial hyperresponsiveness in adults frequently swimming in indoor pools. There is no evidence that in swimming pools chlorination is a risk factor for the recreational swimmer. Also not for the recreational pregnant swimmer. However in small pools, shallow, hot and heavily polluted there can be a risk especially for a baby (methaemoglobinaemia). Adequate ventilation of indoor chlorinated pools requires an air change of 6 to 8 times an hour. (normal is 2-3 times)

Ref: Bernard A et al: Lung hyperpermeability and Asthma prevalence in Schoolchildren:Unexpected Associations with the attendance at Indoor Chlorinated Swimming Pools. Occup. Enviorn. Med.;60 (6) pp 385-394,2003

WHO guideline for swimming pools:WHO (2000b) Guidelines for safe recreational-water environments. Final draft for consultation,August 2000,http://www.who.int/water sanitation health/bathing/eng/recreall-ch4.pdf

Preconception counseling: environmental exposure

Chlorinated drinking-water

- **Chlorinated disinfection by-products:**
  1. **Trihalomethanes, chloroform, bromodichloromethane and bromoform**
  2. **Chloramines (trichloramine = NCl_3)**
  3. **Halocetic acids and acetonitriles**
- **Effects might be spontaneous abortion, but studies are inconclusive (Waller et al. 1998)**
- **Intrauterine growth retardation is found at trihalomethane levels above 40 ppb (Bove et al. 1995)**
- **An increase in stillbirths was associated with trihalomethane concentrations in the United Kingdom**
- **No relation has been found with prematurity (Hanke & Sram 2003)**

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Several studies are performed to reproductive effects of the chlorination of drinking water. Total trihalomethane is routinely monitored, but other classes of disinfection byproducts like halocetic acids and acetonitriles have also a potential for adverse reproductive effects.

Ref: Klotz JB and Pyrch LA: A case-control of neural tube defects and drinking water contaminants. PB98-111644.Springfield, VA:National Technical Information Service, 1998

Spontaneous abortion is dubious.

Waller K et al: Trihalomethanes in drinking water and spontaneous abortion: relation to amount and source of drinking water and spontaneous abortion. Epidemiology 9;134-140(1998)

Intrauterine growth retardation is found in relation to levels of **trihalomethane** concentrations above 40 ppb. Drinking more than 5 glasses of chlorinated water is too much.

Ref: Bove et al: public drinking water contamination and birth outcomes. Am. J. Epidemiol. 1995 141:850-862

Stillbirth is a consistent finding in areas with a higher concentration of trihalomethane (>60 µg/L)

Ref: Toledano MB et al: Children's health article: Relation of Trihalomethane Concentrations in Public Water Supplies to Stillbirth and Birth weight in Three Water regions in England. Env. Health perspectives 2005;113 (2):1-9

WHO (2000a) Environmental health criteria 216. Disinfectants and disinfectant by-products. ISBN 9241572167, internet: http://www.who.int/ipcs/publications/ehc/ehc 216/en/.

WHO (2004) Guidelines for Drinking Water quality. Third edition, Volume 1 Recommendations. WHO geneva. ISBN 9241546387

Hanke W. and Sram R. Assessment of Environment and Health Research in Europe. Environmental exposure and the risk of adverse reproductive outcomes.

Baseline Report SCALE (CON(2003)338 DG Env. EU

Cosmetics

- **Phthalates are present to fix the odour; phthalates are known endocrine disrupters with an estrogenic effect**
- **Synthetic musks, persistent compounds, are often present: especially after-shave, body lotion, and deodorant spray contain these chemicals**
- **Sunscreens to prevent sunburn have estrogenic activity**
- **Be cautious and avoid these products in pregnancy**

Sunscreens contain chemicals with an estrogenic activity.These chemicals are persistent and can be detected in breastmilk. Examples are benzophenone-3 and methoxicinnamate.

Ref: Schlumpf M. et al : Estrogen active UV screens. SÓFW-Journal , 127 ;7(2001)

Schlumpf et al : In vitro and in vivo Estrogenicity of UV Screens. Environ. Health Pers. 109 nr3;239-44 (2001).

