

TRAINING FOR THE HEALTH SECTOR
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ENDOCRINE DISORDERS AND CHILDREN

Children's Health and the Environment

WHO Training Package for the Health Sector

World Health Organization

www.who.int/ceh

October 2011

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<<NOTE TO USER: This module presents several examples of risk factors that affect development, you can find more detailed information in other modules of the training package that deal with specific risk factors, such as lead, mercury, pesticides, persistent organic pollutants; or disease outcomes, such as developmental origins of disease, reproductive effects, neurodevelopmental effects, immune effects, respiratory effects, and others.>>

Endocrine disorders and children

LEARNING OBJETIVES

- ❖ To understand the anatomy and functioning of the endocrine system
- ❖ To describe endocrine diseases that could be linked to the environment
- ❖ To present current knowledge of endocrine disrupting chemicals

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Endocrine disorders and children

OVERVIEW

- ❖ Anatomy and physiology of the endocrine system
- ❖ Major endocrine diseases in children, such as:
 - ❖ Thyroidal dysfunctions
 - ❖ Diabetes
 - ❖ Obesity
 - ❖ Precocious puberty
 - ❖ Hypospadias and cryptorchidism
 - ❖ Endocrine cancers
- ❖ Endocrine disrupting chemicals

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<<NOTE TO USER: If your audience is already familiar with the endocrine system, you may skip the introductory slides.>>

Endocrine disorders and children

THE ENDOCRINE SYSTEM

Major glands that make up the human endocrine system are:

- ❖ **Hypothalamus**
- ❖ **Pituitary**
- ❖ **Thyroid**
- ❖ **Parathyroids**
- ❖ **Adrenals**
- ❖ **Pineal body**
- ❖ **Reproductive glands, which include the ovaries and testes**

The pancreas is also part of this hormone-secreting system, even though it is also associated with the digestive system because it also produces and secretes digestive enzymes.

Although the endocrine glands are the body's main hormone producers, some non-endocrine organs — such as the brain, heart, lungs, kidneys, liver, thymus, pancreas, skin, and placenta — also produce and release hormones.

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HORMONES



C Alonzo



C Alonzo

- ❖ The word hormone is derived from the Greek "*hormao*" meaning "I excite or arouse"
- ❖ Hormones communicate this effect by their unique chemical structures recognized by specific receptors on their target cells, by their patterns of secretion and their concentrations in the general or localized circulation

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HORMONES - FUNCTIONS

- ❖ Reproduction and sexual differentiation
- ❖ Development and growth
- ❖ Maintenance of the internal environment
- ❖ Regulation of metabolism and nutrient supply



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Image: WHO

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HORMONES - FUNCTIONS

- ❖ The endocrine system keeps our bodies in balance, maintaining homeostasis and guiding proper growth and development
- ❖ A single hormone may affect more than one of these functions and each function may be controlled by several hormones



WHO

Hormone functions can be broadly grouped into several categories. For example, thyroid hormone is essential in development as well as many aspects of homeostasis and metabolism, while glucocorticoids, such as cortisol, are important both in growth and nutrient supply and are also modulators of immune function. The roles several hormones play in one function is exemplified by the control of blood glucose that involves the pancreatic peptide insulin and its counter regulatory hormone, glucagon, as well as cortisol, growth hormone and epinephrine. Hormones act in concert and thus, an abnormality in a controlled variable, such as blood glucose concentration may result from defects in the control of any one of several hormones.

Image: WHO

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CHALLENGES WITH THE ENDOCRINE SYSTEM

- ❖ Too much or too little of any hormone can be harmful to the body
- ❖ If the pituitary gland produces too much growth hormone, a child may grow excessively tall
- ❖ If it produces too little, a child may be abnormally short

Controlling the production of or replacing specific hormones can prevent many endocrine disorders in children and adolescents.

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THYROIDAL DYSFUNCTION AND ENVIRONMENTAL CHEMICALS

Thyroid hormones are essential for normal brain development during a critical period beginning *in utero* and extending through the first 2 years postpartum



POTENTIAL IMPACT ON BRAIN DEVELOPMENT

Thyroid hormones are essential for brain development and adverse exposures during critical periods could have an impact on brain development.

Ref.

•Porterfield S. Thyroidal dysfunction and environmental chemicals - potential impact on brain development. *Environ Health Perspect*, 2000, 108:3,433-438

Certain polyhalogenated aromatic hydrocarbons such as polychlorinated biphenyls (PCBs) and dibenzo-p-dioxins (dioxins, 2,3,7, 8-tetrachlorodibenzo-p-dioxin) have been shown to have neurotoxic effects and to alter thyroid function during critical periods of thyroid hormone-dependent brain development. This has led to the suggestion that some of the neurotoxic effects of these compounds could be mediated through the thyroid system. Thyroid hormones are essential for normal brain development during a critical period beginning in utero and extending through the first 2 years postpartum. They regulate neuronal proliferation, migration, and differentiation in discrete regions of the brain during definitive time periods. Even transient disruption of this normal pattern can impair brain development. Thyroid hormones are necessary for normal cytoskeletal assembly and stability and the cytoskeletal system is essential for migration and neuronal outgrowth. In addition, they regulate development of cholinergic and dopaminergic systems serving the cerebral cortex and hippocampus. Animals perinatally exposed to certain environmental organohalogenes such as many of the PCBs and dioxins have abnormal thyroid function and neurologic impairment. Although there are both species and congener variabilities, most reports show exposure results in thyroid enlargement and reduced serum T(4) levels with normal T(3) levels. Initial research concentrated on studying the direct actions of xenobiotics on the thyroid; however, some of these compounds bear a structural resemblance to the natural thyroid hormones and have high affinity with thyroid hormone-binding proteins such as transthyretin. These compounds could act as agonists or antagonists for receptors of the thyroid/steroid/retinoic acid superfamily. These structurally similar organohalogenes could act at multiple points to alter thyroid hormone action. The similarity of the neurologic impairment seen in thyroid disorders to that seen following PCB or dioxin exposure suggests that one mechanism of neurotoxicity of these compounds could involve interaction with the thyroid system.

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HYPERTHYROIDISM

- ❖ Hyperthyroidism is a condition in which the levels of thyroid hormones in the blood are excessively high
- ❖ Symptoms may include:
weight loss, nervousness, tremors, excessive sweating, increased heart rate and blood pressure, protruding eyes, and a swelling in the neck from an enlarged thyroid gland (goiter)

In children, the condition is usually caused by Graves' disease, an autoimmune disorder in which specific antibodies produced by the immune system stimulate the thyroid gland to become overactive.

The disease may be controlled with medications or by removal or destruction of the thyroid gland through surgery or radiation treatments.

Endocrine disorders and children

HYPOTHYROIDISM

- ❖ Hypothyroidism is a condition in which levels of thyroid hormones in the blood are abnormally low. Thyroid hormone deficiency slows body processes
- ❖ Symptoms may include fatigue, slow heart rate, dry skin
- ❖ In children: **slower growth and delayed puberty**
- ❖ Hashimoto's thyroiditis, which results from an autoimmune process that damages the thyroid and blocks thyroid hormone production, is the **most common cause of hypothyroidism in kids**

Infants can also be born with an absent or underdeveloped thyroid gland, resulting in hypothyroidism. It can be treated with oral thyroid hormone replacement.

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ENDEMIC CRETINISM ENVIRONMENTAL DISEASE

Children with endemic cretinism suffer from hypothyroidism that begins at conception because the dietary iodine deficiency prevents synthesis of normal levels of thyroid hormones

Symptoms include :

- ❖ Mental retardation that can be profound
- ❖ Spastic dysplasia
- ❖ Problems with gross and fine motor control resulting from damage to both the pyramidal and the extrapyramidal systems

Children with endemic cretinism suffer from hypothyroidism that begins at conception because the dietary iodine deficiency prevents synthesis of normal levels of thyroid hormones. It is more severe than that seen in congenital hypothyroidism because the deficiency occurs much earlier in development and results in decreased brain thyroid hormone exposure both before and after the time the fetal thyroid begins functioning. Damage occurs both to structures such as the corticospinal system that develop relatively early in the fetus and structures such as the cerebellum that develop predominantly in the late fetal and early neonatal period. If postnatal hypothyroidism is present, there is growth retardation and delayed or absent sexual maturation.

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THYROID FUNCTION AND ENDOCRINE DISRUPTING CHEMICALS

- ❖ Animals perinatally exposed to certain environmental organohalogenes such as Polychlorinated Biphenyls (PCBs) and dioxins have abnormal thyroid function and neurologic impairment
- ❖ Although there are both species and congener variabilities, most reports show exposure results in thyroid enlargement and reduced serum T₄ levels with normal T₃ levels

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DIABETES

- ❖ Group of diseases marked by high levels of blood glucose resulting from defects in insulin production, insulin action, or both
- ❖ Diabetes can lead to serious complications and premature death
- ❖ More than 220 million people worldwide have diabetes
- ❖ More than 80% of diabetes deaths occur in low- and middle-income countries

The disease can cause long-term complications including kidney problems, nerve damage, blindness, and early coronary heart disease and stroke. To control their blood sugar levels and reduce the risk of developing diabetes complications, children with this condition need regular injections of insulin. People with diabetes can take steps to control the disease and lower the risk of complications.

Diabetes and its complications have a significant economic impact on individuals, families, health systems and countries. For example, WHO estimates that in the period 2006-2015, China will lose 558 billion US dollars in foregone national income due to heart disease, stroke and diabetes alone.

Refs:

•CDC National diabetes fact sheet, 2007. Available at www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf – accessed 15 June 2011

•WHO. Diabetes fact sheet, 2011. Available at www.who.int/mediacentre/factsheets/fs312/en/ - accessed 15 June 2011.

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TYPE 1 DIABETES

- ❖ Previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes
- ❖ Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells. This form of diabetes usually affects children and young adults
- ❖ Risk factors for type 1 diabetes may be autoimmune, genetic or environmental

Symptoms include excessive thirst, hunger, urination, and weight loss.

In children and teens, the condition is usually an autoimmune disorder in which specific immune system cells and antibodies produced by the immune system attack and destroy the cells of the pancreas that produce insulin.

To survive, people with type 1 diabetes must have insulin delivered by injection or a pump. In adults, type 1 diabetes accounts for 5% to 10% of all diagnosed cases of diabetes.

Ref:

❖ CDC National diabetes fact sheet, 2007. Available at www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf – accessed 15 June 2011

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CHEMICALS AND TYPE 1 DIABETES

- ❖ Chemicals or drugs can be environmental triggers to diabetes

- ❖ Some that have been considered include:
 - ❖ the chemical Alloxan
 - ❖ the rodenticide Vacor
 - ❖ and the drugs Streptozotocin and Pentamidine

- ❖ All of these may cause an immune system response that could result in the destruction of insulin-producing cells

<<READ SLIDE>>

Ref:

•Davidson JK. Clinical diabetes mellitus: a problem-oriented approach, 3rd edition. *Thieme, New York*. 2000.

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TYPE 2 DIABETES

- ❖ Previously called non–insulin-dependent diabetes mellitus (NIDDM) or adult onset diabetes
- ❖ Type 2 diabetes comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity.
- ❖ Symptoms may be similar to those of Type 1 diabetes, but are often less marked. As a result, the disease may be diagnosed several years after onset, once complications have already arisen.
- ❖ Until recently, this type of diabetes was seen only in adults but it is now also occurring in children

Rising prevalence of this type of diabetes in children has paralleled the dramatically increasing rates of obesity among children

Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. Children and teens with the condition tend to be overweight, and it is believed that excess body fat plays a role in the insulin resistance that characterizes the disease.

