

TRAINING FOR THE HEALTH SECTOR
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**CASE STUDIES OF
FEMALE REPRODUCTIVE
HEALTH AND THE
ENVIRONMENT**
(Draft for review)

Training Module 3
Children's Environmental Health
Public Health and the Environment
World Health Organization
www.who.int/ceh

October 2011 1

<<NOTE TO USER: Please add details of the date, time, place and sponsorship of the meeting for which you are using this presentation in the space indicated.>>

<<NOTE TO USER: This is a large set of slides from which the presenter should select the most relevant ones to use in a specific presentation. These slides cover many facets of the issue. Present only those slides that apply most directly to the local situation in the region. You should replace the case studies as well as the figures with those relevant to your area and your audience>>

<<NOTE TO USER: This module presents several examples of risk factors that affect reproductive health. 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, endocrine disruptors, occupational exposures; or disease outcomes, such as developmental origins of disease, reproductive effects, neurodevelopmental effects, immune effects, respiratory effects, and others.>>

<<NOTE TO USER: For more information on reproductive health, please visit the website of the Department of Reproductive Health and Research at WHO: www.who.int/reproductivehealth/en/>>

LEARNING OBJECTIVES

To understand the importance of specific case studies involving toxicant exposure and the resulting endpoints for female reproductive health

1. Diethylstilbestrol (DES)
2. Methylmercury
3. Pesticides
4. Dioxins

<<READ SLIDE.>>

This presentation will provide you with specific examples of environmental exposure scenarios and their impacts on female reproductive health.

By the end of the presentation, individuals will be able to understand and recognize the importance of specific case studies involving toxicant exposure and the resulting endpoints for female reproductive health. Specific case studies will be reviewed to emphasize unique pathways of exposure, the mechanisms of action of certain environmental agents, and documented health endpoints related to female reproductive health. These case studies will include an overview of exposure to diethylstilbestrol, methylmercury, pesticides, and dioxins.

<<NOTE TO USER: This module will present case studies of specific exposure scenarios, thus if you would like more background information about female environmental reproductive health, please reference Module 1: Reproductive Environmental Health and Module 2: Female Environmental Reproductive Health.>>

Ref:

•WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference. New York, United States of America, *World Health Organization*, 1946.

FEMALE REPRODUCTIVE HEALTH

- ❖ Disorders related to female reproductive health may develop during fetal development, childhood, adolescence, or adulthood
- ❖ Multiple causes for alterations in female reproductive functioning
- ❖ Recent focus on potential environmental causes



WHO

3

Reproductive health involves all of the reproductive processes, functions and systems at all stages of human life. This definition implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so. Women should have access to appropriate health care services that will enable them to go safely through pregnancy and childbirth and provide couples with the best chance of having a healthy infant.

Reproductive health is a universal concern, but is of special importance for women particularly during the reproductive years.

Several female reproductive disorders may affect the health status and overall quality of life of a woman. Female reproductive disorders may develop during various life phases of the female. Alterations in proper reproductive functioning may be the result of various occurrences and experiences throughout fetal development, childhood, adolescence, or adulthood.

While much is known about the female reproductive system, its development, and many causes of specific disorders, the research pertaining to the mechanisms of action for certain pathologies is still largely unknown. However, exposure to environmental contaminants has been proposed in recent years to potentially contribute to female reproductive disorders. Research has been focused on exposures that occur during critical periods of development, however this is an emerging field of research that demands greater scientific investigation.

Refs:

•UNDP/UNFPA/WHO/World Bank. Social science methods for research on reproductive health topics. Geneva, Switzerland, *UNDP/UNFPA/WHO/World Bank Special Programme on Research, Development, and Training in Human Reproduction*, 2006. Available at whqlibdoc.who.int/hq/1999/WHO_RHR_HRP_SOC_99.1.pdf - accessed 22 June 2010.

•WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference. New York, United States of America, *World Health Organization*, 1946.

Image: WHO

REPRODUCTIVE HEALTH AND THE ENVIRONMENT

- ❖ Focuses on exposure to contaminants found in the environment, specifically during critical periods of development.
- ❖ All the physical, chemical, biological and social factors that may affect the origin, growth, development and survival of a person in a given setting.

Some examples include:

- **Specific synthetic chemicals**
- **Some metals**
- **Air contaminants**

Still an emerging issue!

4

Reproductive health and the environment focuses on exposures to environmental contaminants during critical periods of human development. These periods are directly related to reproductive health throughout the life course, including the period before conception, at conception, fertility, pregnancy, child and adolescent development, and adult health. Exposures to different environmental contaminants may influence reproductive health status of the individual and its offspring, through the process of epigenetics.

Environmental toxins may potentially induce effects in human reproductive processes. However, the extent of this hypothesis must be supported through greater levels of research. Currently, women's health care providers and gynecologists are growing increasingly aware of the potential for environmental factors to influence female health and reproductive status.

Refs:

•WHO. Global assessment of the state of the science of endocrine disruptors. Geneva, Switzerland, *WHO/PCS/EDC*, 2002. Available at www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/ - accessed 23 June 2010.

•Woodruff T. Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: executive summary. *Fertility and Sterility*, 2003, 89 (2),1-20.

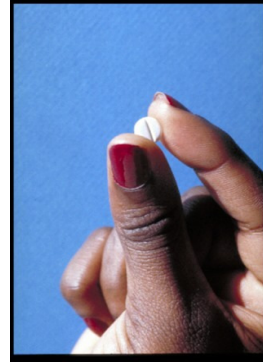
<< **NOTE TO USER: For further information, please refer to the module on "Developmental and Environmental Origins of Disease">>**

Case Study 1: Diethylstilbestrol (DES)

The first case study that will be presented will be about exposure to the drug diethylstilbestrol (DES). This is a significant example, as DES was widely used several decades ago and has since become the model for estrogenic effects of endocrine-disrupting chemicals. Potential endocrine disruptors include chemicals, pesticides, disinfection by-products, plants, drugs, among others.

CASE STUDY 1: DIETHYLSTILBESTROL (DES)

- ❖ Synthetic form of estrogen
- ❖ Used to promote fetal growth and block spontaneous abortion
- ❖ In the U.S, 5 to 10 million pregnant women were exposed to DES (from 1938 to 1971)
- ❖ In 1971, the Food and Drug Administration (FDA) advised physicians to stop prescribing DES to pregnant women because it was linked to a rare vaginal cancer in female offspring



WHO

6

<<READ SLIDE.>>

Diethylstilbestrol (DES) is a chemical compound that acts as a synthetic estrogen within the body. Throughout the United States, doctors prescribed diethylstilbestrol (DES) to five to ten million pregnant women between around 1940 and 1970 as a medication to protect against adverse health effects during pregnancy, including protection from spontaneous abortion and in order to promote fetal growth. It was discovered after administration of this medication that children of mothers exposed to diethylstilbestrol (DES) experienced developmental disorders and a greater risk for developing vaginal cancer.

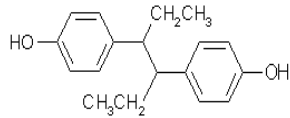
Many others were exposed to diethylstilbestrol (DES) through prenatal vitamins and in food supply because it was given to cattle until 1979 in the US.

Refs:

- CDC. About DES. *Centers for Disease Control*. Available at www.cdc.gov/des/consumers/about/index.html - accessed 21 March 2010.
- Baird DD, Newbold R. Prenatal diethylstilbestrol (DES) exposure is associated with uterine leiomyoma development. *Reproductive Toxicology*, 2005, 20:81–84 115.
- Diamanti-Kandarakis E. et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. 2009. *Endocrine reviews*. 30(4): 293-342.
- Hoover RN et al. Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol. *N Engl J Med*. 2011; 365:1304-1314.
- McLachlan JA. Commentary: prenatal exposure to diethylstilbestrol (DES): a continuing story. *International Journal of Epidemiology*, 2006, 35:868 – 870.
- McLachlan JA et al. Reduced fertility in female mice exposed transplacentally to diethylstilbestrol (DES). *Fertility and Sterility*, 1982, 38: 364 –371.

Image: WHO

WOMEN EXPOSED TO DIETHYLSTILBESTROL (DES) WHILE PREGNANT



4,4'-(1,2-diethyl-1,2-ethene-diyl)bisphenol
diethylstilbestrol
DES

www.chemistrydaily.com/chemistry/Diethylstilbestrol

Women who took DES while pregnant face a 30% greater risk for breast cancer

Women who know that they were exposed to DES during pregnancy should follow a regular schedule for breast cancer screenings

7

Women who took diethylstilbestrol (DES) while pregnant are at an increased risk for developing breast cancer. Studies have consistently demonstrated a 30% increased risk for women prescribed DES while pregnant. A study conducted by Titus-Ernstoff in 2001 included more than 6,000 women and compared breast cancer rates of women exposed to DES with rates of women who were not exposed. This study followed participants over a longer period of time than earlier research on breast cancer risks associated with DES. The findings confirmed an increased breast cancer risk of approximately 30% for women prescribed DES while pregnant. Considering breast cancer risks across a lifetime, one in six women prescribed DES during pregnancy will get breast cancer. In comparison, only one in eight unexposed women will get breast cancer across their lifetime.

The 2002 National Cancer Institute recommends DES-exposed women follow the National Cancer Institute breast cancer-screening schedule for their age category. Mammography is recommended every 1 to 2 years for women in their forties.