Cosmetics contain phthalates, synthetic musks and parabenes, all known to be endocrine disruptors. Phthalates are known endocrine disruptors with an estrogenic effect. Wellknown are the effects of phthalates on early menarche in Puerto-Rican girls.

Ref:Colon I., Caro D., Bourdony C.J., Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ Health Perspect 108:895-900 (2000)

Use of sunscreens in the baby is also not recommended because it inhibits Vitamin D production.

DEHP-metabolites were found in significant higher concentrations in children, due to a slow metabolisation. In a study to the effects of phthalates on semen a dose-dependent relationship was seen between monobutyl and monobenzyl phthalate and one or more semen parameters. *Duty S.M., Silva M.J., BArr D.B., et al. Phthalate exposure and human semen parameters. Epidemiology 14:269-277 (2003)*

Preconception counseling: environmental exposure

Polycyclic aromatic hydrocarbons

- **There are about 30 different polycyclic aromatic hydrocarbons, but the most frequently detected are naphthalene and phenanthrene indoors**
- **Sources are: particulate matter from combustion, tobacco smoke and diesel vehicles**
- **Exposure in early pregnancy is related to intrauterine growth retardation and smaller head circumference**
- **Barbecued meat is a source of toxic polycyclic aromatic hydrocarbons**
- **Polycyclic aromatic hydrocarbons are carcinogenic, and babies more often have DNA adducts than the mother**

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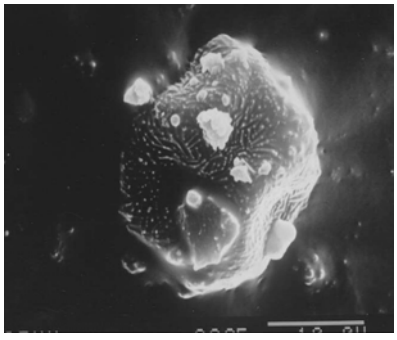
Studies to effects of carcinogenic polycyclic aromatic hydrocarbons are done in New York and in Czech-republic (North-Bohemia).An increase in DNA-adducts is found in cord blood in higher concentration than in the mother.Effects are intra-uterine growth retardation (IUGR), related to levels early in pregnancy.

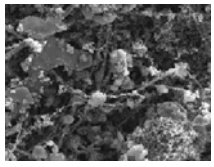
Ref: Perera et al: Effects of transplacental exposure to environmental pollutants on birth outcomes in a multi-ethnic population. Environ. Health Perspect.111:201-5 and Sram R.et al: Ambient Air Pollution and Pregnancy Outcomes: A review of the literature. Env. Health Perspectives vol 113: 375-383

Dioxins, PCBs and PBBs belong also to this category but are addressed under the heading of PBTs (Persistent Bioaccumulating Toxicants) slide 12 and 13.

Preconception counseling: environmental exposure

POLLEN AND ULTRAFINE PARTICLES





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Generally the association between air pollution from motorised transport and asthma and allergies is complex. It is well established that children with asthma and allergies of the respiratory tract are especially sensitive to high air pollution episodes and especially to soot and ultra-fine particles: Symptoms-scores, hospital admissions, drug use etc. increase with air pollution.

The introduction of allergic disease is a more complex issue. While it is well established that genetic factors play a major role, the causes for the tremendous increase in atopy prevalence is not so well understood. Immunological mechanisms at an early stage of life (Hygiene-Hypothesis) are important, but fine particles and some irritant gases also contribute when they hit during a vulnerable time window in early life. Epidemiological findings on that are still somewhat contradictory but this could well be because of the fact that this time window is not yet exactly defined.

This slide highlights the atmospheric reactions between pollen (and other natural allergens) and ultra-fine particles. (Photos kindly provided by Herwig Schinko, Linz).