Refs:

•Centers for Disease Control and Prevention National diabetes fact sheet, 2007. Available at www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf – accessed 15 June 2011

•WHO. Diabetes fact sheet, 2011. Available at www.who.int/mediacentre/factsheets/fs312/en/ - accessed 15 June 2011.

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THE EPIDEMIC OF OBESITY IN CHILDREN AND ADOLESCENTS

- ❖ Prevalence of obesity has reached alarming levels
- ❖ It affects both industrialized and developing countries of all socio-economic groups, irrespective of age, sex or ethnicity



WHO

Nearly 43 million children under the age of five were overweight in 2010 (WHO)

Worldwide obesity has more than doubled since 1980.

Childhood obesity is one of the most serious public health challenges of the 21st century. Overweight children are likely to become obese adults. They are more likely than non-overweight children to develop diabetes and cardiovascular diseases at a younger age, which in turn are associated with a higher chance of premature death and disability.

Overweight and obesity are defined as "abnormal or excessive fat accumulation that may impair health".

Body mass index (BMI) – the weight in kilograms divided by the square of the height in meters (kg/m²) – is a commonly used index to classify overweight and obesity in adults. WHO defines overweight as a BMI equal to or more than 25, and obesity as a BMI equal to or more than 30.

Refs:

•de Onis M, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr*, 2010, 92(5):1257-64.

Childhood obesity is associated with serious health problems and the risk of premature illness and death later in life. Monitoring related trends is important. OBJECTIVE: The objective was to quantify the worldwide prevalence and trends of overweight and obesity among preschool children on the basis of the new World Health Organization standards. DESIGN: A total of 450 nationally representative cross-sectional surveys from 144 countries were analyzed. Overweight and obesity were defined as the proportion of preschool children with values >2 SDs and >3 SDs, respectively, from the World Health Organization growth standard median. Being "at risk of overweight" was defined as the proportion with values >1 SD and ≤2 SDs, respectively. Linear mixed-effects modeling was used to estimate the rates and numbers of affected children. RESULTS: In 2010, 43 million children (35 million in developing countries) were estimated to be overweight and obese; 92 million were at risk of overweight. The worldwide prevalence of childhood overweight and obesity increased from 4.2% (95% CI: 3.2%, 5.2%) in 1990 to 6.7% (95% CI: 5.6%, 7.7%) in 2010. This trend is expected to reach 9.1% (95% CI: 7.3%, 10.9%), or ≈60 million, in 2020. The estimated prevalence of childhood overweight and obesity in Africa in 2010 was 8.5% (95% CI: 7.4%, 9.5%) and is expected to reach 12.7% (95% CI: 10.6%, 14.8%) in 2020. The prevalence is lower in Asia than in Africa (4.9% in 2010), but the number of affected children (18 million) is higher in Asia. CONCLUSIONS: Childhood overweight and obesity have increased dramatically since 1990. These findings confirm the need for effective interventions starting as early as infancy to reverse anticipated trends.

•Kosti, R, Panagiotakos D. The epidemic of obesity in children and adolescents in the world. *Cent Eur J Publ Health*, 2006, 14 (4): 151–159.

•WHO. Obesity fact sheet. 2011. Available at www.who.int/mediacentre/factsheets/fs311/en/ - accessed June 2011

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OBESITY: CONTRIBUTING FACTORS

- ❖ Genetic
- ❖ Behavioural
- ❖ Environment

Home, child care, school and community environments can influence children's behaviors related to food intake and physical activity



WHO

Supportive environments and communities are fundamental in shaping people's choices and preventing obesity. Children's choices, diet and physical activity habits are influenced by their surrounding environment. Social and economic development as well as policies in the areas of agriculture, transport, urban planning, environment, education, food processing, distribution and marketing influence children's dietary habits and preferences as well as their physical activity patterns. Increasingly, these influences are promoting unhealthy weight gain leading to a steady rise in the prevalence of childhood obesity.

Ref:

•WHO. Obesity fact sheet. 2011. Available at www.who.int/mediacentre/factsheets/fs311/en/ - accessed June 2011

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WHY IS CHILDHOOD OBESITY CONSIDERED A HEALTH PROBLEM?

- ❖ Heart disease, caused by:
 - ❖ high cholesterol and/or
 - ❖ high blood pressure
- ❖ Type 2 diabetes
- ❖ Asthma
- ❖ Sleep apnea
- ❖ Social discrimination

Doctors and scientists are concerned about the rise of obesity in children and youth because obesity may lead to the following health problems:

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Childhood obesity is associated with various health-related consequences. Obese children and adolescents may experience immediate health consequences and may be at risk for weight-related health problems in adulthood.

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OBESITY AND CHEMICALS?

- ❖ Endocrine-disrupting chemicals (EDCs) are compounds that mimic or interfere with the normal actions of all endocrine hormones
- ❖ Some EDCs are lipophilic, resistant to metabolism, and/or able to bioconcentrate up the food chain.
- ❖ These substances become stored in body fats and can be transferred to the developing offspring via the placenta
- ❖ In spite of the accumulating substantial evidence for an obesity epidemic, our knowledge about the effect of environmental chemicals on weight gain and the magnitude of human or wildlife exposure to these chemicals is limited.

Ref:

•Elobeid MA, Allison DB. Putative environmental-endocrine disruptors and obesity: A review. *Curr Opin Endocrinol Diabetes Obes.* 2008, 15(5):403–408

Purpose of the review—There has been a substantial increase in the prevalence of obesity in the last several decades. Recent evidence suggests that endocrine disrupting chemicals, e.g. halogenated aromatic hydrocarbons, may cause perturbations in endogenous hormonal regulation and alter other mechanisms involved in weight homeostasis, which may lead to weight gain by increased volume of adipose tissue. Synthetic chemicals derived from industrial processes are suspected to play a contributory role. Yet of the approximately 70,000 documented synthetic chemicals, few have been examined to determine their effects on the endocrine system. Recent findings—The present study examines prior laboratory, epidemiological and experimental research findings. Data demonstrate migration of endocrine disruptors in the environment and are beginning to catalogue their effects on adiposity. We present postulated relationships between these chemicals, their mechanisms of action, and the obesity epidemic.

Summary—Endocrine disruptors may adversely impact human and environmental health by altering physiological control mechanism. Obesity, which is known to increase medical costs and reduce quality and length of life, may be increasing as a function of endocrine disruptor exposure. This merits concern among scientists and public health officials and warrants additional vigorous research in this area.

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PREVENTION: HOW TO MAINTAIN A HEALTHY WEIGHT ?

Policy and environmental change initiatives that make healthy choices in nutrition and physical activity available, affordable, and easy will likely prove most effective in combating obesity

Balancing calories

- Help children develop healthy eating habits
- Help children eat organic food
- Help children stay active and reduce sedentary time

Curbing the global obesity epidemic requires a population-based multisectoral, multi-disciplinary, and culturally relevant approach.

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PRECOCIOUS PUBERTY

- ❖ Puberty is the process of physical maturation manifested by an increase in growth rate and the appearance of secondary sexual characteristics
- ❖ Precocious puberty has most commonly been defined as the onset of puberty (appearance of any sign of secondary sexual maturation) before the age of 8 yr in girls and before the age of 9 yr in boys.
- ❖ It involves early physical changes of puberty & also linear growth acceleration and acceleration of bone maturation, which leads to early epiphyseal fusion and short adult height.

Body changes associated with puberty may occur at an abnormally young age in some kids if the pituitary hormones that stimulate the gonads to produce sex hormones rise prematurely.

By definition, males who have precocious puberty must develop secondary sexual characteristics when younger than 9 years. The classic definition of sexual precocity for girls is the onset of secondary sexual characteristics prior to age 8 years. The current guidelines recommend the evaluation of any girl younger than 8 years who has an advanced bone age or a rapid progression through puberty.

Ref:

•Oerter Klein K. Precocious puberty: who has it? Who should be treated? *JCEM*, 1999, 84 (2):411.

<<NOTE TO USER: For more information, please go to the modules on reproductive health and environment.>>

Endocrine disorders and children

PRECOCIOUS PUBERTY & ENVIRONMENTAL EXPOSURES

- ❖ Mycotoxins - mycoestrogen Zearalenone produced by the fungus *Fusarium* spp. suspected to be a triggering factor for precocious puberty development in girls
- ❖ DDT, DDE, PCBs and phthalates have been associated with early puberty
- ❖ Drug exposure: compounds with estrogenic activity may be present in some drugs like oral contraceptives

Refs:

- Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009
- Massart F et al. High growth rate of girls with precocious puberty exposed to estrogenic mycotoxins. *J Pediatr*, 2008,152(5):690-5.
- Mendola P et al. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. *Fertility and Sterility*. 2008, 89(1):e81
- Wolff MS et al. Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. *Environmental Health Perspectives*. 2010, 118(7):1039-1046.

<<NOTE TO USER: For more information, please go to the modules on reproductive health and environment.>>

DDT: dichlorodiphenyltrichloroethane. DDT breaks down into two similar products: DDE (1,1-dichloro-2,2-bis(chlorophenyl) ethylene) and DDD (1,1-dichloro-2,2-bis(p-chlorophenyl) ethane).
PCBs: Polychlorinated biphenyls

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ENVIRONMENTAL FACTORS AND PUBERTY TIMING

Available experimental animal and human data support a possible role of endocrine-disrupting chemicals and body size in relation to alterations in pubertal onset and progression in boys and girls



Buck Louis GM et al, 2008



WHO

Ref:

•Buck Louis GM et al Environmental factors and puberty timing: expert panel research needs. *Pediatrics*, 2008, 121:S192-S207.

<<NOTE TO USER: For more information, please go to the modules on reproductive health and environment.>>

Endocrine disorders and children

HYPOSPADIAS

- One of the most common birth defects
- Incidence: 1 in 250 newborn males; the number has doubled in the last 3 decades (Paulozzi,1997)
- Etiology: remains unknown but there is a correlation with maternal environmental exposure and endocrine disruptors

<<READ SLIDE>>

Refs:

•Baskin L. Can we prevent hypospadias? *Fertil Steril*, 2008, 89(2):e39.

Hypospadias is one of the most common birth defects. The etiology remains unknown, except for in a small number of cases where it can be attributed to specific defects in either androgen metabolism or the androgen receptor. The incidence is approximately 1 in 250 newborn males, and according to studies from the Center for Disease Control, the number of newborn males born with hypospadias has doubled over the last three decades. Hypospadias can be defined as an anatomical defect in the formation of the urethra on the ventral aspect of the penis, an arrest in the development of the normal circumferential prepuce, and varying degrees of penile curvature. Hypospadias can be quite mild with the urethral opening on the proximal aspect of the glans, quite severe, where there is penile scrotal transposition and the urethra exits within the scrotum or the perineum or gradations of severity between these two extremes. A working hypothesis to explain the etiology of hypospadias as well as the increase in hypospadias is maternal environmental exposure or endocrine disruptors. A myriad of epidemiologic papers have been published on the incidence of hypospadias related to environmental exposure. To study the effects of endocrine disruptors on the developing urethra, an animal model has been validated using CD1 mice. The critical time for urethral development is between embryonic days 12 and 17, out of a total gestation of 21 days in these animals. Exposing pregnant dams to physiologic doses of endocrine disruptors and analyzing the urethral anatomy via histology, three dimensional computer reconstruction, and plastic resin cast has shown the utility of this technique. It has now been confirmed that estrogens such as 17 estradiol, pesticides such as vincolizin, pharmaceutical products such as the antihistamine loratadine, and the flame retardant, benzophenone-2, can all cause hypospadias in this animal model at physiologic doses. Further work in humans has analyzed genetic markers using microarray analysis of excess skin procured at the time of surgery for correction of hypospadias compared to skin from age matched children undergoing elective circumcision. A number of genes have been shown to be associated with an increased risk of hypospadias based on the array analysis with confirmation using both protein expression within the skin and mRNA expression. Presently, our working hypothesis to explain both the baseline incidence of hypospadias and the increase that has been noted in industrialized nations is a genetic susceptibility combined with environmental exposure during the critical time of embryonic urethral development.