Refs:

- CDC. About DES. Atlanta, Georgia, *Centers for Disease Control*, 2003. Available at www.cdc.gov/des/consumers/about/index.html - accessed 21 March 2010.
- Diamanti-Kandarakis E. et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. 2009. *Endocrine reviews*. 30(4): 293-342.
- Hoover RN et al. Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol. *N Engl J Med*. 2011; 365:1304-1314.
- Ma L et al. Abdominal B (AbdB) Hoxa genes: regulation in adult uterus by estrogen and progesterone and repression in müllerian duct by the synthetic estrogen diethylstilbestrol (DES). *Developmental Biology*, 2000, 197:141-154.
- McLachlan JA et al. Reduced fertility in female mice exposed transplacentally to diethylstilbestrol (DES). *Fertility and Sterility*, 1984, 38: 364 - 371.
- Newbold RR, Moore AB, Dixon D. Characterization of uterine leiomyomas in CD-1 mice following developmental exposure to diethylstilbestrol (DES). *Toxicol Pathology*, 2002, 30:611-616.
- Titus-Ernstoff L et al. Long term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *British Journal of Cancer*, 2001, 84, 126-133.

From 1940 through the 1960s, diethylstilbestrol (DES), a synthetic oestrogen, was given to pregnant women to prevent pregnancy complications and losses. Subsequent studies showed increased risks of reproductive tract abnormalities, particularly vaginal adenocarcinoma, in exposed daughters. An increased risk of breast cancer in the DES-exposed mothers was also found in some studies. In this report, we present further follow-up and a combined analysis of two cohorts of women who were exposed to DES during pregnancy. The purpose of our study was to evaluate maternal DES exposure in relation to risk of cancer, particularly tumours with a hormonal aetiology. DES exposure status was determined by a review of medical records of the Mothers Study cohort or clinical trial records of the Dieckmann Study. Poisson regression analyses were used to estimate relative risks (RR) and 95% confidence intervals (CI) for the relationship between DES and cancer occurrence. The study results demonstrated a modest association between DES exposure and breast cancer risk, RR = 1.27 (95% CI = 1.07-1.52). The increased risk was not exacerbated by a family history of breast cancer, or by use of oral contraceptives or hormone replacement therapy. We found no evidence that DES was associated with risk of ovarian, endometrial or other cancer.

Image: www.chemistrydaily.com/chemistry/Diethylstilbestrol - accessed 22 March 2010. This image is public domain.

REPRODUCTIVE HEALTH ENDPOINTS OF DIETHYLSTILBESTROL (DES) DAUGHTERS

- ❖ **Clear cell adenocarcinoma**
 - A rare type of vaginal and cervical cancer. Approximately one in 1,000 (0.1%) of DES daughters will be diagnosed with clear cell adenocarcinoma
- ❖ **Reproductive tract structural differences**
 - T-shaped uterus, hooded cervix, cervical cockscomb, and pseudopolyp
- ❖ **Pregnancy complications**
 - Ectopic (tubal) pregnancy and pre-term (early) delivery
- ❖ **Infertility**

8

• Following the discovery of reproductive health effects in the daughters of the women who took diethylstilbestrol (DES) during pregnancy, the term “DES daughters” was coined. DES daughters represent the women that were exposed *in utero* to DES.

• The first health problem identified as being associated with DES exposure was clear cell adenocarcinoma (CCA), a rare form of vaginal and cervical cancer. DES Daughters are 40 times more likely to develop CCA of the vagina and cervix than women not exposed to DES. Approximately one of every 1,000 women exposed to DES prenatally will be diagnosed with CCA of the vagina and/or the cervix. Before the use of DES, CCA of the vagina and cervix only occurred in women past childbearing age. In contrast, DES Daughters have been diagnosed with CCA of the vagina and cervix at as early as age 8 and up to their late teens and early 20s. In addition, recent studies have indicated that some DES Daughters have been diagnosed with CCA of the vagina and cervix in their 30s and 40s.

• Some studies have shown that up to one third of DES Daughters have had some form of reproductive tract abnormality of the cervix, uterus, or fallopian tubes, including vaginal adenosis or cervical changes (such as collars, hoods, septae, and cockscombs).

Research demonstrates that DES Daughters are at an increased risk for problems during pregnancy, specifically, increased risk for premature delivery. Approximately 20% of DES Daughters experience pre-term labor, compared with 8% of unexposed women.

• DES Daughters are also at an increased risk for ectopic (tubal) pregnancy and miscarriage. DES Daughter's risk for ectopic pregnancy are between 3-5 times higher than the risk for a woman not exposed to DES. Furthermore, almost 20% of DES Daughters have been found to have a miscarriage during their first pregnancy compared to 10% of unexposed women who experience miscarriage.

• An infertility study showed that 24% of DES Daughters were unable to become pregnant, compared with 18% of women not exposed to DES. DES exposure was most strongly associated with infertility caused by uterine problems (such as the shape of the uterus).

Recent research findings raise additional concerns about health problems associated with DES exposure for women exposed before birth.

Refs:

- Diamanti-Kandarakis E. et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. 2009. *Endocrine reviews*. 30(4): 293-342.
- Hatch EE et al. Cancer risk in women exposed to diethylstilbestrol in utero. *Journal of the American Medical Association*, 1998, 280, 630–634.
- *The association between in utero exposure to diethylstilbestrol (DES) and clear cell adenocarcinoma (CCA) of the vagina and cervix is well known, yet there has been no systematic study of DES-exposed daughters to determine whether they have an increased risk of other cancers. As many as 3 million women in the United States may have been exposed to DES in utero.*
- *Objective.— To determine whether women exposed to DES in utero have a higher risk of cancer after an average of 16 years of follow-up.*
- *Design. A cohort study with mailed questionnaires and medical record review of reported cancer outcomes.*
- *Participants. A cohort of 4536 DES-exposed daughters (of whom 81% responded) and 1544 unexposed daughters (of whom 79% responded) who were first identified in the mid-1970s.*
- *Main Outcome Measures. Cancer incidence in DES-exposed daughters compared with population-based rates and compared with cancer incidence in unexposed daughters.*
- *Results. To date, DES-exposed daughters have not experienced an increased risk for all cancers (rate ratio, 0.96; 95% confidence interval [CI], 0.58-1.56) or for individual cancer sites, except for CCA. Three cases of vaginal CCA occurred among the exposed daughters, resulting in a standardized incidence ratio of 40.7 (95% CI, 13.1-126.2) in comparison with population-based incidence rates. The rate ratio for breast cancer was 1.18 (95% CI, 0.56-2.49); adjustment for known risk factors did not alter this result.*
- Herbst AL et al. Behavior of estrogen-associated female genital tract cancer and its relation to neoplasia following intrauterine exposure to diethylstilbestrol (DES). *Gynecology Oncology*, 1999, 76, 147–156.
- Hoover RN et al. Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol. *N Engl J Med*. 2011; 365:1304-1314.
- Kaufman RH et al. Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. *Obstetrical Gynecology*, 2000, 96, 483–489.
- *Objective: To evaluate long-term pregnancy experiences of women exposed to diethylstilbestrol (DES) in utero compared with unexposed women.*
- *Methods: This study was based on diethylstilbestrol-exposed daughters, the National Collaborative Diethylstilbestrol Adenosis cohort and the Chicago cohort, and their respective nonexposed comparison groups. Subjects who could be traced were sent a detailed questionnaire in 1994 that contained questions on health history, including information on pregnancies and their outcomes. We reviewed 3373 questionnaires from exposed daughters and 1036 questionnaires from unexposed women.*
- *Results: The response rate was 88% among exposed and unexposed women. Diethylstilbestrol-exposed women were less likely than unexposed women to have had full-term live births and more likely to have had premature births, spontaneous pregnancy losses, or ectopic pregnancies. Full-term infants were delivered in the first pregnancies of 84.5% of unexposed women compared with 64.1% of exposed women identified by record review (relative risk [RR] 0.76, confidence interval [CI] 0.72, 0.80). Preterm delivery of first births occurred in 4.1% of unexposed compared with 11.5% of exposed women, and ectopic pregnancies in 0.77% of unexposed compared with 4.2% of exposed women. Spontaneous abortion was reported in 19.2% of DES-exposed women compared with 10.3% in control women (RR 2.00, CI 1.54, 2.60). According to complete pregnancy histories (many women had more than one pregnancy), preterm births were more common in DES-exposed women (19.4% exposed versus 7.5% unexposed (RR 2.93 CI 2.23, 3.86). Second-trimester spontaneous pregnancy losses were more common in DES-exposed women (6.3% versus 1.6%; RR 4.25, CI 2.36, 7.66). More first-trimester spontaneous abortions occurred in DES-exposed women than in controls (RR 1.31, CI 1.13, 1.53), and DES-exposed women had at least one ectopic pregnancy more often than unexposed women (RR 3.84, CI 2.26, 6.54).*
- *Conclusion: Pregnancy outcomes in DES-exposed women were worse than those in unexposed women.*
- Palmer R et al. Infertility among women exposed prenatally to diethylstilbestrol. *American Journal of Epidemiology*, 2001, 154, 316–321.
- *Although it is well established that women exposed to diethylstilbestrol in utero have an increased risk of spontaneous abortion, ectopic pregnancy, and preterm delivery, it is not known whether they also have an increased risk of infertility. The authors assessed this question in data from a collaborative follow-up study of the offspring of women who took diethylstilbestrol during pregnancy. In 1994, 1,753 diethylstilbestrol-exposed and 1,050 unexposed women from an ongoing cohort study (National Cooperative Diethylstilbestrol Adenosis Study and Dieckmann cohorts) provided data on difficulties in conceiving and reasons for the difficulty. Age-adjusted relative risks were computed for the association of diethylstilbestrol exposure with specific types of infertility. A greater proportion of exposed than unexposed women were nulligravid (relative risk (RR) = 1.3, 95% confidence interval (CI): 1.1, 1.5), and a greater proportion had tried to become pregnant for at least 12 months without success (RR = 1.8, 95% CI: 1.6, 2.1). Diethylstilbestrol exposure was significantly associated with infertility due to uterine and tubal problems, with relative risks of 7.7 (95% CI: 2.3, 25) and 2.4 (95% CI: 1.2, 4.6), respectively. The present findings indicate that diethylstilbestrol-exposed women have a higher risk of infertility than do unexposed women and that the increased risk of infertility is primarily due to uterine or tubal problems.*