Center: Light microscopy of alder pollen. Their surface is covered by fine particles (soot). The soot in this picture is in red (after electronical transformation of picture data by picture analysis system “LUCIA”). Note the sometimes very high burden of soot on airborne pollen grains. Specimen taken from the Burkard pollen trap situated in the center of Linz.

Source: Herwig Schinko und Roland Schmidt: Assoziation von Luftallergenen und partikulären Aerosolen in Linz 1991 - II. Teil. City of Linz, 1994, Linz.

Raster-electron microscopic pictures of birch (left) and willow (right) (pictures also provided by Schinko). Take note of the anorganic particles on the pollen surfaces.

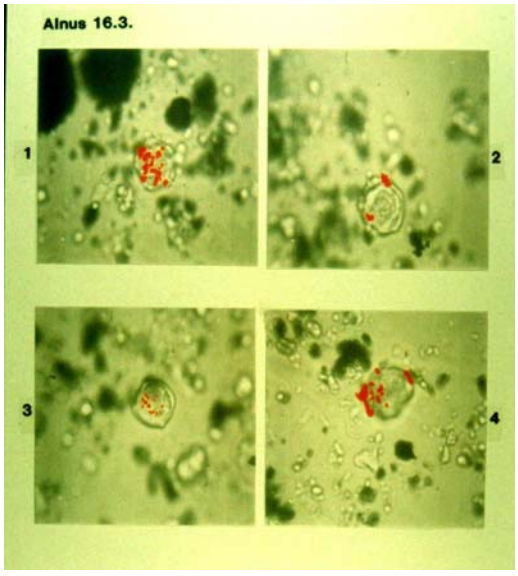
Bottom right: raster electron microscopy of soot on a filter.

Soot and pollen interact in the air (especially under damp conditions) or in the airways. Soot sticks to the pollen surface and induces swelling and rupturing of pollen grains. Allergenic pollen structures previously coated by the pollen surface become free in the ruptured pollen particles. Parts of pollen that are substantially smaller than the whole pollen grain remain airborne for a considerably longer period of time and reach deeper parts of the airways upon inhalation.

Acknowledgement:

PPT copied from Hanns Moshammer, module on Children and transport.

Preconception counseling: environmental exposure



Ultrafine particles. The slide is reproduced from the “Children and transport” module.

Preconception counseling: environmental exposure

Ionizing radiation

- **Particulate radiation: electrons, neutrons, protons and alpha particles ionize matter by direct atomic collisions**
- **Electromagnetic radiation or photons, X-rays or gamma rays ionize matter by other types of atomic interactions**

- **Effects: carcinogenic, defective immunity, lower IQ and impaired brain development**
- **Preconception exposure of the father means more stillbirths and childhood cancer**
- **In pregnancy there is no safe dose**

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In 1969 it became clear that obstetric X-rays (low dose of external exposure) a total dose of 10 mSv (Sievert) = 5 x the natural annual background in the UK causes 40 % increase in childhood cancer.

Ref: Wakeford R and Little M.P.: Risk coëfficients for childhood cancer after intra-uterine irradiation: a review. Intern. J. Radiat. Biol. 79, 293-309.(2003)

After Chernobyl effects in children were detected like thyroid cancer, heart attacks, immune system abnormalities, lower IQ and abnormal brain development.

Ref:UNSCEAR 2000.United Nations Scientific Committee on the Effects of Atomic Radiation. UN New York.

In areas of high natural background there is a genetic natural selection for radiation resistance because of cell repair efficiency.

Radon is a naturally occurring radio-active gas, that can form radon-daughters, with a slow half-life of years versus radon 3.8 days. It is known to cause lung cancer, but there are no pregnancy data. Buildings with plaster can give off radon gas and ventilation is necessary.

A significant risk of stillbirths among offspring of radiation workers is detected and increased rates of childhood leukaemia and non-hodgkin's lymphoma are found in children of fathers preconceptionally exposed to a total dose of 100 mSV or more.

Ref:Parker et al. Stillbirths among offspring of male radiation workers at Sellafield. Lancet, vol 354, 1407-13 (1999) and Gardner et al: results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. BMJ vol 300;423-9 (1990).