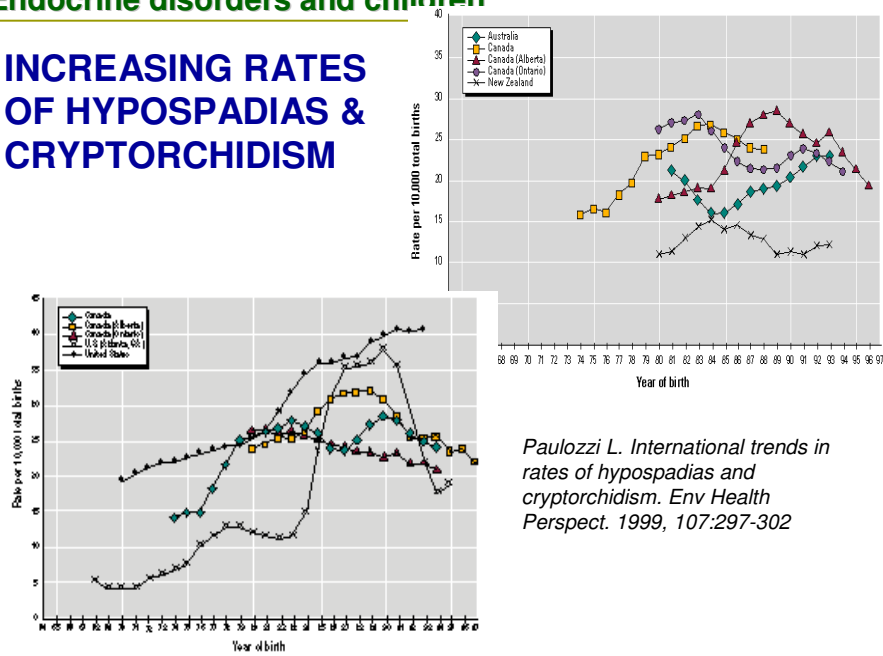
•Baskin LS, Ebbers MB. *Hypospadias: anatomy, etiology, and technique. J Pediatr Surg.* 2006, 41:463–72.

•Paulozzi L, Erickson D, Jackson R. Hypospadias trends in two US surveillance systems. *Pediatrics.* 1997, 100:831–834

<<NOTE TO USER: For more information, please go to the modules on reproductive health and environment.>>

Endocrine disorders and children

INCREASING RATES OF HYPOSPADIAS & CRYPTORCHIDISM



Images from:

•Paulozzi L. International trends in rates of hypospadias and cryptorchidism. *Env Health Perspect.* 1999, 107:297-302. doi:10.1289/ehp.99107297

Researchers from seven European nations and the United States have published reports of increasing rates of hypospadias during the 1960s, 1970s, and 1980s. Reports of increasing rates of cryptorchidism have come primarily from England. In recent years, these reports have become one focus of the debate over endocrine disruption. This study examines more recent data from a larger number of countries participating in the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) to address the questions of whether such increases are worldwide and continuing and whether there are geographic patterns to any observed increases. The ICBDMS headquarters and individual systems provided the data. Systems were categorized into five groups based on gross domestic product in 1984. Hypospadias increases were most marked in two American systems and in Scandinavia and Japan. The increases leveled off in many systems after 1985. Increases were not seen in less affluent nations. Cryptorchidism rates were available for 10 systems. Clear increases in this anomaly were seen in two U.S. systems and in the South American system, but not elsewhere. Since 1985, rates declined in most systems. Numerous artifacts may contribute to or cause upward trends in hypospadias. Possible "real" causes include demographic changes and endocrine disruption, among others.

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MATERNAL & PATERNAL RISK FACTORS FOR CRYPTORCHIDISM AND HYOSPADIAS

- ❖ Paternal pesticide exposure - cryptorchidism
- ❖ Paternal smoking - hyospadias
- ❖ Small gestational age - hyospadias
- ❖ Preterm birth - cryptorchidism

Pierik et al, 2004

<<READ SLIDE>>

Ref:

•Pierik FH et al. Maternal and paternal risk factors for cryptorchidism and hyospadias: a case-control study in newborn boys. *Environ Health Perspect.* 2004, 112:1570-1576.

Little is known on environmental risk factors for cryptorchidism and hyospadias, which are among the most frequent congenital abnormalities. The aim of our study was to identify risk factors for cryptorchidism and hyospadias, with a focus on potential endocrine disruptors in parental diet and occupation. In a case-control study nested within a cohort of 8,698 male births, we compared 78 cryptorchidism cases and 56 hyospadias cases with 313 controls. The participation rate was 85% for cases and 68% for controls. Through interviews, information was collected on pregnancy aspects and personal characteristics, lifestyle, occupation, and dietary phytoestrogen intake of both parents. Occupational exposure to potential endocrine disruptors was classified based on self-reported exposure and ratings of occupational hygienists based on job descriptions. Our findings indicate that paternal pesticide exposure was associated with cryptorchidism [odds ratio (OR) = 3.8; 95% confidence interval (95% CI), 1.1-13.4]. Smoking of the father was associated with hyospadias (OR = 3.8; 95% CI, 1.8-8.2). Maternal occupational, dietary, and lifestyle exposures were not associated with either abnormality. Both abnormalities were associated with suboptimal maternal health, a lower maternal education, and a Turkish origin of the parents. Being small for gestational age was a risk factor for hyospadias, and preterm birth was a risk factor for cryptorchidism. Because paternal pesticide exposure was significantly associated with cryptorchidism and paternal smoking was associated with hyospadias in male offspring, paternal exposure should be included in further studies on cryptorchidism and hyospadias risk factors.

<<NOTE TO USER: For more information, please go to the modules on reproductive health and environment.>>

Endocrine disorders and children

DIETHYLSTILBESTROL (DES) AND CRYPTORCHIDISM

- ❖ Prenatal exposure to DES, a synthetic estrogen, increases risk of male urogenital abnormalities and the association is strongest for exposure that occurs early in gestation
- ❖ Study findings support the hypothesis that endocrine disrupting chemicals may be a cause of the increased prevalence of cryptorchidism that has been seen in recent years

Palmer et al, 2009

<<READ SLIDE>>

Diethylstilbestrol (DES) is one of the most well known endocrine disruptors. It was prescribed to women in the early 1900s to prevent miscarriages. It is a synthetic estrogen that was taken in high doses. Studies later showed that when pregnant women took this compound during a specific developmental period and exposed the fetus in utero, many anatomic reproductive tract abnormalities were observed in future generations as well as increased incidence of some cancers. This case study led to the idea that synthetic compounds can affect endocrine systems profoundly.

Ref:

•Palmer JR et al. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environmental Health*. 2009, 18(8):837

<<NOTE TO USER: For more information, please go to the modules on reproductive health and environment.>>

Endocrine disorders and children

DIETHYLSTILBESTROL (DES) & ENDOCRINE CANCERS

The first observation of the impact of endocrine disruptors in humans was done by Herbst and Bern in 1981:



8 cases of clear cell adenocarcinoma (CCA) of the vagina in young women who had been exposed *in utero* one to two decades earlier to DES, a synthetic estrogen prescribed to pregnant women in the 1950s and 1960s to prevent miscarriage

Landrigan et al, 2003

<<READ SLIDE>>

Ref.

•Landrigan P, Garg A, Droller B. Assessing the effects of endocrine disruptors in the National Children's Study. *Environmental Health Perspectives*. 2003, 111(13):1678.

Children are uniquely vulnerable to toxic chemicals in the environment. Among the environmental toxicants to which children are at risk of exposure are endocrine disruptors (EDs)--chemicals that have the capacity to interfere with hormonal signaling systems. EDs may alter feedback loops in the brain, pituitary, gonads, thyroid, and other components of the endocrine system. They can affect development. Effects of EDs have been described in wildlife populations, in animals exposed experimentally, and to a more limited extent in humans. Mechanisms of action of EDs are increasingly being elucidated, and genetic polymorphisms that convey differential susceptibility to EDs are beginning to be explored. It is hypothesized that in utero and early childhood exposures to EDs may be responsible, at least in part, for decreases in semen quality; increasing incidence of congenital malformations of the reproductive organs, such as hypospadias; increasing incidence of testicular cancer; and acceleration of onset of puberty in females. The National Children's Study (NCS) will provide a unique opportunity to test the validity of these hypotheses in the context of a large prospective multiyear epidemiologic investigation. It will be essential in the NCS to assess exposures to a range of putative natural and synthetic EDs, to assess outcomes possibly due to ED exposure, to examine the potential interplay between EDs and genetic polymorphisms, and to seek links between ED exposures in early life and endocrine, reproductive, neurobehavioral, and other outcomes throughout the life span.

Endocrine disorders and children

WHAT IS AN ENDOCRINE DISRUPTING CHEMICAL? (EDC)

Exogenous substance or mixture that alters the function(s) of the hormonal system and consequently causes adverse effects in an intact *organism* or its *progeny* or its *sub-population*

- Effects**
- multiple and complex
 - many mechanisms of action
 - multiple pathways
 - end-effect may be a functional change
- not a “toxic end-point”**

<<READ SLIDE>>

Endocrine disrupting chemicals (EDCs) were defined by the EDC-International Programme on Chemical Safety Working Group as: exogenous substance or mixture that alters the function(s) of the hormonal system and consequently causes adverse effects in an intact organism, or its progeny or its sub-population.

The substances may be of *natural* or *synthetic* origin.

- ❖ An example of EDCs of natural origin is the "phytoestrogens" present in plants.
- ❖ The synthetic ones include some pesticides, industrial by-products, chemicals used in plastics, pharmaceuticals that enter the natural environment, and persistent organic pollutants (POPs) (addressed in the next slides).

The potential effects are FUNCTIONAL and not a toxic end-point.

These functional changes *may or may not* lead to an adverse event.

It is difficult to distinguish between the direct and indirect effects and to distinguish the primary from the secondary effects.

The effects are complex as they result from multiple mechanisms of action on a hormonal system with close interconnections and "cross-talk".

Ref:

•WHO. Global assessment of the state-of-the-science of endocrine disruptors. *WHO*, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.

Endocrine disorders and children

ENDOCRINE DISRUPTING CHEMICALS (EDCs)

Natural

- Phytoestrogens
- Fungal estrogens

Synthetic

- Hormones
- Some pesticides
- Industrial by-products ("dioxin-like")
- Pharmaceuticals
- Some persistent organic pollutants (POPs)



FAO

Examples of natural and synthetic chemicals considered as potential endocrine disrupting chemicals are:

Natural

Phytoestrogens:

- ❖ isoflavonoids in soya beans and legumes;
- ❖ lignanes in grain, fruits and vegetables; and
- ❖ coumestans in clover and alfalfa.

Fungal estrogens.

Synthetic

- ❖ Hormones – oral contraceptives, estrogen replacement in postmenopausal women
- ❖ Some pesticides - DDT
- ❖ Industrial by-products ("dioxin-like")
- ❖ Pharmaceuticals
- ❖ Some persistent organic pollutants (POPs)

<<READ SLIDE>>

Ref:

❖ WHO. Global assessment of the state-of-the-science of endocrine disruptors. WHO, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.

Endocrine disorders and children

BACKGROUND

- ❖ Rachel Carson first to describe dichlorodiphenyl trichloroethane (DDT) as an endocrine disruptor in the wild in *Silent Spring* (1962)
- ❖ Theo Colburn et al. – modern day observations of puzzling endocrine health effects seen in the wild in *Our Stolen Future* (1997)
- ❖ Put forth the notion that small changes in hormone levels in fetal life may have effects on future generations

There has been much concern in recent years regarding endocrine disruptors and their potential effects on human and wildlife populations.