DIETHYLSTILBESTROL (DES) DAUGHTERS AND BREAST CANCER

A cohort of DES-exposed and unexposed women has been followed since the 1970s by mailed questionnaires

Women with prenatal exposure to DES have an increased risk of breast cancer after age 40 years

9

In addition to the classic endpoints of reproductive toxicity, *in utero* diethylstilbestrol (DES) exposure has been shown to increase a woman's risk of breast cancer after the age of 40. Women with prenatal exposure to DES seem to have an increased risk of breast cancer development, but only after the age of 40.

Ref:

•Hoover RN et al. Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol. *N Engl J Med.* 2011; 365:1304-1314.

•Palmer JR et al. Prenatal Diethylstilbestrol Exposure and Risk of Breast Cancer. *Cancer Epidemiology, Biomarkers & Prevention*, 2006 15(8); 1509-1514.

It has been hypothesized that breast cancer risk is influenced by prenatal hormone levels. Diethylstilbestrol (DES), a synthetic estrogen, was widely used by pregnant women in the 1950s and 1960s. Women who took the drug have an increased risk of breast cancer, but whether risk is also increased in the daughters who were exposed in utero is less clear. We assessed the relation of prenatal DES exposure to risk of breast cancer in a cohort of DES-exposed and unexposed women followed since the 1970s by mailed questionnaires. Eighty percent of both exposed and unexposed women completed the most recent questionnaire. Self-reports of breast cancer were confirmed by pathology reports. Cox proportional hazards regression was used to compute incidence rate ratios (IRR) for prenatal DES exposure relative to no exposure. During follow-up, 102 incident cases of invasive breast cancer occurred, with 76 among DES-exposed women (98,591 person-years) and 26 among unexposed women (35,046 person-years). The overall age-adjusted IRR was 1.40 [95% confidence interval (95% CI), 0.89-2.22]. For breast cancer occurring at ages 40 years, the IRR was 1.91 (95% CI, 1.09-3.33) and for cancers occurring at ages 50 years, it was 3.00 (95% CI, 1.01-8.98). Control for calendar year, parity, age at first birth, and the factors did not alter the results. These results, from the first prospective study on the subject, suggest that women with prenatal exposure to DES have an increased risk of breast cancer after age 40 years. The findings support the hypothesis that prenatal hormone levels influence breast cancer risk.

DIETHYLSTILBESTROL (DES) AND REPRODUCTIVE HEALTH: CONSIDERATIONS

It is known that:

- ❖ DES mimics estrogen in the body
- ❖ Appropriate estrogen levels are essential for reproductive organ development and healthy functioning throughout various life stages

1. *Could DES exposure be responsible for other female reproductive cancers or fibroids that are not yet recognized?*
2. *Can other estrogenic compounds result in the same female reproductive health endpoints?*

10

<<NOTE TO USER: If desired, you may allow for group discussion of these considerations.>>

<<NOTE TO USER: For more information about estrogenic compounds and the mechanism of action of these chemicals, please refer to Module 1: Reproductive Health and the Environment.>>

Refs:

- Herbst AL et al. Behavior of estrogen-associated female genital tract cancer and its relation to neoplasia following intrauterine exposure to diethylstilbestrol (DES). *Gynecology Oncology*, 1999, 76, 147–156.
- Hoover RN et al. Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol. *N Engl J Med*. 2011; 365:1304-1314.

RECOMMENDATIONS FOR PERSONS EXPOSED TO DIETHYLSTILBESTROL (DES)

- ❖ The health effects of DES exposure for persons as they age are unknown
 - essential that health care providers continue to identify persons exposed to DES and continue to offer increased surveillance
- ❖ Questionable safety of hormonal contraceptive use for DES daughters
- ❖ Necessary to enhance preconception care



Courtesy of Women Make Movies, www.wmm.com

11

There is a lack of research concerning the potential adverse effects of contraception use on daughters exposed to DES. However, due to their levels of estrogens, it is recommended that hormonal methods of contraception are avoided and alternative, hormone-free methods advised for this specific population.

Preconception counseling of women exposed to DES should include a discussion of increased risks of infertility, ectopic pregnancy, miscarriage, premature labor, and premature birth. Diagnostic testing should include a pelvic examination to assess for vaginal anomalies, hysterosalpingogram to assess for upper genital tract anomalies, and an endometrial biopsy for the diagnosis of luteal phase defect. It is also very important that an early diagnosis of pregnancy is ascertained and followed with close monitoring for ectopic pregnancy.

The slide shows the picture of a mother who was exposed to DES while pregnant and her baby girl. The baby in this photo was exposed to DES *in utero* and in later life, suffered from DES-related cervical cancer.

Animal studies show effects beyond the first generation, so DES daughters' children could also be followed up.

Refs:

•Hammes B. Diethylstilbestrol (DES) update: Recommendations for the identification and management of DES-exposed individuals. *Journal of Midwifery and Women's Health*, 2003, 48(1), 19-29.

The 2002 National Cancer Institute recommends DES-exposed women follow the National Cancer Institute breast cancer-screening schedule for women in their age category. Women in their forties and older should be screened every 1 to 2 years with mammography. Women, who are at higher than average risk of breast cancer, based on family history other than DES exposure, should seek expert medical advice about whether they should begin screening before age 40 and the frequency of screening they should consider.

Parts of the routine annual gynecologic examination that are unchanged for the DES in utero-exposed woman include clinical breast examination, bimanual, and rectal examination. Because changes of the vulva have not been associated with DES exposure, inspection of the vulva is routine. The National Cancer Institute guidelines for women of the same age category should be followed regarding mammogram scheduling.

In conducting a speculum examination, excess mucous, which is sometimes present in a DES-exposed woman, may be gently removed with a moist cotton swab. Carefully rotate the speculum so that both the anterior and posterior vaginal walls are visible, allowing the epithelial portion of the vagina to be carefully inspected. Gross adenosis may appear red and granular, whereas squamous metaplasia may be indistinguishable from normal epithelium.

A routine cervical Papanicolaou test is not adequate for DES-exposed daughters. The cervical Papanicolaou test must be supplemented with a special Papanicolaou test of the vagina called a "four-quadrant" Papanicolaou test, in which cell samples are taken from all sides of the upper vagina.

Vaginal and cervical palpation is a crucial part of the DES examination and may provide the only evidence of a clear cell adenocarcinoma, especially on the rare occasion when it is located beneath the mucosa. The entire length of the vagina and fornices should be carefully assessed. Vaginal ridges and structural changes of the cervix may be noted. Areas of thickening or induration should raise suspicion and be biopsied.

•Hoover RN et al. Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol. *N Engl J Med*. 2011; 365:1304-1314.

•McLachlan JA. Commentary: prenatal exposure to diethylstilbestrol (DES): a continuing story. *International Journal of Epidemiology*, 2006, 35:868 – 870.

Image: Courtesy of Women Make Movies, www.wmm.com. Available at www.wmm.com/filmcatalog/collect22.shtml - Accessed 12 July 2010.

Case Study 2: Methylmercury exposure: Lessons from Minamata Bay

The second case study will explain the effects of methylmercury exposure on female reproductive health by describing the disaster of Minamata Bay, Japan.

<<NOTE TO USER: You can find more detailed information in the modules on mercury, developmental origins of disease, neurodevelopmental effects, immune effects, and others.>>

For more information on the effects of mercury on vulnerable populations, please consult:
WHO. Children's Exposure to Mercury Compounds. Available at
www.who.int/ceh/publications/children_exposure/en/index.html

CASE STUDY 2: THE MINAMATA BAY EPIDEMIC

- ❖ In 1953, residents near Minamata bay, Japan, began observing strange health conditions and strange animal behaviors
- ❖ In 1956, formal reported discovery of an “epidemic of unknown disease of the central nervous system”
 - First reference to “Minamata disease”
- ❖ 2,265 victims of Minamata disease have been officially recognized as of 2001 (1,784 of whom had died)

13

- In the year 1953, residents of a Japanese fishing town surrounding the Minamata bay observed that cats had begun to go mad and to die inexplicably. Additionally, fish in the bay were found floating dead in the water and some birds fell into the sea while flying. However, the most alarming discovery was that large number of children in the area were born with a congenital birth defect, known as cerebral palsy. Cerebral palsy is a term used to describe a wide array of non-contagious and non-progressive motor dysfunctions that lead to physical disability.
- On May 1st 1956, a local hospital director formally reported to the public health service that an epidemic was underway in the community. This problem was named “Minamata disease,” and was an unknown condition of the central nervous system.
- Since the time that the disease was discovered, it is estimated that 2,265 victims of Minamata disease have been recognized. Within this group of diagnosed individuals, 1,784 have died.