Solar and ultraviolet radiation

- UVB wavelengths: 280–320 nm
- UVA wavelengths: 320–400 nm
- Visible (blue-red): 400–660 nm

- Since 1980, the intensity of solar ultraviolet radiation has increased due to the depletion of the stratospheric ozone layer
- Ultraviolet radiation affects the skin (sunburn and producing vitamin D), eyes (cataracts), produces immunosuppression and increases the concentrations of air pollutants at ground level

During pregnancy there are no effects of solar or UV radiation on the fetus. The production of vitamin D in the skin of the mother is favorable.Intermittent sun exposure from recreational activities in childhood leading to sunburn are a significant risk factors for malignant melanoma later in life. *Ref: IARC Monographs vol.55 p 316 Solar and Ultraviolet Radiation. Lyon (1992).*

Preconception counseling: environmental exposure

Noise

- Occupational exposure >85 decibels (dB(A)) during eight hours in pregnancy is related to high-frequency hearing impairment in the children
- Living near airports might negatively influence birth weight, but evidence is weak
- No evidence for congenital malformations
- Recommendation: avoid continuous (more than eight hours per day) noise of more than 85 dB(A) in pregnancy

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Globally noise exposure is increasimng dramatically. In 1990 30 million people were exposed to more than 85 decibel daily in the USA compared with 9 million in 1980. Excessive noise has been linked with hearing impairment, hypertension, ischemic heart disease, adverse work performance and increased aggressive behaviour. In a study in miltary women an association of noise and standing on adverse pregnancy outcome (pretem delivery) is found. When controlling for standing there was still a trend.

Ref: Magann E.F.; Evans S.F.; Chauhan S.P.; Nolan T.E.; henderson J.;Klausen J.H.; newnham J.P.;Morrison J.C. The effects of standing, lifting and noise exposure on preterm birth, growth restriction, and perinatal death in helathy low-risk working military women. The J. of Maternal-Fetal and Neonatal Medicine;2005;18 (3) :155-162.

Occupational exposure to levels of noise of more than 85 decibel are related to high frequency hearing impairment in children. Women being a drummer in a band must be advised to stop when planning a pregnancy.

Daniel T. et al: Observations clinique et experiences concernant l' état de lápparеil cochleo-vestibulaire des sujets exposes au bruit durant la vie foetale. Rev. Laryngol Otol Rhin (1982) 103:313-8

Lalande NM et al. Is occupational noise during pregnancy a risk factor of damage to the auditory system of the fetus? Am J Ind Med (1985) ,10 (4):427-35.

Incubators in neonatal departments:

Closing of incubator ports with a loud smack causes acute stress in the baby. Continuous low frequency noise of the motor (ventilator) must be lower than 60 decibel.

Ref: PINCHE QLK4-2002-02395 (2005) Noise

Preconception counseling: environmental exposure

Waste landfill sites

- **People living within 3 km of a landfill site have more congenital malformations (EUROHAZCON project)**
- **Significant increase in neural tube defects, malformations of the cardiac septa and anomalies of major arteries and veins**
- **Borderline significant increase in tracheoesophageal anomalies, hypospadias and gastroschisis**
- **Recommendation: use folic acid supplementation, because these anomalies can be prevented with help of folic acid, perhaps in combination with other vitamins**

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The EUROHAZCON project studied 21 waste landfill sites in Europe. Residence within 3 km of the site was associated with a significantly increased risk of congenital anomalies. There was a fairly consistent decrease in the risk with the distance from the site.

Ref: Dolk H et al. Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. Lancet 1998;352:427–432.

The anomalies described are all known to be related to folic acid deficiency (see slide 5) so supplementation with folic acid, probably in combination with vitamin B_{12}, seems essential in these circumstances.

Three months of preconception leave for fathers?

- Semen is produced during a three-month cycle
- Three months before conception, fathers should stop smoking, drinking, working with solvents or other hazards and move away from regions with high air pollution to avoid polycyclic aromatic hydrocarbons