In 1962, Rachel Carson wrote a publication called "Silent Spring" that critically examined pesticide use after World War II and especially the use of dichlorodiphenyltrichloroethane (DDT). She found that DDT used to control mosquito populations had also caused reproductive abnormalities in bird populations (specifically thinning of bird eggshells) and therefore a significantly decreased bird population → leading to a "silent spring" without the wonderful bird calls/chirps normally heard at that time of year. In the past 50 years, there has been significant research devoted to toxic chemicals and their health effects due to her publication.

Theo Colburn is a pharmacist turned zoologist who co-wrote "Our Stolen Future" which notes many observations of wildlife and human endocrine health effects and postulates endocrine disruptors as the main cause of these effects. It is written as a scientific mystery that is our responsibility as a society to solve. This book was the first major publication in general circulation to infer that small hormone changes in fetal life may have effects on many future generations to come. Past US vice-president Al Gore has written a foreword in this book discussing the importance of its contents.

Refs:

- Carson R. *Silent Spring*. Boston University Press, Boston, Massachusetts. 1962.
- Colburn T, Dumanoski D, Myers JP. *Our Stolen Future*. Plume Books, US. 1997.

Endocrine disorders and children

IMPORTANT ISSUES IN ENDOCRINE DISRUPTION

- ❖ Age at exposure
- ❖ Latency from exposure
- ❖ Importance of mixtures
- ❖ Non traditional dose-response dynamics
- ❖ Transgenerational, epigenetic effects



MN Bruné

Important issues to consider when addressing endocrine disruption include:

- Age at exposure: exposure of a fetus, an infant or an adult may have different consequences.
- Latency from exposure: the consequences of exposure may not be apparent immediately but later on in life.
- Importance of mixtures: our environments are complex and in our daily lives, we are not only exposed to one environmental factor but to many. We can be exposed to many different kinds of endocrine disruptors which can have additive or synergistic effects.
- Non traditional dose-response dynamics: even low levels of exposure during critical windows of development can have more potent or different effects than higher doses. Many endocrine disrupting chemicals do not have traditional dose-response curves.
- Transgenerational, epigenetic effects: endocrine disrupting chemicals may have effects not only on the individual but also in its progeny. Effects might be transmitted by regulatory factors that control gene expression.

Ref:

- Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009

<<NOTE TO USER: See module on developmental origins of disease for more information.>>

Endocrine disorders and children

ENDOCRINE DISRUPTING CHEMICALS AND ADVERSE EFFECTS ON REPRODUCTION

- Amply documented in both marine and terrestrial species, in laboratory animals and emerging evidence in humans
- Endocrine disruptors may turn on, shut off, or modify signals that hormones carry and thus affect the normal functions of tissues and organs
- Major concern is the fact that endocrine disruptors interfering with reproduction may have profound effects on sexual differentiation

<<READ SLIDE>>

Refs:

•WHO. Global assessment of the state-of-the-science of endocrine disruptors. *WHO*, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.

•Wuttke W, Jarry H, Seidlova-Wuttke D. Definition, classification and mechanism of action of endocrine disrupting chemicals. *Hormones*. 2010, 9(1):15

Endocrine disorders and children

POSSIBLE MECHANISMS OF ENDOCRINE DISRUPTION

- ❖ Mimic effects of endogenous hormones
- ❖ Antagonize effects of endogenous hormones
- ❖ Disrupt synthesis and metabolism of endogenous hormones
- ❖ Disrupt synthesis of hormone receptors
- ❖ Alter target cell sensitivity
- ❖ Limitations of in vivo animal models

<<READ SLIDE>>

Refs:

- Amaral Mendes JJ. The endocrine disruptors: a major medical challenge. *Food and Chemical Toxicology*. 2002, 40(6): 781-788.
- Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009

Endocrine disorders and children

POLYCHLORINATED BIPHENYLS (PCBs) AND DIOXINS

- ❖ Exert their neurotoxic effects through multiple mechanisms
- ❖ The classical mechanism is through interactions with the aryl hydrocarbon (Ah) receptor
- ❖ In addition, many of the congeners of polychlorinated biphenyls (PCBs) and dioxins alter thyroid function

Because thyroid hormones are essential for normal brain development, it is possible that the xenobiotics could produce neurotoxicity indirectly by altering thyroid-regulated brain development. Many of the neurotoxic effects of organohalogenes reported in humans and experimental animals resemble those seen in fetal/neonatal hypothyroidism.

Note: Xenobiotics are chemicals found in an organism but that are not normally produced or expected to be present in it.

Refs:

•Porterfiel SP. Thyroidal dysfunction and environmental chemicals - potential impact on brain development. *Environmental Health Perspectives*. 2000, 108:S3

•WHO. Global assessment of the state-of-the-science of endocrine disruptors. *WHO*, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.

Endocrine disorders and children

EXAMPLES OF POTENTIAL HORMONE DISRUPTORS

- ❖ Atrazine: heavily used herbicide, banned in the European Union due to concerns of groundwater contamination
- ❖ Bisphenol A (BPA)
 - synthetic estrogen used in common products (baby bottles, sport bottles, linings of cans for food and infant formula)
 - linked to early puberty and alterations of mammary gland development in animal studies

Atrazine: heavily used herbicide, banned in the European Union due to concerns of groundwater contamination. Animal studies identify it as an endocrine disruptor.

Bisphenol A (BPA) is a widely used chemical in polycarbonate plastic and epoxy resins

- Consumer exposure via food can occur through migration of BPA from food contact materials
- Concern has been raised because of potential toxic and hormonal properties of BPA
- Hazard assessments by major regulatory and advisory bodies are in agreement that the overall no-observed-adverse-effect level (NOAEL) for BPA from robust data is 5 mg/kg body weight/day. This is minimally five hundred-fold above conservative estimates of human exposure, including in bottle-fed infants.
- Several areas of uncertainty remain in the risk assessment of BPA:

Effects have been reported from animal experiments on neurobehaviour following exposure to BPA during the developmental period at doses below the overall NOAEL

Kinetics of absorption, metabolism and excretion of BPA show important differences between primates, including humans (lower internal dose), and rodents, and between routes of exposure, so care is needed in extrapolation of animal studies to humans;

Many countries have banned use of BPA completely or in baby products as a precautionary approach.

Refs:

•Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009

•Fan W et al. Atrazine-induced aromatase expression is SF-1 dependent: implications for endocrine disruption in wildlife and reproductive cancers in humans. *Environ Health Perspect*. 2007, 115(5):720-7.

BACKGROUND: Atrazine is a potent endocrine disruptor that increases aromatase expression in some human cancer cell lines. The mechanism involves the inhibition of phosphodiesterase and subsequent elevation of cAMP.

METHODS: We compared steroidogenic factor 1 (SF-1) expression in atrazine responsive and non-responsive cell lines and transfected SF-1 into nonresponsive cell lines to assess SF-1's role in atrazine-induced aromatase. We used a luciferase reporter driven by the SF-1-dependent aromatase promoter (ArPII) to examine activation of this promoter by atrazine and the related simazine. We mutated the SF-1 binding site to confirm the role of SF-1. We also examined effects of 55 other chemicals. Finally, we examined the ability of atrazine and simazine to bind to SF-1 and enhance SF-1 binding to ArPII.

RESULTS: Atrazine-responsive adrenal carcinoma cells (H295R) expressed 54 times more SF-1 than nonresponsive ovarian granulosa KGN cells. Exogenous SF-1 conveyed atrazine-responsiveness to otherwise nonresponsive KGN and NIH/3T3 cells. Atrazine induced binding of SF-1 to chromatin and mutation of the SF-1 binding site in ArPII eliminated SF-1 binding and atrazine-responsiveness in H295R cells. Out of 55 chemicals examined, only atrazine, simazine, and benzopyrene induced luciferase via ArPII. Atrazine bound directly to SF-1, showing that atrazine is a ligand for this "orphan" receptor.

CONCLUSION: The current findings are consistent with atrazine's endocrine-disrupting effects in fish, amphibians, and reptiles; the induction of mammary and prostate cancer in laboratory rodents; and correlations between atrazine and similar reproductive cancers in humans. This study highlights the importance of atrazine as a risk factor in endocrine disruption in wildlife and reproductive cancers in laboratory rodents and humans.

Endocrine disorders and children

EXAMPLES OF POTENTIAL HORMONE DISRUPTORS

❖ Dichlorodiphenyl trichloroethane (DDT)

- Insecticide widely used until it was banned in the 70's
- Linked to precocious and early puberty, reduced fertility in daughters of women exposed, increased breast cancer risks

❖ Phthalates

- Family of compounds used as a plasticizers in polyvinyl chloride (PVC), cosmetics, fragrance, others
- Some phthalates were banned from children's products in 2008
- Studies link them to premature thelarche

<<READ SLIDE>>

Refs:

- Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009
- WHO. Global assessment of the state-of-the-science of endocrine disruptors. *WHO*, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.
- WHO. Persistent organic pollutants: impact on child health. *WHO*, 2010. Available at www.who.int/ceh/publications/persistent_organic_pollutant/en/index.html - accessed March 2011.

Endocrine disorders and children

EXAMPLES OF POTENTIAL HORMONE DISRUPTORS

❖ Polychlorinated biphenyls (PCBs):

- Compounds used as coolants and insulation in electrical equipment.
- Banned in the 70's due to their toxicity
- Rat studies link early life exposure to neuroendocrine effects in two generations & behavioral changes
- Action on estrogen receptors and neurotransmitter receptors

❖ Dioxins

- ❖ Family of compounds that are by-products of some manufacturing and incineration processes
- ❖ Fetal exposure in rats connected to altered breast development and increased susceptibility for mammary cancer

<<READ SLIDE>>

Refs:

- Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009
- WHO. Persistent organic pollutants: impact on child health. WHO, 2010. Available at www.who.int/ceh/publications/persistent_organic_pollutant/en/index.html - accessed March 2011.

Endocrine disorders and children

PERSISTENT ORGANIC POLLUTANTS (POPs)

PESTICIDES

Aldrin
Dieldrin
Chlordane
DDT
Endrin
Heptachlor
Mirex
Toxaphene
Chlordecone
Hexachlorocyclohexanes
Lindane,
Pentachlorobenzene

Stockholm Convention: global treaty ratified by international community lead by UNEP – calls for the elimination and/or phasing out of POPs

INDUSTRIAL CHEMICALS

Hexachlorobenzene
Polychlorinated biphenyls
Hexabromobiphenyl
Hexabromodiphenyl ether
Heptabromodiphenyl ether
Pentachlorobenzene
Perfluorooctane sulfonic acid, its salts
Perfluorooctane sulfonyl fluoride
Tetrabromodiphenyl ether
Pentabromodiphenyl ether

UNINTENDED BY-PRODUCTS

Dibenzodioxins
Dibenzofurans
alpha hexachlorocyclohexane, beta hexachlorocyclohexane and pentachlorobenzene

www.chem.unep.ch/pops/default.html

POPs: manufactured organic chemicals that persist for years in environment (long range transport-global pollution). They are lipophilic and remain in adipose tissues. They accumulate in the food chain and the highest levels are found in marine mammals. Their toxicity at high levels is well characterized.

These are the persistent organic pollutants – grouped according to their use and origin:

- 8 pesticides
- 2 industrial chemicals
- 2 unintended industrial by-products.

<<READ SLIDE.>>

The Stockholm Convention is a global treaty ratified by the international community and led by the United Nations Environment Programme (UNEP) that calls for the elimination and/or phasing out of 12 POPs, called the "dirty dozen". More information is available at: www.chem.unep.ch/pops/default.html

Refs:

•Stockholm Convention on Persistent Organic Pollutants. Available at chm.pops.int/Home/tabid/36/language/en-US/Default.aspx – accessed March 2011.