<<NOTE TO USER: More information about the Minamata Bay problem can be found on the website of the Japanese Institute on Minamata disease: www.nimd.go.jp/english/index.htm>>

Refs:

- Harada, M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Critical Reviews in Toxicology*, 1995, 25; 1-24.
It was in May 1956, that Minamata disease was first officially “discovered” in Minamata city, south-west region of Japan’s Kyushu Island. The marine products in Minamata bay displayed high levels of Hg contamination (5.61 to 35.7 ppm). The Hg content in hair of patients, their family and inhabitants of the Shiranui Sea coastline were also detected at high levels of Hg (max. 705 ppm). Typical symptoms of Minamata disease are as follows: sensory disturbances (glove and stocking type), ataxia, dysarthria, constriction of the visual field, auditory disturbances and tremor were also seen.
- Takeuchi T, Eto K. The pathology of Minamata disease. A tragic story of water pollution. Fukuoka: *Kyushu University Press*, 1999.

DIAGNOSIS: METHYLMERCURY POISONING



en.wikipedia.org/wiki/Image:Minamata_map_illustrating_Chisso_factory_effluent_routes2.png

- ❖ A chemical company had been dumping methylmercury into the Minamata bay
- ❖ Biological sampling determined severe methylmercury poisoning of local residents
- ❖ Residents were exposed to methylmercury by ingestion of polluted fish and shellfish for almost 20 years
- ❖ Biggest concern was fetal methylmercury poisoning
 - ❖ Serious disturbances in mental and motor development

14

- A thorough investigation into the Minamata bay problem revealed extremely high levels of methylmercury chloride in the waters surrounding the Minamata community. The methylmercury chloride, produced as a by-product of a nearby acetaldehyde plant, was being dumped directly into the waters of the Minamata bay.
- Methylmercury, the organic form of the chemical element mercury, is known to accumulate into the aquatic food chain once present in water systems.

The primary route of exposure of methylmercury to the individuals suffering from Minamata disease was found to be maternal consumption of fish and shellfish contaminated with methylmercury. Methylmercury poisoning within the population was confirmed via hair samples. It was determined that the residents of the community had been exposed to methylmercury contaminated fish for several years and even numerous decades.

Fetal developmental disorders were the most common health endpoints in the Minamata bay community. Serious disturbances in mental and motor developments were observed in all cases of fetal methylmercury poisoning. Children showed significant impairments in chewing, swallowing, speech, gait, other coordination and involuntary movement. These symptoms were induced by the diffuse damage to the brain. The Harada et. al study specifically reported that the symptoms of the fetal methylmercury exposure included psychomotor disturbance and intellectual disability, personality disturbance, epileptic fits, and neurological symptoms.

Refs:

- Ekino, S et. al. Minamata disease revisited: An update on the acute and chronic manifestations of methyl mercury poisoning. *Journal of the Neurological Sciences*. 2007, 262:(1-2), 131-144.
 - Harada Y. Congenital (or Fetal) Minamata disease. In: Study group of Minamata disease, ed. Minamata disease. Kumamoto: Kumamoto University, 1968: 93–117.
 - Yorifuji T et al. Long-term exposure to methylmercury and neurologic signs in Minamata and neighboring communities. *Epidemiology*. 2008, 19(1):3-9.
- It is well known that large-scale poisonings caused by methylmercury occurred in Japan (Minamata, in the 1950s) and Iraq. However, in contrast to Iraq, there have been few sound epidemiologic studies in Minamata. We evaluated the effect of methylmercury on neurologic signs using data from a 1971 population-based study. METHODS: Villages in 3 areas were selected for study: the Minamata area (a high-exposure area), the Goshonoura area (a medium-exposure area), and the Ariake area (a low-exposure area). We used place of residence as the exposure indicator. We examined associations between methylmercury exposure and the following neurologic signs measured on clinical examination: paresthesia of whole body, paresthesia of extremities, paresthesia around the mouth, ataxia, dysarthria, tremors, and pathologic reflexes. RESULTS: Total population was 1120 in the high-exposure villages, 1845 in the medium-exposure villages, and 1165 in the low-exposure villages. In the Minamata area, 87% (n=833) of the eligible population (age 10 years and older) participated in the 1971 investigations, in the Goshonoura area, 93% (n = 1450), and in the Ariake area, 77% (n = 755). Compared with subjects in the Ariake area, the subjects in the Minamata area manifested neurologic signs more frequently. The highest prevalence odds ratio was observed for paresthesia around the mouth (1.10; 95% confidence interval = 1.6-8.20). Although residents in the Goshonoura area had been exposed less heavily than those in the Minamata area, Goshonoura residents also had increased prevalence of neurologic signs. CONCLUSION: Long-term exposure to methylmercury has a strong adverse impact on neurologic signs among residents in a local community.*

Image: Minamata bay. Wikimedia Commons.

en.wikipedia.org/wiki/Image:Minamata_map_illustrating_Chisso_factory_effluent_routes2.png - accessed 13 July 2010. This image is public domain.

DEVASTATING HEALTH EFFECTS IN MINAMATA

Health effects in children:

- ❖ congenital cerebral palsy
- ❖ malformation of heart, skeleton, eyes, limbs
- ❖ mental deficits
- ❖ additional severe neuro-developmental disorders

Mothers were often asymptomatic

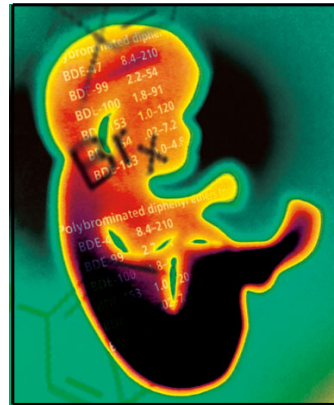
In the decades following the discovery of Minamata disease, infants in the area surrounding the bay were born with severe mental retardation, cerebral palsy, blindness, deafness, and other physical and mental malformations. However, mothers were typically without any sort of symptoms.

Refs:

- Harada, M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Critical Reviews in Toxicology*, 1995, 25; 1-24.
- Takeuchi T, Eto K. The pathology of Minamata disease. A Tragic Story of Water Pollution. Fukuoka: *Kyushu University Press*, 1999.

COMMON SYMPTOMS OF METHYLMERCURY EXPOSURE IN UTERO

- ❖ Mental retardation
- ❖ Cerebral palsy
- ❖ Malformation of limbs and tissues
- ❖ Deficits in motor function and coordination
- ❖ Hearing and vision loss
- ❖ Problems with memory formation



EHP

16

<<READ SLIDE.>>

<<NOTE TO USER: For more information regarding mercury exposure and resulting health effects, please see the training module, "Mercury">>

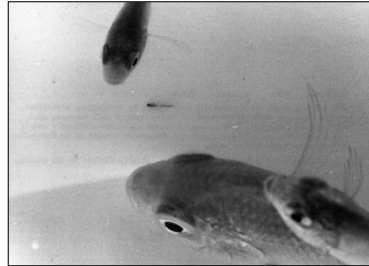
Refs:

- Casarett and Doull. Toxicology. The basic science of poisons. 5th Ed..Ed: Klaassen. *Mc-Graw-Hill*, 1996.
- Grandjean P et al. Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Faroese birth cohort. *Journal of Pediatrics*, 2004, 144(2):169.

Image: Environmental Health Perspectives, 2003, 111:9.

THE TOXICITY OF METHYLMERCURY

- ❖ When consumed, 95% absorbed in the gastrointestinal tract then widely distributed through all tissues
- ❖ Vulnerability of exposure *in utero*
 - ❖ Crosses placenta and blood brain barrier
 - ❖ Can be secreted in breast milk in small amounts
- ❖ **Primary toxicity** - central nervous system
- ❖ **Secondary toxicity** - cardiovascular system



WHO

17

•Methylmercury can result in adverse health endpoints when consumed as part of the diet. Once methylmercury enters the gastro-intestinal tract, approximately 95% of it can be absorbed and carried throughout the body. This means that many different organs can be exposed to the effects of methylmercury.

The most critical period of vulnerability to methylmercury exposure is prenatal as methylmercury is able to cross the placental barrier. This will be explained in more detail in the following slide. Minimal amounts of methylmercury may also be transmitted in maternal breast milk. However it is important to note that breastfeeding is extremely important to the healthy development of an infant. Therefore, the health risks of methylmercury in breast milk do not outweigh the benefits of breastfeeding. The WHO strongly supports exclusive breastfeeding during the first 6 months of life.

• Methylmercury exerts its primary toxicity on the central nervous system, as seen through the neuro-developmental disorders of children in previous slides. Secondary toxicity involves adverse impacts on the cardiovascular system, though greater research is still needed to thoroughly understand this health endpoint.

<<NOTE TO USER: For more information about WHO recommendations for breastfeeding, please refer to the breastfeeding fact sheet, available at www.who.int/nutrition/topics/exclusive_breastfeeding/en/index.html>>

Refs:

•Clarkson TW et al. The toxicology of mercury –current exposures and clinical manifestations. *New England Journal of Medicine*, 2003, 349: 1731.

•Dorea JG. Mercury and lead during breast-feeding. *British Journal of Nutrition*, 2004, 92(1):21.

Hg and Pb are of public health concern due to their toxic effects on vulnerable fetuses, persistence in pregnant and breast-feeding mothers, and widespread occurrence in the environment. To diminish maternal and infant exposure to Hg and Pb, it is necessary to establish guidelines based on an understanding of the environmental occurrence of these metals and the manner in which they reach the developing human organism. In the present review, environmental exposure, acquisition and storage of these metals via maternal-infant interaction are systematically presented. Though Hg and Pb are dispersed throughout the environment, the risk of exposure to infants is primarily influenced by maternal dietary habits, metal speciation and interaction with nutritional status. Hg and Pb possess similar adverse effects on the central nervous system, but they have environmental and metabolic differences that modulate their toxicity and neurobehavioural outcome in infant exposure during fetal development. Hg is mainly found in protein matrices of animal flesh (especially fish and shellfish), whereas Pb is mainly found in osseous structures. The potential of maternal acquisition is higher and lasts longer for Pb than for Hg. Pb stored in bone has a longer half-life than monomethyl-mercury acquired from fish. Both metals appear in breast milk as a fraction of the levels found in maternal blood supplied to the fetus during gestation. Habitual diets consumed by lactating mothers pose no health hazard to breast-fed infants. Instead, cows' milk-based formulas pose a greater risk of infant exposure to neurotoxic substances.

•Mahaffey KR et al. Blood organic mercury and dietary mercury intake: National Health and Nutrition Examination Survey, 1999 and 2000, *Environmental Health Perspectives*, 2004, 112 (5): 562

METHYLMERCURY EFFECTS ON THE DEVELOPING FETUS

- ❖ Developing fetus extremely susceptible to methylmercury toxicity
- ❖ Developing fetal brain is target organ
- ❖ Methylmercury interferes with cellular differentiation
- ❖ Methylmercury changes DNA and RNA molecules
- ❖ Potential results include neurodevelopmental disorders, lowered IQ, malformations of physical structures, and cognitive disorders

18

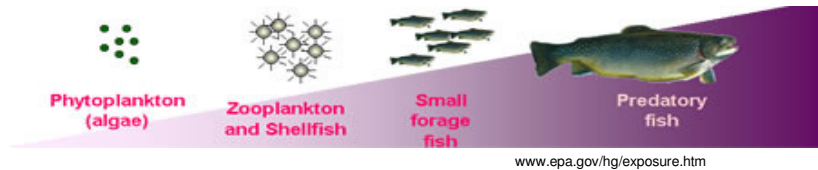
The fetal brain is the target organ for methylmercury toxicity in the developing fetus. Methylmercury interferes with the cell differentiation process necessary for the development of the fetal brain. Methylmercury has been shown to bind with microtubules in the brain and thus hamper normal cell division and migration. Furthermore, there is evidence that methylmercury may bind to, and subsequently augment DNA and RNA molecules. This potential change to the genetic sequence of the DNA and RNA may result in altered gene expressions. This may result in significant developmental health effects.

Refs:

- Aschner J.L. Mercury neurotoxicity: mechanisms of blood-brain barrier transport. *Neurosci. Biobehavior*, 1990, 14,169–176.
- Choi H. Effects of methylmercury on the developing brain, *Prog. Neurobiology*, 1989, 32, 447–470.

DIETARY EXPOSURE TO METHYLMERCURY

- ❖ Methylmercury = organic form of mercury
- ❖ Mercury dumped into Minamata bay from industrial source was integrated directly into the food chain
- ❖ Individuals living in region consumed extremely high levels of methylmercury because of traditional diet of fish



19

Mercury is a heavy metal, an element, and therefore cannot be created or destroyed. Each of its 3 forms: elemental (or metallic), inorganic (mercuric chloride) and organic (methyl- and ethylmercury), induced different health effects.

An investigation at Minamata bay determined that the primary poisonings and subsequent health effects resulted from consumption of methylmercury poisoned fish and shellfish in the Minamata bay region.

Once mercury enters the waterway, it is biotransformed to methylmercury by bacteria. Methylmercury then enters the aquatic food chain, starting from phytoplankton and reaching its highest concentration in carnivorous fish.

Humans are thus exposed to methylmercury via consumption of fish. This consumed methylmercury is degraded slowly by the human body, with 45-70 day half life in adults. The individuals living in the Minamata bay region were therefore exposed to extremely high levels of methylmercury through the dietary pathway.

This figure shows the bioaccumulation of methylmercury (purple bar) up the food chain. The largest, carnivorous fish often have the highest levels of methylmercury contamination.

Refs:

•Clarkson TW et al. The toxicology of mercury –current exposures and clinical manifestations, *N Engl J Med*, 2003, 349:1731

•Mahaffey KR et al. Blood organic mercury and dietary mercury intake: National Health and Nutrition Examination Survey, 1999 and 2000, *Environ Health Perspect.* 2004, 112 (5): 562

Image: Environmental Protection Agency, EPA (2009). Methylmercury exposure. Available at www.epa.gov/hg/exposure.htm - accessed 13 July 2010.

ADDITIONAL EXAMPLE: FAROE ISLANDS STUDY

- ❖ Cohort of 1022 consecutive births in 1986-87 followed 7 and 14 years
- ❖ Cord blood methylmercury levels related to deficits in language attention, memory, decreased auditory evoked potential
- ❖ Neuropsychological dysfunctions (age 7)
 - Language
 - Attention
 - Memory
- ❖ Neurophysiologic dysfunctions (age 14)
 - Delayed brainstem auditory evoked potentials
 - Decreased autonomic heart rate variability
 - Attributed to prenatal exposure

20

The Faroe Islands study assessed the association between maternal consumption of methylmercury contaminated fish and neurological endpoints in the children of these women. This study has been used in various risk assessments for methylmercury exposure regulations.

Neurological symptoms of intrauterine methylmercury exposure may include mental retardation, ataxia and cerebral palsy, seizures, vision and hearing loss, delayed developmental milestones, language disorders, and problems with motor function, visual spatial abilities, and memory.

Please note the high consumption, in this case, of whale meat, which is at the top of the food chain and can present high levels of mercury. Other studies of seafood consumption have found that with consumption of smaller fish the effect of mercury is counteracted by the demonstrable beneficial effects of nutrients such as omega-3 fatty acids, iodine etc that have major beneficial effects on the neurocognitive system.

Ref:

•Grandjean P et al. Cognitive deficit in 7 year old children with prenatal exposure to methylmercury, *Neurotoxicology and teratology*, 1997, 19: 417.

A cohort of 1022 consecutive singleton births was generated during 1986-1987 in the Faroe Islands. Increased methylmercury exposure from maternal consumption of pilot whale meat was indicated by mercury concentrations in cord blood and maternal hair. At approximately 7 years of age, 917 of the children underwent detailed neurobehavioral examination. Neuropsychological tests included Finger Tapping; Hand-Eye Coordination; reaction time on a Continuous Performance Test; Wechsler Intelligence Scale for Children-Revised Digit Spans, Similarities, and Block Designs; Bender Visual Motor Gestalt Test; Boston Naming Test; and California Verbal Learning Test (Children). Clinical examination and neurophysiological testing did not reveal any clear-cut mercury-related abnormalities. However, mercury-related neuropsychological dysfunctions were most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions. These associations remained after adjustment for covariates and after exclusion of children with maternal hair mercury concentrations above 10 microgram(s) (50 nmol/g). The effects on brain function associated with prenatal methylmercury exposure therefore appear widespread, and early dysfunction is detectable at exposure levels currently considered safe.

•WHO. Children's Exposure to Mercury Compounds Available at www.who.int/ceh/publications/children_exposure/en/index.html – accessed 10 June 2011

ASSESSING VULNERABLE SUBPOPULATIONS

1. Pregnant women and women of child-bearing age

Low dose mercury exposure to women affects fetal development

2. Developing fetus

Neurotoxicants (methylmercury) exert adverse effects during embryonic and fetal development



During fetal life, the blood-brain barrier of the unborn baby is immature and neurons are particularly susceptible to toxicants because of their large surface area and fat composition (many chemicals of concern being lipophilic).

<<READ SLIDE>>

<<NOTE TO USER: For more information about how to reduce MeHg and Hg exposures, please see Module 6 of this series: "Prevention" as well as the modules on mercury or neurodevelopment>>

Refs:

•Rice D et al. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models, *Environ Health Perspectives*, 2000, 108 (3):511-33.

Vulnerable periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the temporal and regional emergence of critical developmental processes (i.e., proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Evidence from numerous sources demonstrates that neural development extends from the embryonic period through adolescence. In general, the sequence of events is comparable among species, although the time scales are considerably different. Developmental exposure of animals or humans to numerous agents (e.g., X-ray irradiation, methylazoxymethanol, ethanol, lead, methyl mercury, or chlorpyrifos) demonstrates that interference with one or more of these developmental processes can lead to developmental neurotoxicity. Different behavioral domains (e.g., sensory, motor, and various cognitive functions) are subserved by different brain areas. Although there are important differences between the rodent and human brain, analogous structures can be identified. Moreover, the ontogeny of specific behaviors can be used to draw inferences regarding the maturation of specific brain structures or neural circuits in rodents and primates, including humans. Furthermore, various clinical disorders in humans (e.g., schizophrenia, dyslexia, epilepsy, and autism) may also be the result of interference with normal ontogeny of developmental processes in the nervous system. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function. This concern is compounded by the fact that developmental neurotoxicity that results in small effects can have a profound societal impact when amortized across the entire population and across the life span of humans.