Initial 12 POPs

Initially, twelve POPs have been recognized as causing adverse effects on humans and the ecosystem and these can be placed in 3 categories:

- *Pesticides: aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, toxaphene;*
- *Industrial chemicals: hexachlorobenzene, polychlorinated biphenyls (PCBs); and*
- *By-products: hexachlorobenzene; polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/PCDF), and PCBs.*

Nine new POPs

At its fourth meeting held from 4 to 8 May 2009, the Conference of the Parties (COP) adopted amendments to Annexes A (elimination), B (restriction) and C (unintentional production) of the Stockholm Convention to list nine additional chemicals as persistent organic pollutants.

- *Pesticides: chlordecone, alpha hexachlorocyclohexane, beta hexachlorocyclohexane, lindane, pentachlorobenzene;*
- *Industrial chemicals: hexabromobiphenyl, hexabromodiphenyl ether and heptabromodiphenyl ether, pentachlorobenzene, perfluorooctane sulfonic acid, its salts and perfluorooctane sulfonyl fluoride, tetrabromodiphenyl ether and pentabromodiphenyl ether; and*
- *By-products: alpha hexachlorocyclohexane, beta hexachlorocyclohexane and pentachlorobenzene.*

•Webster P. Persistent toxic substances: study finds heavy contamination across vast Russian Arctic. *Science*, 2004, 306:1875.

•WHO. Persistent organic pollutants: impact on child health. WHO, 2010. Available at www.who.int/ceh/publications/persistent_organic_pollutant/en/index.html - accessed March 2011.

•WHO/UNEP/ILO. Guidelines on the prevention of toxic exposures: education and public awareness activities. WHO, Geneva, 2004.

PCBs: polychlorinated biphenyls

HCB: hexachlorocyclohexane

DDT: dichlorodiphenyl trichloroethane.

Endocrine disorders and children

ABUSING DDT...



Norsk Barnemuseum

Fig: Norsk Barnemuseum. www.norskbarne.museum.no/html/barn100.htm Used with copyright permission.

DDT: dichlorodiphenyl trichloroethane.

Endocrine disorders and children

EFFECTS OF ENDOCRINE DISRUPTORS

<i>Estrogenic</i>	dichlorodiphenyl trichloroethane (DDT), dieldrin, endosulfan, methoxychlor, polychlorinated biphenyls (PCBs), alkylphenols, phthalates, mycotoxins, phytoestrogens
<i>Anti-estrogenic</i>	dioxin, PCBs, phytoestrogens
<i>Anti-androgenic</i>	DDT, vinclozolin
<i>Anti-thyroid</i>	PCBs, dioxin
<i>Anti-progestin</i>	PCBs, DDT

This slide illustrates the complexity of effects that may be caused by different chemicals, and the fact that the same chemical may have different effects.

For example, DDT may have estrogenic, anti-estrogenic or anti-progestin effects.

Phytoestrogens may be both estrogenic and anti-estrogenic.

PCBs: polychlorinated biphenyls

DDT: dichlorodiphenyl trichloroethane.

<<READ SLIDE>>

Endocrine disorders and children

WHY ARE WE CONCERNED ABOUT ENDOCRINE DISRUPTORS?

- ❖ Homeostatic mechanisms are determined in early fetal/infant life
- ❖ Once these hormones have been "programmed" they cannot be changed in the future
- ❖ This programming can be affected by endocrine disruptors in the environment

<<READ SLIDE>>

Homeostasis can be thought of as how the body responds to changes in the outside and internal environments to maintain a state of equilibrium.

There are many different organs involved in the endocrine system and they interact with one another through multiple mechanisms to regulate overall homeostasis.

Endocrine disorders and children

EFFECTS ON HUMAN HEALTH

- ❖ Immune system
- ❖ Neurological system
- ❖ Reproductive
- ❖ Developmental



C Alonzo

The toxic effects of endocrine disruptors may include effects on the developmental, immune, neurological, and reproductive systems. The research and evidence supporting these effects do not point to a cause and effect type relationship due to a lack of exposure data. Instead, many of them are inferred from animal studies and observations made in human studies.

A number of observations have been made about endocrine disrupting chemicals' effects on the immune system, neurological system, reproductive and developmental systems.

Immune system effects have been observed in children after *in utero* exposure to polychlorinated biphenyls (PCBs). A higher prevalence of respiratory symptoms and other infectious diseases were seen. These effects have been seen only after high dose exposures. It is thought that the mechanism involves thymic atrophy and therefore decreased thymocytes in neonates and infants.

In terms of neurologic effects, we do know that many chemicals at high exposures can cause short term neurologic effects potentially mediated by endocrine mechanisms. For low dose effects, it is known that PCBs interfere with the thyroid receptor in animal studies but human studies have not been able to show consistent exposure effect data.

Reproductive abnormalities have been seen with chemicals such as Diethylstilbestrol (DES) but many more are hypothesized to occur. One specific issue includes declining sperm counts and increasing incidence of male reproductive tract abnormalities. Although the rates of certain specific diseases such as testicular cancer are known to be increasing, the data does not support a strong causal relationship to endocrine disruptors at this time.

For the reproductive system, it has been postulated that a number of male reproductive system effects including decreasing sperm production, increasing rates of hypospadias and cryptorchidism can be attributed to EDCs. This is controversial and has not been proven at this time.

We do know that high dose exposures to some chemicals such as chlordecone and dibromochloropropane have caused infertility in adult men but do not know the mechanism of action.

Developmental abnormalities encompass many different systems but usually growth and psychologic testing are used as indicators of developmental status. The evidence supporting neurodevelopmental abnormalities with PCB exposure is judged to be moderate in nature.

Ref:

•WHO. Global assessment of the state-of-the-science of endocrine disruptors. WHO, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.

Image: Cristina Alonzo. Used with permission.

Endocrine disorders and children

EXAMPLES OF EFFECTS ON WILDLIFE

- Reproductive impairment and malformations
- Immune system sensitivity
- Increased risk of tumors



National Oceanic and Atmospheric Administration

MAMMALS:

- ❖ Polychlorinated biphenyls (PCBs) exposure in minks led to declining populations
- ❖ Reproductive, immune, and other endocrine effects in Baltic seals due to PCB and dichlorodiphenyl trichloroethane (DDT)

BIRDS:

- ❖ Eggshell thinning, reduced fertility, suppression of egg formation, altered chick-rearing behaviours in multiple species due to DDT, PCBs and organochlorines
- ❖ Offspring: increased mortality, teratological effects

<<NOTE TO USER: Read first three points of the slide.>>

Fish-eating mammals may be particularly vulnerable to endocrine disrupting chemicals effects given their dependence on aquatic food for survival.

Some examples of effects of exposure observed in wildlife are given in the slide.

Mammals: Minks exposed to fish contaminated with organochlorines such as polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzodioxins (PCDD) in the Great Lakes (US) region showed a number of adverse reproductive outcomes. In laboratory experiments exposing minks to PCBs showed increased fetal death, decreased kit survival, and decreased kit growth.

Populations of Baltic and grey seals have declined rapidly over the past 100 years. These seals have been exposed to PCBs and dichlorodiphenyltrichloroethane (DDT) through their diet. Interruptions during early pregnancy, and partial or complete sterility have been observed in this population. Although the true mechanism is not known, it has been shown that increased levels of these contaminants are associated with increased reproductive and immune abnormalities.

Birds: Eggshell thinning has been observed in many different species due to 1,1-dichloro-2,2-bis(chlorophenyl) ethylene (DDE) exposure; altered gonadal development in connection to DDT has been observed; and embryonic abnormalities due to PCB exposure have been seen.

PCBs: polychlorinated biphenyls

DDT: dichlorodiphenyl trichloroethane.

Ref:

•WHO. Global assessment of the state-of-the-science of endocrine disruptors. WHO, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.

Image: National Oceanic and Atmospheric Administration

Endocrine disorders and children

EXAMPLES OF EFFECTS ON WILDLIFE

REPTILES: decline in alligator population by 90% after difocol, DDT, DDE chemical spill

- ❖ Smaller penis size
- ❖ Abnormal gonad morphology
- ❖ Altered sex steroid concentrations



National Oceanic and Atmospheric Administration

FISH: reproductive alterations when exposed to sewage treatment waste

Reptiles – In Lake Apopka, Florida, a chemical spill of difocol and DDT, DDE, chloro-DDT occurred in 1980. Subsequently, the population of alligators declined by 90%. Studies of juvenile alligators showed developmental abnormalities including abnormal gonad morphology, altered gonadal steroidogenesis, and changes in sex steroid concentrations in males and females. These alligators were found to have depressed testosterone and elevated estrogen levels. Many different mechanisms of action were theorized such as abnormal interactions with the alligator estrogen receptor, DDE acting as an androgen antagonist in juvenile alligators, and overall disruptions to the thyroid gonadal axis. This was a sentinel study in endocrine disruptor science and paved the path for further studies of low level exposures.

In fish who swim in waters where sewage treatment waste is dumped, a number of endocrine effects have been observed including: alterations in vitellogen (egg protein produced by females) production and changes in sex steroid hormone production. These changes have been attributed to environmental estrogens (natural and synthetic)

Refs:

- Guillette LJ Jr et al. Developmental abnormalities of the gonad and abnormal sex hormone concentrations in juvenile alligators from contaminated and control lakes in Florida. *Environmental Health Perspectives*, 1994, 102(8):680-688.
- WHO. Global assessment of the state-of-the-science of endocrine disruptors. WHO, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.

DDT: dichlorodiphenyl trichloroethane

DDE: 1,1-dichloro-2,2-bis(chlorophenyl) ethylene

Image: National Oceanic and Atmospheric Administration

Endocrine disorders and children

EXAMPLES OF EFFECTS ON HUMAN HEALTH

Widespread and persistent, chlorinated hydrocarbons - may mimic the biological effects of estrogens.

Excessive estrogen exposure is a key risk factor for gynaecologic malignancies and benign proliferative disorders – *e.g. endometriosis and leiomyoma.*

Also on hormone-dependent physiological processes

- *e.g. conception; fetal development*
- *Possibly on osteoporosis and cardiovascular disease*

As increasingly more women enter the workforce, they may be exposed to a variety of occupational chemicals and hazards that may lead to adverse health and reproductive effects. In addition, smoking, alcohol consumption, and other lifestyle factors play an increasingly important role in determining the health status of women. There is now abundant evidence that environmental factors may contribute to many of the disease processes discussed above. Some examples of likely environmental impact on women's health include the following:

Among the most widespread and persistent environmental toxicants are chlorinated hydrocarbons (such as dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyls), which are known to possess estrogenic potential, i.e., the ability to mimic the biological effects of estrogens. Imbalanced or unopposed estrogen exposure is a leading risk factor for many gynecologic malignancies, as well as benign proliferative disorders such as endometriosis and leiomyoma. The potential impact of these compounds on hormone-dependent physiological processes such as conception and fetal development, as well as on disease processes such as osteoporosis and cardiovascular disease, demands further exploration.

DDT: dichlorodiphenyl trichloroethane

Refs:

- Anger DL, Foster WG. The link between environmental toxicant exposure and endometriosis. *Frontiers in Bioscience*, 2008, 13:1578-1593.
- Best Start. Workplace reproductive health: research and strategies. Best Start. *Ontario's Maternal Newborn and Early Child Development Resource Centre*, 2001.
- Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009

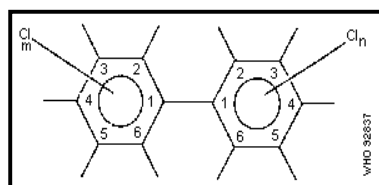
Endocrine disorders and children

POLYCHLORINATED BIPHENYLS

A range of adverse, persistent effects were observed in children born to mothers exposed to relatively high levels of PCBs (in the "Yusho" and "Yu-Chen" poisoning incidents).