•Zahir et. al. Low dose mercury toxicity and human health. *Environmental Toxicology and Pharmacology*, 2005, 20(2), 351-360.

Image: Brown VJ Methylmercury and IQ: Dose-Response Estimate of Prenatal Effect. Environ Health Perspect, 2007, 115:A212-A212.

Case Study 3: Dioxin exposure: Effects of the Seveso Incident

The fourth and final case study will overview an industrial accident in Seveso, Italy which released an environmental contaminant known as dioxin. The health effects of this incident will also be reviewed.

<<NOTE TO USER: You can find more detailed information in the module on persistent organic pollutants.>>

SEVESO DIOXIN ACCIDENT

- ❖ In 1976, a pesticide factory in Seveso, Italy exploded
- ❖ Tetrachlorodibenzodioxin (TCDD), a type of dioxin, released into the area
- ❖ Residential populations in surrounding villages also exposed
- ❖ Several scientific studies and industrial regulations followed the event

23

<<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.
- Eskenazi, B et al. Serum dioxin concentrations and endometriosis: a cohort study in Seveso, Italy. *Environ Health Perspect*, 2002. 110(7):629-34.
- Eskenazi, B et al. Serum dioxin concentrations and menstrual cycle characteristics. *Am J Epidemiol*, 2002. 156(4):383-92.
- European Commission for the Environment. Seveso, Italy. Brussels, Belgium, European Commission, 2010. Available at ec.europa.eu/environment/seveso/index.htm - accessed 20 July 2010.

The "Seveso" accident happened in 1976 at a chemical plant in Seveso, Italy, manufacturing pesticides and herbicides. A dense vapour cloud containing tetrachlorodibenzoparadioxin (TCDD) was released from a reactor, used for the production of trichlorofenol. Commonly known as dioxin, this was a poisonous and carcinogenic by-product of an uncontrolled exothermic reaction. Although no immediate fatalities were reported, kilogramme quantities of the substance lethal to man even in microgramme doses were widely dispersed which resulted in an immediate contamination of some ten square miles of land and vegetation. More than 600 people had to be evacuated from their homes and as many as 2000 were treated for dioxin poisoning.

- Warner, M., et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect*, 2002. 110(7):625-8.

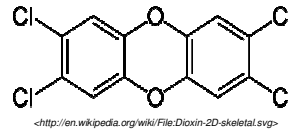
WHAT IS TCDD?

❖ Type of dioxin

- ❖ 2,3,7,8-TCDD is sometimes just called by the name “dioxin”
- ❖ The most studied dioxin due to toxicity in animal studies

❖ Dioxins are lipophilic

- ❖ Bioaccumulate in fat tissue



❖ Produced in manufacturing of chemicals

- ❖ Some produced in combustion

24

Tetrachlorodibenzo-dioxin, known by the acronym, TCDD, is a type of dioxin. A dioxin is not a molecule, but a structural element comprised of many different molecules. TCDD is usually known simply as “dioxin” and is the most referenced and most studied of the dioxins. It has been shown to be extremely toxic in laboratory animals.

Dioxins are not easily soluble in water, but are very lipophilic. This means that they have a special affinity for fat molecules. For this reason, when humans are exposed to dioxins, these chemical compounds remain in the fatty tissue and build up over time. This process is known as bioaccumulation. This means that humans may potentially have large amounts of dioxins in their fatty tissue following exposure that remain present over some period of time. Within the environment, dioxins have been shown to bind to sediments and other organic substances. Dioxins are produced in the industrial process though they may also be by-products of combustion.

<<NOTE TO USER: For more information about dioxin, please visit the WHO fact sheet, accessible at: www.who.int/mediacentre/factsheets/fs225/en/index.html.>>

Refs:

- Brown NM et al. Prenatal TCDD and predisposition to mammary cancer in the rat. *Carcinogenesis*. 1998, 19:1623–1629.
- Jenkins S et al Pre- natal TCDD exposure predisposes for mammary cancer in rats. *Reprod Toxicol*, 2007, 23:391–396.
- Minegishi T et al. Effect of IGF-1 and 2,3,7,8-tetrachlorodibenzo-p- dioxin (TCDD) on the expression of LH receptors during cell differentiation in cultured granulosa cells. *Mol Cell Endocrinol*, 2003, 202:123–131.
- Nayyar T. et al. Developmental exposure of mice to TCDD elicits a similar uterine phenotype in adult animals as observed in women with endometriosis. *Reprod Toxicol*. 2007, 23:326 –336.
- Rier SE et al. Serum levels of TCDD and dioxin-like chemicals in Rhesus monkeys chronically exposed to dioxin: correlation of increased serum PCB levels with endometriosis. *Toxicol Sci*. 2001, 59:147–159.
- WHO. Dioxins and their effects on human health. Fact sheet 225. Geneva, Switzerland, *World Health Organization*, 2010. Available at www.who.int/mediacentre/factsheets/fs225/en/index.html - accessed 14 July 2010.

Image: TCDD. Wikimedia Commons. Available at en.wikipedia.org/wiki/File:Dioxin-2D-skeletal.svg - accessed 14 July 2010. This image is public domain.

EVIDENCE OF DIOXIN HEALTH EFFECTS

- ❖ Classified as a human carcinogen
- ❖ Potential endocrine disruptors
 - ❖ Estrogenic when high levels of estrogen present *in utero*
 - ❖ Anti-estrogenic in absence of estrogen *in utero*
- ❖ Dioxins may:
 - ❖ Disrupt hormone signaling
 - ❖ Reduce fertility and interfere with embryo development



WHO

25

<<READ SLIDE.>>

TCDD: Tetrachlorodibenzodioxin

Refs:

- Brown NM et al. Prenatal TCDD and predisposition to mammary cancer in the rat. *Carcinogenesis*. 1998, 19:1623–1629.
- Chen S et al. Endocrine disruptor, dioxin (TCDD)-induced mitochondrial dysfunction and apoptosis in human trophoblast-like JAR cells. *Molecular Human Reproduction*. 2010, 16(5):361-372.
- Jenkins S et al Pre- natal TCDD exposure predisposes for mammary cancer in rats. *Reprod Toxicol*, 2007, 23:391–396.
- Minegishi T et al. Effect of IGF-1 and 2,3,7,8-tetrachlorodibenzo-p- dioxin (TCDD) on the expression of LH receptors during cell differentiation in cultured granulosa cells. *Mol Cell Endocrinol*, 2003, 202:123–131.
- Nayyar T et al. Developmental exposure of mice to TCDD elicits a similar uterine phenotype in adult animals as observed in women with endometriosis. *Reprod Toxicol*. 2007, 23:326 –336.
- Rier SE et al. Serum levels of TCDD and dioxin-like chemicals in Rhesus monkeys chronically exposed to dioxin: correlation of increased serum PCB levels with endometriosis. *Toxicol Sci*. 2001, 59:147–159.
- WHO. Dioxins and their effects on human health. Fact sheet 225. Geneva, Switzerland, *World Health Organization*, 2010. Available at www.who.int/mediacentre/factsheets/fs225/en/index.html - accessed 14 July 2010.

Image: WHO

DIOXIN HEALTH EFFECTS IN SEVESO

- ❖ Lack of adequate human exposure assessments
- ❖ Many different observed female health effects:
 - ❖ Earlier menopause
 - ❖ Possibly higher rate of endometriosis
 - ❖ Significant increased risk of breast cancer
 - ❖ No change in ovarian function
- ❖ Investigations still continue and children's health currently being studied



WHO

26

A team of Italian researchers as well as staff from the United States Centers for Disease Control (US CDC) conducted an investigation into the incident. The researchers conducted blood tests on the women residing in the area to determine the amount of dioxin that has been taken up by the body. Some women in the area were exposed prior to the age of menarche, while others were exposed after menarche. Due to dioxin's action as an estrogen or anti-estrogen, health effects depend heavily on the life stage of a woman when exposed, due to the levels of hormones present in her body in different phases of her reproductive life. This fact may result in different reproductive health endpoints for women at different stages in their reproductive life.

Some of the studies conducted in the region showed inconclusive results. However, a specific study showed that women with higher levels of dioxin in their blood demonstrated an earlier age of menopause onset. An additional study demonstrated that women with higher levels of dioxin in their blood also demonstrated a potentially higher risk of endometriosis and a significant increased risk of breast cancer. While the mechanism of action of dioxin on the female reproductive system is not entirely clear, its action as a potential endocrine disruptor indicates that this compound potentially alters normal hormonal function.

Due to the lack of certainty regarding these studies, research is ongoing in this region and currently, the effects of children's health and dioxin exposure from the incident are being investigated.