The children presented

- **Low birth weight**
- **Reduced growth**
- **Hyperpigmented skin**
- **Gingival hyperplasia**
- **Eye oedema**
- **Dentition at birth**
- **Abnormal calcification**



- **Men exposed before 20 years: lower chances to have a boy**

Polychlorinated biphenyls (PCBs) are toxic compounds used in industrial processes. Many different forms of PCBs exist and persist in the environment today. Because of adverse health outcomes with PCB exposures in the past, many industrial countries decided to decrease or ban its production.

Exposure of the general population to PCBs occurs principally through contaminated food items.

Babies will be exposed through the mother's milk.

Two large episodes of intoxication in humans have occurred in Japan (Yusho) and China, Province of Taiwan (Yu-Cheng).

The main symptoms in Yusho and Yu-Cheng patients have frequently been attributed to contaminants in the PCB mixtures, specifically, to PCDFs. Expert groups concluded that the symptoms may have been caused by the combined exposure to PCBs and PCDFs.

In children of Yusho and Yu-Cheng patients, diminished growth, dark pigmentation of the skin and mucous membranes, gingival hyperplasia, xenophthalmic oedematous eyes, dentition at birth, abnormal calcification of the skull, rocker bottom heel, and a high incidence of low birth weight were observed. Whether or not a correlation existed between the exposure and the occurrence of malignant neoplasms in these patients could not be definitely concluded, because the number of deaths was too small. However, a statistically significant increase was observed in male patients, with regard to mortality from all neoplasms, liver and lung cancer.

Developmental effects – Four epidemiological studies performed in the Netherlands examine the association between background PCB exposure and thyroid effects. These studies examined thyroid hormone levels in persons exposed to PCBs *in utero* and found that higher PCB exposure was associated with higher thyrotrophin-stimulating hormone (TSH) and lower T4 hormone levels in infancy and up to one year of age. These changes could affect neurodevelopment *in utero* as well as in neonatal and infant life. Studies examining neurodevelopment in relation to low level PCB exposure have found hypotonia and psychomotor delays in early life.

PCBs have been widely used in electrical equipment, and smaller volumes of PCBs are used as fire-resistant liquid in nominally closed systems. By the end of 1980, the total world production of PCBs was in excess of 1 million tonnes and, since then, production has continued in some countries. Despite increasing withdrawal from use, and restrictions on the production of PCBs, very large amounts of these compounds continue to be present in the environment, either in use or as waste. In recent years, many industrialized countries have taken steps to control and restrict the flow of PCBs into the environment. The most influential force leading to these restrictions has probably been a 1973 recommendation from the Organisation for Economic Co-operation and Development (OECD) (WHO, 1976; IARC, 1978; OECD, 1982). Since then, the 24 OECD member countries have restricted the manufacture, sales, importation, exportation and use of PCBs, as well as establishing a labelling system for these compounds. Current sources of PCB release include volatilization from landfills containing transformer, capacitor, and other PCB-containing wastes, sewage sludge, spills, and dredge spoils, and improper (or illegal) disposal in open areas. Pollution may occur during the incineration of industrial and municipal waste. Most municipal incinerators are not effective in destroying PCBs. Explosions or overheating of transformers and capacitors may release significant amounts of PCBs into the local environment.

Refs:

•Brouwer A et al. Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. *Environmental Health Perspectives*, 1999, 107:639-49.

•Landrigan P, Garg A, Droller D. Assessing the effects of endocrine disruptors in the National Children's Study. *Environmental Health Perspectives*. *Environmental Health Perspectives*, 2003, 111(13): 1678.

•WHO. Persistent organic pollutants: impact on child health. WHO, 2010. Available at www.who.int/ceh/publications/persistent_organic_pollutant/en/index.html - accessed March 2011.

<<NOTE TO USER: See module on persistent organic pollutants for more information.>>

Endocrine disorders and children

Seveso, Italy - 10 July 1976, chemical explosion that releases the highest levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure experienced by a human population.

Seveso Women's Health Study: 1996 retrospective cohort study of females

- ❖ Age of menopause: increase risk of early menopause
 - ❖ Breast cancer: associated with individual high TCDD levels
 - ❖ Menstrual cycles: more regular
 - ❖ Endometriosis: doubled, non-significant risk
 - ❖ Leiomyoma: ...seems to have an anti-estrogenic effect on myometrium
 - ❖ Ovarian function: no evidence
 - ❖ Menarche: no evidence
-
- ❖ Confusing picture: in some tissues TCDD may be estrogen like (breast) and in others it may be blocking estrogen (uterus).
 - ❖ Timing of exposure seems to be important
 - ❖ Excess of female births in a region after toxic chemical spill of TCDD

In Seveso Italy, 2,3,7,8 tetrachlorodibenzo-*p*- dioxin (TCDD) was released when a chemical factor exploded. In the years that followed, males were born at half the rate of females in families where the father was exposed to the chemical. This study has not been reproduced in animals or humans.

<<READ SLIDE>>

Refs:

- Eskenazi B et al. Seveso Women's Health Study: a study of the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on reproductive health. *Chemosphere*, 2000, 40(9-11):1247-53.
- Landrigan P, Garg A, Droller D. Assessing the effects of endocrine disruptors in the National Children's Study. *Environmental Health Perspectives*, 2003, 111(13): 1678.
- WHO. Persistent organic pollutants: impact on child health. WHO, 2010. Available at www.who.int/ceh/publications/persistent_organic_pollutant/en/index.html - accessed March 2011.

<<NOTE TO USER: See module on persistent organic pollutants for more information.>>

Endocrine disorders and children

Another type of cancer: Diethylstilbestrol (DES) as a model for environmental estrogens

- ❖ DES administered to pregnant women 1940-1960 for high-risk pregnancies but later to promote "healthier babies" as well.
- ❖ Female offspring developed clear-cell carcinoma of the vagina, vaginal adenosis, cervical ectropion, and other abnormalities.
- ❖ Males: reproductive tract abnormalities.

Has human cancer incidence resulting from DES exposure peaked? DES daughters are reaching post-menopause, the age of endometrial carcinoma...

- ❖ DES may be a model compound for other environmental agents with estrogenic potential.

<<READ SLIDE>>

Ref:

•Diethylstilbestrol (DES) as a model for environmental estrogens. *Environews, NIEHS news*. 1993. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC1519726/pdf/envhper00372-0021b-color.pdf – accessed 15 June 2011.

DES was administered to pregnant women during the 1940s through 1960s, originally for high-risk pregnancies but later to promote "healthier babies" as well. Subsequently, the drug was linked to the development of an otherwise extremely rare malignancy, clear-cell carcinoma of the vagina, in young female offspring exposed in utero. In addition, a number of more common non-neoplastic changes in the reproductive tract of DES-exposed daughters were identified, including vaginal adenosis, cervical ectropion, and numerous other structural abnormalities. Although the public health hazards associated with further exposure to DES have been largely eliminated, there are a number of compelling reasons for the continued study of DES-exposed women, as well as for basic research on the biological effects of DES and other environmental estrogenic compounds.

First, it is unclear whether the human cancer incidence resulting from DES exposure has peaked. Although the majority of DES daughters have passed the age range for vaginal carcinoma development, few have reached the age range (postmeno-pausal) in which endometrial carcinoma typically occurs in the DES unexposed population, and endometrial carcinoma occurs with a much higher prevalence than vaginal carcinoma in DES-treated mice. Similarly, the threat of breast cancer is still a concern in this population. The identification of molecular genetic markers for DES carcinogenicity is therefore a continuing priority; such markers would also be of value in predicting risk for third-generation DES offspring, for whom little is known about potential health risks.

Second, DES may be viewed as a model compound for other environmental agents with estrogenic potential. The bioaccumulation of these environmental estrogens is recognized as a problem of increasing magnitude, and certain human populations in the United States have been shown to carry amounts of these fat-soluble compounds which, in fish and other wildlife, cause significant endocrine dysfunction and developmental anomalies of the reproductive tract. Insights into the biological effects of DES should therefore provide a foundation upon which future environmental health problems may be effectively addressed.

NIEHS has a long history of accomplishments in conducting and supporting research on estrogen action, hormonal carcinogenesis, and other types of estrogen-related pathology, particularly for DES and similar compounds. More recent achievements have provided insights into basic mechanisms of estrogen receptor action at the molecular level. A transgenic mouse that overexpresses the estrogen receptor is being developed to study tissue susceptibility and mechanisms for hormonal carcinogenesis. New endeavors include the analysis of human and animal tumors resulting from DES exposure in utero for molecular genetic alterations. Rapid advances in the fields of molecular and developmental biology have provided numerous insights into relevant genes and molecular pathways involved in reproductive tract development. Epidemiologic studies are fo-cused on a broad range of health effects among DES-exposed men and women. Expanded research efforts are necessary to use this knowledge in exploring the epigenetic effects of DES in relation to reproductive tract malformations at the molecular level.

In addition to the estrogen receptor, research on the role of "orphan receptors" in environmental disease is promising. Identification and characterization of orphan receptors and their endogenous ligands will provide a link to understanding the molecular mechanisms through which exogenous chemicals may exert toxic effects and through which natural substances influence physiologic processes. For example, a recently discovered member of the nuclear receptor family apparently recognizes a class of foreign chemicals called peroxisome proliferators, which includes industrial plasticizers, herbicides, and hypolipidemic agents. Similarly, a receptor from another gene family exists for the ubiquitous xenobiotic dioxin, or TCDD. A related example is the retinoids, which regulate differentiation and growth of a variety of epithelial tissues including mammary gland, cervical, vaginal, and uterine epithelium. Ongoing research at NIEHS is directed toward understanding the process of squamous differentiation in gynecologic epithelial tissues by retinoids and estrogens, and interactions between the retinoic acid receptor and estrogen receptor signaling pathways. Further research is necessary to define these pathways at the molecular level and to elucidate possible therapeutic applications of retin-oids in breast and other cancers.

An additional complexity is that age and the timing of exposures to environmental agents can have a profound effect on individual susceptibility. For example, the well-known adverse effects of the antimiscarriage drug diethylstilbestrol (DES) and subsequent development of vaginal cancer in the daughters who were exposed during in utero development and the perinatal DES-exposed experimental animal model point to critical stages of susceptibility. In fact, the hypothesis that exposure to environmental agents early in life is of greater health significance than adult exposure is currently being investigated by NIEHS researchers studying the effects of endocrine-disrupting chemicals during development and the importance of timing of exposure in cancer risk. Yet another aspect of timing that complicates environmental health research is that the appearance of disease often occurs much later than the causative exposure. This was the case with DES, and this delay makes identifying the contributing factor(s) difficult but challenging, requiring both laboratory- and human population-based studies

Endocrine disorders and children

DDE, DDT & PBBs

- ❖ DDE exposure through breast milk may alter duration of lactation by acting through the estrogen receptor
- ❖ DDE exposures prenatally may have potential effects on adolescent growth and sexual maturation
- ❖ DDT might be connected to breast cancer
- ❖ PBBs and accelerated onset of puberty

DDT: dichlorodiphenyl trichloroethane
DDE: 1,1-dichloro-2,2-bis(chlorophenyl) ethylene
PBBs: polybrominated biphenyls

Studies performed in North Carolina (US) and Northern Mexico showed a statistically significant association between DDE levels in breast milk, maternal serum, and cord blood and duration of lactation. It was thought that DDE acts through an estrogen receptor to oppose prolactin activity (for normal milk production, estrogen falls and prolactin rises) and interfere with milk synthesis.

In a US study, it was found that the higher the DDE exposure prenatally, the taller and heavier boys were at 14 years of age. There was no effect on when pubertal milestones were reached.