Refs:

- Eskenazi, B et al. Serum dioxin concentrations and age at menopause. *Environ Health Perspect*, 2005, 113(7):858-62.
- 2,3,7,8-Tetrachlorobenzo-p-dioxin (TCDD), a halogenated compound that binds the aryl hydrocarbon receptor, is a by-product of numerous industrial processes including waste incineration. Studies in rats and monkeys suggest that TCDD may affect ovarian function. We examined the relationship of TCDD and age at menopause in a population of women residing near Seveso, Italy, in 1976, at the time of a chemical plant explosion. We included 616 of the women who participated 20 years later in the Seveso Women's Health Study. All women were premenopausal at the time of the explosion, had TCDD levels measured in serum collected soon after the explosion, and were ≥ 35 years of age at interview. Using proportional hazards modeling, we found a 6% nonsignificant increase in risk of early menopause with a 10-fold increase in serum TCDD. When TCDD levels were categorized, compared with women in the lowest quintile (< 20.4 ppt), women in quintile 2 (20.4–34.2 ppt) had a hazard ratio (HR) of 1.1 (p = 0.77), quintile 3 (34.3–54.1 ppt) had an HR of 1.4 (p = 0.14), quintile 4 (54.2–118 ppt) had an HR of 1.6 (p = 0.10), and quintile 5 (> 118 ppt) had an HR of 1.1 (p = 0.82) for risk of earlier menopause. The trend toward earlier menopause across the first four quintiles is statistically significant (p = 0.04). These results suggest a nonmonotonic dose-related association with increasing risk of earlier menopause up to about 100 ppt TCDD, but not above.*
- 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.
- Eskenazi, B et al. Serum dioxin concentrations and endometriosis: a cohort study in Seveso, Italy. *Environ Health Perspect*, 2002, 110(7): 629-34.
- Eskenazi, B et al. Serum dioxin concentrations and menstrual cycle characteristics. *Am J Epidemiol*, 2002, 156(4):383-92.
- Eskenazi, B et al. Maternal serum dioxin levels and birth outcomes in women of Seveso, Italy. *Environ Health Perspect*, 2003, 111(7):947-53.
- Eskenazi, B et al., Relationship of serum TCDD concentrations and age at exposure of female residents of Seveso, Italy. *Environ Health Perspect*, 2004, 112(1):22-7.
- Eskenazi, B et al., Serum dioxin concentrations and risk of uterine leiomyoma in the Seveso Women's Health Study. *Am J Epidemiol*, 2007, 166(1):79-87.
- Warner, M et al. Serum dioxin concentrations and quality of ovarian function in women of Seveso. *Environ Health Perspect*, 2007, 115(3):336-40.
- Warner M et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect*, 2002, 110(7):625-8.
- Warner M et al. Serum dioxin concentrations and age at menarche. *Environ Health Perspect*, 2004, 112(13):1289-92.

Image: WHO

Case Study 4:
Pesticide exposure:
Organophosphates in
Nicaragua

The third case study will overview the extensive use of pesticides in Nicaragua.

<<NOTE TO USER: You can find more detailed information in the modules on pesticides, developmental origins of disease, neurodevelopmental effects, immune effects, cancer, respiratory effects, and others.>>

WIDESPREAD PESTICIDE USE IN NICARAGUA

- ❖ Cotton growing region of northern plain sprayed with organophosphate insecticide
- ❖ In 1984, 27 clinical poisonings reported
 - ❖ Believed that only approximately 1/3 of poisoning was reported to clinicians
- ❖ Children living in cotton picking communities experienced:
 - nausea
 - muscle twitching
 - inability to walk
 - unconsciousness



WHO

28

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The Latin American nation of Nicaragua has experienced a long history with pesticide exposures and poisonings. The northern coast of Nicaragua is largely reserved for cotton production and is routinely dusted with pesticides known as insecticides, which are made to kill and prevent damage to crops from insects. A specific class of insecticides known as organophosphates is spread on these cotton crops. The different classes of pesticides will be described in the next slides. Clinical symptoms of acute organophosphate poisoning depend on severity of exposure, but commonly include headache, nausea, muscle twitches, inability to walk, unconsciousness, and seizures.

Refs:

- Curl CL et al. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives*, 2002, 110(12):A787-A792.
- Goldman L, Tran N. Toxics and Poverty: The impact of toxic substances on the poor in developing countries. Washington, DC, *The International Bank for Reconstruction and Development/The World Bank*, 2002.
- Sudakin DL, Power LE. Organophosphate Exposure in the United States: A Longitudinal Analysis of Incidents Reported to Poison Centers. *Journal of Toxicology & Environmental Health: Part A*, 2007, 70(1):141.

Image: WHO

DIAGNOSIS: ORGANOPHOSPHATE PESTICIDE EXPOSURE

- ❖ Children were experiencing symptoms of organophosphate pesticide poisonings even if they were not working in agriculture
- ❖ Investigators determined that the organophosphate pesticide runoff had contaminated local waterways
- ❖ Runoff situation indicated that hundreds of unaware community members faced risk of exposure



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29

Organophosphates can be absorbed via ingestion, inhalation and dermal contact. They inhibit the action of cholinesterase, the enzyme that breaks down acetylcholine to acetic acid and choline. Effects may appear as early as 10 minutes to as late as two hours post exposure, depending on the amount absorbed. Organophosphates in liquid preparation are usually dissolved in petroleum distillate solvents like kerosene and xylene. Isopropanol is another solvent used together with petroleum distillates. In water based formulations, the concentration of isopropanol may be higher. These solvents are symphatomimetic agents and so may mask the cholinergic manifestations of the organophosphate. Note the cholinergic effects may be muscarinic, nicotinic, or central depending on the amount absorbed. From: WHO/SEARO. Manual of pesticide poisoning. Available at www.wpro.who.int/hse/pages/organophosphate.html – accessed 21 September 2011.

<<READ SLIDE.>>

Refs:

- Curl CL et al. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives*, 2002, 110(12):A787-A792.
- Goldman L, Tran N. Toxics and Poverty: The impact of toxic substances on the poor in developing countries. Washington, DC, *The International Bank for Reconstruction and Development/The World Bank*, 2002.
- Sudakin DL, Power LE. Organophosphate Exposure in the United States: A Longitudinal Analysis of Incidents Reported to Poison Centers. *Journal of Toxicology & Environmental Health: Part A*, 2007, 70(1):141.

Image: WHO

SYMPTOMS OF ACUTE PESTICIDE POISONING

| Organ System | High Exposure | Low Exposure |
|-------------------|---|--------------------------|
| Gastro-intestinal | Haemorrhage; gut perforation | Nausea, abdominal cramps |
| Respiratory | Respiratory arrest | Cough, airway irritation |
| Nervous | Coma, paralysis, seizure | Headache, tremor |
| Cardiovascular | Bradycardia, myocardial infarction | Mild hypertension |
| Metabolism | Severe electrolyte imbalance | Short fever |
| Renal | Renal failure | Polyuria |
| Muscular | Muscle rigidity | Muscle weakness |
| Dermatologic | 2 nd /3 rd degree burns | Oedema, swelling |

30

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<<NOTE TO USER: For more information, about how to diagnosis acute pesticide poisoning, please see www.who.int/bulletin/volumes/86/3/07-041814/en/index.html>>

Refs:

- Curl CL et al. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives*, 2002, 110(12):A787-A792.
- Thundiyil J et al. Acute pesticide poisoning: a proposed classification tool. Geneva, Switzerland, WHO, 2008. *Bulletin of the World Health Organization*, 86(3), 205-209.

Image: WHO

EPIDEMIOLOGIC CASE DEFINITION: ACUTE PESTICIDE POISONING

Must meet *one* criterion in *each* category:

1. Exposure

- a. Observation of pesticide residue or odour by doctor
- b. Plausible description of exposure via witnessed report or written record
- c. Biological monitoring via biomarkers
- d. Environmental sampling of area where exposure occurred

2. Health effects

- a. Characteristic toxic effect from pesticide documented by doctor
- b. Positive laboratory test with unlikely alternative cause for symptoms
- c. Three or more compatible symptoms with pesticide exposure
- d. Autopsy evidence of pesticide exposure

3. Causality

- a. Temporal cause-effect relationship with exposure and health effects

31

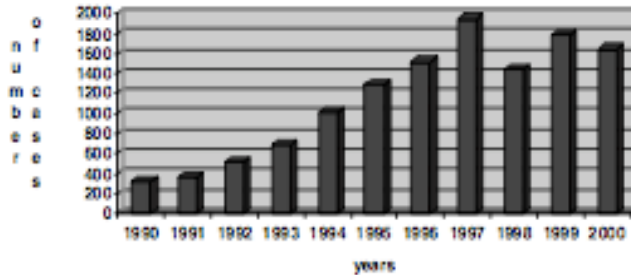
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<<NOTE TO USER: For more information, about how to diagnosis acute pesticide poisoning, please see www.who.int/bulletin/volumes/86/3/07-041814/en/index.html>>

Refs:

- Curl CL et al. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives*, 2002, 110(12):A787-A792.
- Thundiyil J et al. Acute pesticide poisoning: a proposed classification tool. Geneva, Switzerland, WHO, 2008. *Bulletin of the World Health Organization*, 86(3), 205-209.

CONTINUED POISONING IN NICARAGUA



Ministry of Health of Nicaragua, 2005.

- ❖ Mandatory reporting system exists, but underreporting is common
- ❖ Predominantly young agricultural workers
- ❖ Exposure occupational and residential
 - Water runoff containing pesticides found in distant communities

32

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This graph demonstrates a continued trend of pesticide poisoning throughout Nicaragua. This is significant because high levels of under-reporting exist.