CB-153 and DDE in semen of 149 Swedish fishermen from the eastern Baltic coast had a high proportion of Y-chromosome bearing semen. Also high levels of persistent organic pollutants in blood.

Higher prevalence of cryptorchidism in Lithuania. Environmental factors may be changing the ratio of sperm carrying the X or Y (sex determining) chromosomes and may be contributing to male reproductive disorders

Exposure to p,p'-DDT early in life may increase breast cancer risk. Many U.S. women heavily exposed to DDT in childhood have not yet reached 50 years of age. The public health significance of DDT exposure in early life may be large.

1973: Accidental contamination of Michigan food chain by a fire retardant containing PBBs. 4000 people ingested contaminated meat and milk. Maternal PBB exposure and/or exposure through breastfeeding seemed to cause earlier onset of puberty in their daughters Farm families. Gestation and breast milk.

DDT: dichlorodiphenyl trichloroethane
DDE: 1,1-dichloro-2,2-bis(chlorophenyl) ethylene
PBBs: polybrominated biphenyls

Refs:

- Cohn BA. DDT and breast cancer in young women: New data on the significance of age at exposure. *Environmental Health Perspectives*, 2007, 115(10):1406-14.
- Landrigan P, Garg A, Droller D. Assessing the effects of endocrine disruptors in the National Children's Study. *Environmental Health Perspectives*, 2003, 111(13): 1678.
- Rogan WJ and Ragan NB. Evidence of effects of environmental chemicals on the endocrine system in children. *Pediatrics*, 2003, 112; 247-252.
- WHO. Persistent organic pollutants: impact on child health. WHO, 2010. Available at www.who.int/ceh/publications/persistent_organic_pollutant/en/index.html - accessed March 2011.

Endocrine disorders and children

PLASTICS AND ENDOCRINE DISRUPTION? PHTHALATES

- ❖ Phthalates are a group of man-made chemicals widely used as plasticizers in the manufacture of flexible vinyl plastics
- ❖ Consumer products: flooring, wall covering, food contact applications, medical devices, personal-care products (e.g. perfumes, lotions, cosmetics), lacquers, varnishes, coatings, including those used to provide timed releases in some pharmaceuticals

Human exposure to phthalates is widespread and occurs through ingestion, inhalation and dermal contact.

<<READ SLIDE>>

Ref:

•Hauser R. Calafat AM. Phthalates and human health. *Occupational and Environmental Medicine*. 2005, 62:806-818

Endocrine disorders and children

PLASTICS AND ENDOCRINE DISRUPTION? PHTHALATES

- ❖ Special population highly exposed
- ❖ Parenteral exposure from medical devices and products containing phthalates are important sources of high exposure
- ❖ Animals: reproductive and developmental toxicities
- ❖ Human studies: possible associations with
 - ❖ Altered semen quality
 - ❖ Shortened gestation
 - ❖ Reduced anogenital distance in baby boys
 - ❖ Premature breast development
 - ❖ Obesity

Hauser, Occupational and Environmental Medicine 2005

Human exposure to phthalates is widespread and occurs through ingestion, inhalation and dermal contact.

<<READ SLIDE>>

Ref:

•Hauser R. Calafat AM. Phthalates and human health. *Occupational and Environmental Medicine*. 2005, 62:806-818

Endocrine disorders and children

AND MORE PLASTICS....

- ❖ **Bisphenol A is found in the linings of cans and in baby bottles. It can leach from plastic when it is heated or there is a change in acid–base balance.**
- ❖ **Possible link between bisphenol A and obesity**
- ❖ **According to certain studies, bisphenol A has exhibited endocrine disruption in animals and humans at ppb doses**
- ❖ **Other studies have linked similar doses with cancer of the prostate and mammary gland in offspring**

Vom Saal et al Expert Panel Consensus, *Reprod Toxicol.* 2007, 24:131-138

<<READ SLIDE>>

Ref:

•Stemp Morlock G. Chemical exposures: exploring developmental origins of obesity. *Environ Health Perspect.* 2007, 115(5): A242.

Endocrine disorders and children

Connecticut first state to ban BPA. It became the first state in the nation to ban the chemical bisphenol A from infant formula and baby food cans and jars. The legislation also bans BPA from reusable food and beverage containers. The law goes into effect Oct. 1, 2011.

Denmark has introduced a temporary ban on bisphenol A (BPA) in all food contact materials for young children amid fears the chemical could inhibit brain development. From 1 July, 2010, it will be illegal to manufacture baby bottles, sippy cups and packaging for baby food containing BPA.

As this issue has generated a lot of attention and in response to Member States queries, WHO is gathering experts for health impact assessment

OTTAWA — The Canadian government moved Friday to ban polycarbonate infant bottles, the most popular variety on the market, after it officially declared one of their chemical ingredients toxic.

Bisphenol A (BPA) is a widely used chemical in polycarbonate plastic and epoxy resins.

- Consumer exposure via food can occur through migration of BPA from food contact materials
- Concern has been raised because of potential toxic and hormonal properties of BPA
- Hazard assessments by major regulatory and advisory bodies are in agreement that the overall no-observed-adverse-effect level (NOAEL) for BPA from robust data is 5 mg/kg body weight/day. This is minimally five hundred-fold above conservative estimates of human exposure, including in bottle-fed infants.
- Several areas of uncertainty remain in the risk assessment of BPA:

Effects have been reported from animal experiments on neurobehaviour following exposure to BPA during the developmental period at doses below the overall NOAEL

Kinetics of absorption, metabolism and excretion of BPA show important differences between primates, including humans (lower internal dose), and rodents, and between routes of exposure, so care is needed in extrapolation of animal studies to humans;

Many countries have banned use of BPA completely or in baby products as a precautionary approach.

Refs:

- Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009
- WHO. INFOSAN Information Note No. 5/2009 - Bisphenol A. *WHO*, 2009.

Endocrine disorders and children

ENDOCRINE DISRUPTING CHEMICALS IN MUNICIPAL WASTEWATER

- ❖ Persistent pharmaceutical pollutants
- ❖ Personal care products pollutants
 - Consumption of oral contraceptives containing ethinylestradiol contaminates waste water
 - This strong estrogen is unmetabolized excreted through the urine and its clearance through bacteria in wastewater is incomplete.
 - Ethinylestradiol is present, in biologically active concentrations in waste water drainages into rivers and this has profound effects on aquatic life in certain areas

<<READ SLIDE>>

There is good evidence that the consumption of oral contraceptives containing ethinylestradiol contaminates waste water

This strong estrogen is unmetabolized excreted through the urine and its clearance through bacteria in wastewater is incomplete.

Therefore, ethinylestradiol is present, in biologically active concentrations in waste water drainages into rivers and this has profound effects on aquatic life in these areas

Refs:

•Bjorkblom C et al. Estrogenic and androgenic effects of municipal wastewater effluent on reproductive endpoint biomarkers in three-spined stickleback (*Gasterosteus aculeatus*). *Environ Toxicol Chem.* 2009, 28:1063-1071.

•Lee YM et al. Endocrine disrupting compounds (EDC) in municipal wastewater treatment: a need for mass balance. *Environ Technol.* 2004, 25:635-645.

Endocrine disorders and children

EXAMPLE OF PLANS ON HOW TO DISPOSE OF PHARMACEUTICALS

- ❖ US: Denver Area - the Metro Wastewater Reclamation District is the wastewater treatment authority for most of the metropolitan Denver area.
- ❖ Drug disposal guidelines on February 2007 were issued to address public health and environmental concerns.
- ❖ The Metro District prefers that unused drugs not be flushed down the toilet.

<<READ SLIDE>>

More information at www.metrowastewater.com/Pages/default.aspx – accessed 17 June 2011

Endocrine disorders and children

EXAMPLE OF PLANS ON HOW TO DISPOSE OF PHARMACEUTICALS

❖ Preferred option

- ❖ Take advantage of community pharmaceutical take-back programs that allow you to bring unused drugs to central locations for proper disposal. Different pharmacies offer different programs. Contact your local pharmacy.

❖ Second option

- ❖ Remove the prescription drug or medication from the original container and mix it with an undesirable substance such as used coffee grounds or kitty litter.
- ❖ Put that mixture in a non-descript container that won't leak such as an empty can or a sealable bag. This ensures the drugs aren't diverted for non-medical use or accidentally ingested by children or pets.
- ❖ Dispose of these containers in the trash.

www.metrowastewater.com/Pages/default.aspx

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More information at www.metrowastewater.com/Pages/default.aspx – accessed 17 June 2011

Endocrine disorders and children

WHY IS THERE CONCERN ABOUT CHILDREN?

New recognition of

- ❖ Special vulnerability of child and developing fetus to toxicants and physical agents

- ❖ Effects are exacerbated by adverse environmental and social conditions



- ❖ Potential developmental effects of endocrine disruptors

Although the special susceptibility of children has been known for decades (every paediatrician knows it!) it is only in the last decade that this vulnerability has been NEWLY recognized.

There is new, more detailed information about the specific effects of some chemicals on the developing fetus.

There is new, more sophisticated knowledge about toxicokinetics and toxicodynamics.

In the more degraded environments, the adverse effects are further exacerbated or magnified. Poverty may force people to eat contaminated foodstuffs and malnutrition and stress may predispose to adverse effects.

Endocrine disorders and children

ROUTES OF EXPOSURE

- ❖ Ingestion
- ❖ Inhalation
- ❖ Dermal absorption
- ❖ Transplacental
- ❖ Breast milk



WHO

Endocrine disrupting chemicals may be ubiquitous in the environment. Many of them are persistent organic pollutants that are deposited in sediment or water and then bioaccumulate in the food supply. Some are aerosolized – children living on or near farms or industrial chemical plants are at increased risk for this exposure.

The rate of absorption depends on the chemical properties, amount of the chemical, length of exposure and the physical state of the molecule. There are also other factors that may contribute to increased absorption. Skin absorption is higher when there is vasodilatation (e.g. in summer, or with heating). Respiratory absorption is many times higher when breathing is more rapid (e.g. when playing or running).

Transplacental exposures are known to occur with many chemicals and are thought to be the most dangerous for the future health of the child.

Endocrine disorders and children

WHY IS THERE CONCERN ABOUT CHILDREN?

- ❖ Increased exposures may occur through specific routes:
 - ❖ Transplacental
 - ❖ Breast milk
- ❖ During critical developmental processes
 - ❖ "Windows of susceptibility"
- ❖ Immature metabolic pathways
- ❖ Latent effects triggered by early exposure

In the case of children, there is special concern for several reasons.

- Increased exposures may occur through specific routes, that are UNIQUE to children:
 - Transplacental – most of the child's exposure through the mother occurs *in utero*.
 - Breast milk – many of the persistent organic pollutants have been found in breast milk, raising controversies concerning the desirability of breastfeeding. **WHO strongly supports breastfeeding –because research has demonstrated that "contaminated" human milk has a more positive effect on the growth and development of small children than artificial formula.**
- ❖ During critical developmental processes:
 - "Windows of susceptibility".
- ❖ Immature metabolic pathways.
- ❖ Latent effects are triggered by early exposure.

Refs:

- ❖ Pronczuk J. Guest editorial: Breast milk: An optimal food, *Environmental Health Perspectives*, 2004, 112 (13):A722
- ❖ WHO/EURO. Results of the third round of WHO-coordinated exposure study on the levels of PCBs, PCDDs and PCDFs in human milk. *Organohalogen Compounds*, 2002 56:311.

Endocrine disorders and children

TIMING OF EXPOSURE – A CRITICAL FACTOR

- ❖ Exposure during “programming” – permanent changes
- ❖ Exposure during adulthood – homeostasis, no effects
- ❖ Exposure to same level during different life stages: different effects
- ❖ *Timing* of exposure will determine both the *nature* and *severity* of effects

- ❖ Exposure during “programming” (fetal stage) may result in permanent changes.
- ❖ Exposure during adulthood tends to be compensated by homeostasis and may not result in detectable effects.
- ❖ Exposure to same level during different life stages may produce different effects.
- ❖ Timing of exposure will determine *both* the nature and severity of effects.

Endocrine disorders and children

WHY IS THERE GROWING CONCERN?

- ❖ Many chemicals have hormonal activity
- ❖ Reproductive/developmental effects observed in wildlife
- ❖ Effects demonstrated in studies in experimental animals
- ❖ Increasing trends of hormone-related cancers
- ❖ Neurobehavioural deficits in children
- ❖ Increasing trends in certain abnormalities in children: hypospadias, cryptorchidism, precocious puberty

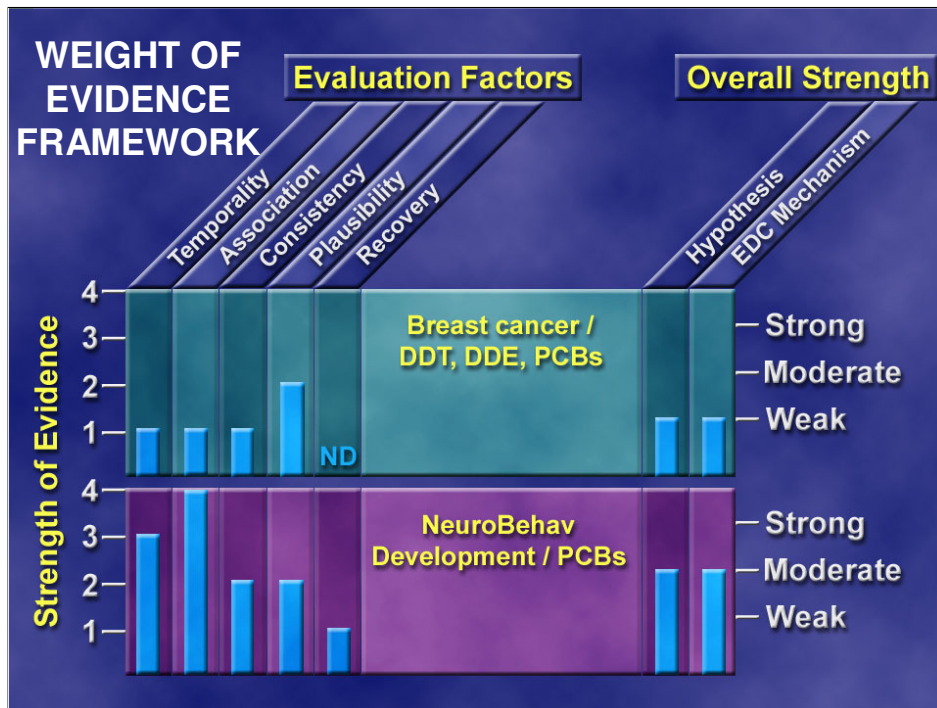
- Many chemicals have hormonal activity.
- Reproductive/developmental effects observed in wildlife.
- Effects demonstrated in studies in experimental animals.
- Increasing trends of hormone-related cancers.
- Neurobehavioural deficits in children.

Endocrine disorders and children

NEW KNOWLEDGE IS DIFFICULT TO GENERATE

- ❖ Endocrine effects are functional (not a toxic end-point)
- ❖ Effects occur at multiple sites
- ❖ Effects occur through multiple mechanisms
- ❖ There is *developmental* sensitivity – particular risks for:
 - "programming" of the fetus
 - child's development
- ❖ Information on exposure is very limited

- Endocrine effects are functional – the effects are not a toxic end-point, but a dysfunction.
- Effects occur at many sites.
- Effects occur through several mechanisms – receptor-mediated responses include the binding of the hormone to its receptor at the cell surface, cytoplasm or nucleus, followed by a complex series of events that lead to changes in gene expression characteristic for a specific hormone. Changes in gene expression represent an early and critical step in the regulation of normal biological functions (e.g. cell proliferation and differentiation).
- *Developmental* sensitivity leads to particular risks for:
 - "programming" of the fetus; and
 - children's development.
- Information on exposure is very limited.



This diagram illustrates the WEIGHT OF EVIDENCE approach from the Global assessment of the state-of-the-science of endocrine disruptors, published by WHO in 2002.

Evidence that relates endocrine disrupting chemicals with neurodevelopmental disorders is "moderate", and evidence relating them with breast cancer is "weak".

PCBs: polychlorinated biphenyls

DDT: dichlorodiphenyl trichloroethane.

DDE: 1,1-dichloro-2,2-bis(chlorophenyl) ethylene

Ref:

❖WHO. Global assessment of the state-of-the-science of endocrine disruptors. WHO, 2002. Available at www.who.int/pcs/publications/new_issues/endocrine_disruptors/en/index.html – accessed 15 June 2011.

Endocrine disorders and children

PERSISTENT ORGANIC POLLUTANTS (POPs) IN HUMAN MILK IN FAROE ISLANDS

- ❖ Concentrations of PCBs (polychlorinated biphenyls) and PBDEs (polybrominated diphenyl ethers) in human milk showed a clear increase over time, and their concentrations from 1999 are among the highest reported so far from Europe, with results of individual samples ranging from 4.7 to 13 nanograms/g fat
- ❖ Although remote from pollution sources, the Faroe Islands show high concentrations of POPs in human milk, particularly PCBs, but also PBDEs.

Fangstrom et al. Environ Health, 2005

<<READ SLIDE>>

Ref.

•Fangstrom B et al. A retrospective study of PBDEs and PCBs in human milk from the Faroe Islands
Environ Health, 2005, 14,4:12

PCBs: polychlorinated biphenyls

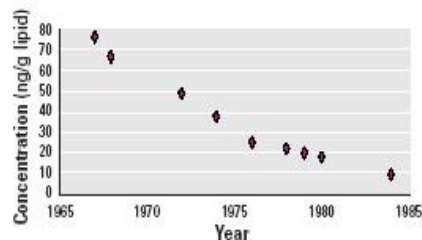
POPs: Persistent organic pollutants

PBDEs: Polybrominated diphenyl ethers

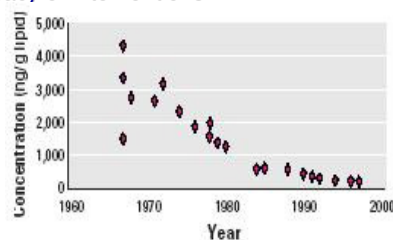
Endocrine disorders and children

PERSISTENT ORGANIC POLLUTANTS IN BREAST MILK

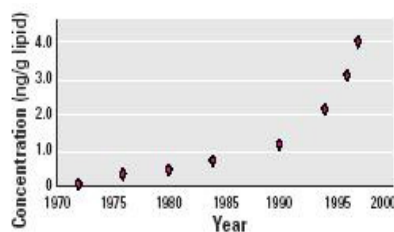
An example of the efficacy of interventions



Dieldrin in breast milk – Sweden



DDT in breast milk – Sweden



PBDE in breast milk – Sweden

Solomon, 2002

- Research on environmentally-related chemical contaminants in milk has been going on for several decades in several countries. Exposure varies according to local chemical use and different diets.

- Breast milk contamination is an important indicator of environmental and public health problems. Many of the POPs (organochlorine pesticides, PCBs and dioxins) have decreased in the countries that have placed bans on their use and production. However, levels of PBDEs are rising.

- When dieldrin and aldrin became internationally used, their levels in breast milk rose dramatically. As countries banned their use, the prevalence of detection remained high, but levels in breast milk dropped significantly. In Sweden, as seen on the figure on the left of the slide, there has been a clear decrease in average levels of Dieldrin in breast milk over several decades.

- Use of DDT in Sweden was restricted in 1970 and banned in 1975. We can see in the figure on the right how the levels of DDT in breast milk declined in direct correlation with the time since its restriction. Other countries where studies have revealed a decrease in the levels over the years include Canada, China, Hong Kong, Special Administrative Region, the Czech Republic, Denmark, India, Israel, Japan, Norway, Switzerland, Turkey, the United Kingdom and Yugoslavia.

- PBDEs came into use as flame retardants and are used in carpets, furniture cushions and construction materials. They may affect hormone function and may be toxic to the developing brain. PBDEs have been associated with non-Hodgkin lymphoma in humans, cancer in rodents and disruptions of thyroid hormone balance. Mothers exposed to PBDEs pass the suspected neurotoxicant to their unborn children. In the figure at the bottom of the slide we can see that the concentrations of PBDE in breast milk in Sweden show a logarithmic increase.

Clearly, restrictions and bans do work, but the problem remains as new threats come "out of the woods".

PCBs: polychlorinated biphenyls.

DDT: dichlorodiphenyltrichloroethane.

PBDEs: polybrominated diphenyl ethers.

Refs:

•Solomon GM. Chemical contaminants in breast milk: time trends and regional variability. *Environmental Health Perspectives*, 2002, 110: A339.

•Washam C. Suspect inheritance: potential neurotoxicants passed to fetuses. *Environmental Health Perspectives*, 2003, 111: A480.

Figures: Solomon, *Chemical contaminants in breast milk: time trends and regional variability. Environmental Health Perspectives*. 2002, 110 (6), A339. Reproduced with permission from EHP.

EPIGENETICS AND DISEASE

After many years of investigation, researchers are beginning to understand the mechanisms by which estrogens and other hormones, especially during development, can alter the genetic program of target cells without altering the sequence of DNA itself

<<READ SLIDE>>

Endocrine disorders and children

EPIGENETICS MECHANISMS AND ENDOCRINE DISRUPTION

- ❖ The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences
- ❖ Such environmentally-induced changes can occur at all levels of biological organization, from the molecular to the organism's behavior and place in society, and tend to be amplified in their consequences as they ascend through these levels
- ❖ Ultimately, these influences may be epigenetic in nature, inducing mitotically heritable alterations in gene expression without changing the DNA

<<READ SLIDE>>

Ref.

•Crews D, McLachlan J. Epigenetics, evolution, endocrine disruption, health and disease. *Endocrinology*. 2006,147(6)S4S10.

Endocrine-disrupting chemicals (EDCs) in the environment have been linked to human health and disease. This is particularly evident in compounds that mimic the effects of estrogens. Exposure to EDCs early in life can increase risk levels of compromised physical and mental health. Epigenetic mechanisms have been implicated in this process. Transgenerational consequences of EDC exposure is also discussed in both a proximate (mechanism) and ultimate (evolution) context as well as recent work suggesting how such transmission might become incorporated into the genome and subject to selection. We suggest a perspective for exploring and ultimately coming to understand diseases that may have environmental or endocrine origins.

Endocrine disorders and children

CRITICAL DATA GAPS PRIORITIZED FOR FUTURE RESEARCH INITIATIVES

- ❖ Etiologic research that focuses on environmentally relevant levels of endocrine-disrupting chemicals and body size in relation to normal puberty as well as its variants
- ❖ Exposure assessment of relevant endocrine- disrupting chemicals during critical windows of human development
- ❖ Basic research to identify the primary signal(s) for the onset of gonadotropin releasing hormone–dependent/central puberty and gonadotropin-releasing hormone–independent/ peripheral puberty

<<READ SLIDE>>

Endocrine disorders and children

CRITICAL ROLE OF HEALTH AND ENVIRONMENT PROFESSIONALS

- ❖ Diagnose and treat endocrine diseases
- ❖ Take the environmental history to the patient and his/her family
- ❖ Report cases that can be related to environmental exposure, as they may be sentinel cases
- ❖ Promote research on endocrine disorders related to main environmental threats
- ❖ Advocate to protect children and mothers from contaminants' exposure

Endocrine disorders and children

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