Refs:

- Costa LG. Current issues in organophosphate toxicology. *Clinica Chimica Acta*, 2005 366(1):1.
- Goldman L, Tran N. Toxics and Poverty: The impact of toxic substances on the poor in developing countries. Washington, DC, *The International Bank for Reconstruction and Development/The World Bank*, 2002.
- Ministry of Health of Nicaragua. Monitoring and evaluation forms. *Pesticide program reports. Managua, Nicaragua*, 2005.

Image: Ministry of Health of Nicaragua. Monitoring and evaluation forms. Pesticide program reports. Managua, Nicaragua, 2005. This image is public domain.

HUMAN EXPOSURE TO PESTICIDES

- ❖ Exposure may be occupational or residential
 - ❖ Take home exposures
 - ❖ Contaminated foods, water, and soil
 - ❖ Airborne dispersion of sprayed pesticides
- ❖ Persistence in the environment responsible for sustained exposure
- ❖ Primary routes of exposure
 - ❖ Ingestion in food, water, soil
 - ❖ Inhalation
 - ❖ Absorption through skin and eyes



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33

• A majority of the individuals who are exposed to high levels of pesticides are commonly exposed occupationally, when working in the agricultural sector. However, it is very important to note that exposure to pesticides is not limited to the occupational setting. Individuals can be exposed to pesticides via numerous pathways as well as exposure scenarios. For example, individuals may be exposed to pesticides non-occupationally through take home exposures from family members that are exposed in the occupational setting. In this case, a family member may bring home pesticides residues on skin, clothing, or hair and expose other family members. Pesticides may also enter the water and soil, thus contaminating communities that are not involved in pesticide spraying. Individuals can ingest foods and water contaminated with pesticides. In addition, pesticides that are sprayed onto crops may be dispersed in the air and settle in distant locations, far removed from the initial sprayed region.

• Pesticides can be inhaled when airborne, ingested through consumption of food or water, or may be absorbed through the skin. Organophosphates specifically are excreted over a period of months or years, and thus may bioaccumulate within the body.

Refs:

•Curl CL et al. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives*, 2002, 110(12):A787-A792.

•Gurunathan S et al. Accumulation of Chlorpyrifos on Residential Surfaces and toys accessible to children. *Environmental Health Perspectives*, 1998, 106(1):9

Chlorpyrifos (a nonpersistent OP) has also been found to accumulate on newly introduced surfaces, such as pillows, carpet and soft toys, when brought into a treated area up to two weeks after application, even if applied according to manufacturer's instructions.

Image: WHO

POTENTIAL FEMALE REPRODUCTIVE HEALTH EFFECTS OF PESTICIDE EXPOSURE

By altering proper functioning of female reproductive hormones, pesticide exposure may result in:

- ❖ **Ovarian cycle irregularities**
 - Disturbances in the ovarian cycle
 - Ovulation problems
- ❖ **Menstrual cycle disturbances**
- ❖ **Infertility**
- ❖ **Developmental defects**



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34

Alteration of female hormonal functioning may lead to disturbances in the reproductive system through modulation of hormone concentrations, and potentially result in ovarian cycle irregularities, and impaired fertility. For example, organochlorine compounds have been shown in animal studies to interrupt the menstrual cycle. A recent study observed that women who were occupationally exposed to pesticides experienced longer menstrual cycles and increased odds of missed periods compared with women who never used pesticides. In addition, women who used probably hormonally active pesticides had a 60–100% increased odds of experiencing long cycles, missed periods, and intermenstrual bleeding compared with women who had never used pesticides.

In a study in the US, infertile women were observed to be three times more likely to ever having been exposed to pesticides and nine times more likely to ever having worked in agriculture than fertile women.

In a well-conducted Finnish study of women in agricultural occupations, the investigators found that exposure to pesticides during the first trimester of pregnancy nearly doubled the risk of cleft lips and palates in offspring.

Refs:

- Farr SL et al. Pesticide use and menstrual cycle characteristics among premenopausal women in the Agricultural Health Study. *American Journal Epidemiology*, 2004, 160:1194-1204.
- Nurminen T et al. Agricultural work during pregnancy and selected structural malformations in Finland. *Epidemiology*, 1995, 6:23-30.
- Smith EM et al. Occupational exposures and risk of female infertility. *J Occup Environ Med*. 1997, 39:138-147.

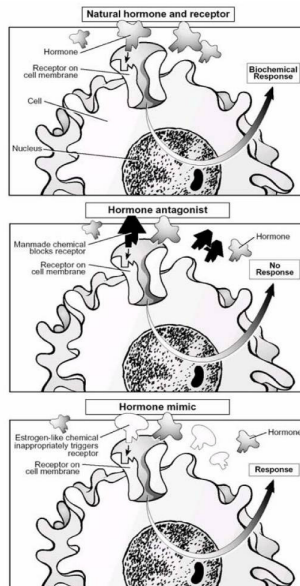
Image: WHO

Case Studies of Female Reproductive Health and the Environment (*Draft for review*)

MECHANISMS OF ACTION

Three mechanisms of hormone receptor binding mechanisms of pesticides:

1. Binding and activating the estrogen receptor
2. Binding without activating the estrogen receptor
3. Binding other receptors



T. Schettler et al. *Generations at Risk: How environmental Toxicants May Affect Reproductive Health in California, A Report by Physicians for Social Responsibility (Greater SF Bay Area & Los Angeles Chapters) and The California Public Interest Research Group Charitable Trust, 1998.*

35

- Research studies have shown that specific pesticides, including organophosphates may interfere with normal hormonal function within the female body.
- Pesticides may alter the hormonal binding process by mimicking the natural hormone (agonists) or by inhibiting receptor binding (antagonists). The antagonist mechanism is based on complete or partial blocking of the specific receptor. Three mechanisms exist for pesticide antagonists and agonists. When a pesticide molecule binds and activates the estrogen receptor, it is known as an agonist and termed estrogenic. If a pesticide molecule binds, but does not activate the estrogen receptor, the substance acts as an antagonist and inactivates the estrogen receptor. Pesticides and their metabolites may also bind with other receptors.
- By altering the normal hormonal function of the female reproductive system, a variety of effects may be witnessed at different stages of life. Some of these effects will be overviewed in the next slide. Pesticides may also alter the metabolism, synthesis and transport of estrogen.

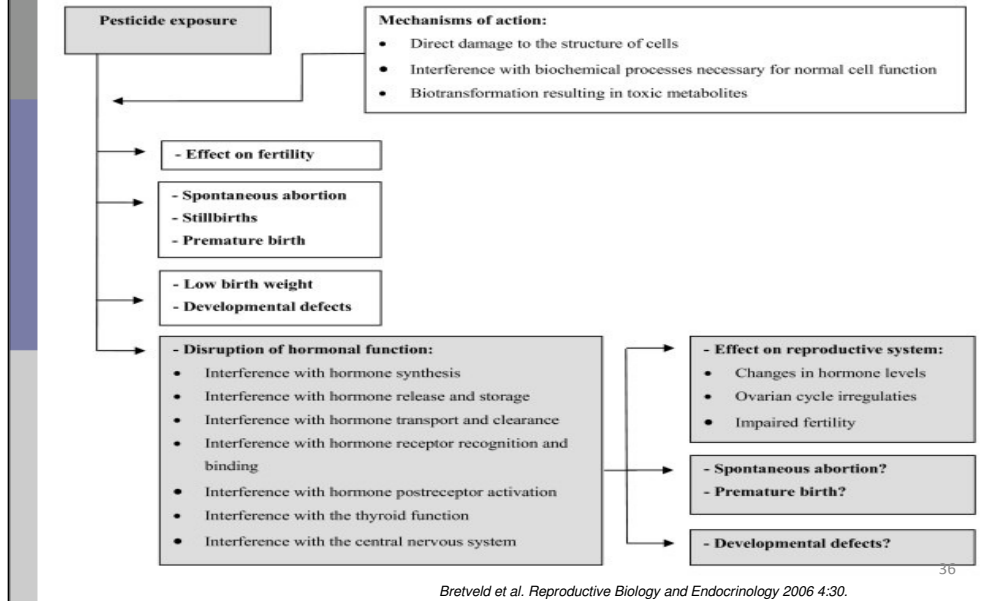
<<NOTE TO USER: For more information on hormone receptor binding, please see Module 1: Introduction to Environmental Reproductive Health as well as the “Pesticide” module.>>

Refs:

- Curl CL et al. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives*, 2002, 110(12):A787-A792.
- Vinggaard AM, Joergensen EC, Larsen JC. Rapid and sensitive reporter gene assays for detection of antiandrogenic and estrogenic effects of environmental chemicals. *Toxicol Appl Pharmacol*. 1999, 155:150-160.

Image: T. Schettler et al. Generations at Risk: How environmental Toxicants May Affect Reproductive Health in California, A Report by Physicians for Social Responsibility (Greater SF Bay Area & Los Angeles Chapters) and The California Public Interest Research Group Charitable Trust, 1995. Available at www.environmentcalifornia.org/reports/environmental-health/environmental-health-reports/generations-at-risk-how-environmental-toxicants-may-affect-reproductive-health-in-california – accessed 31 October 2011. Used with permission, Environment California.

FEMALE REPRODUCTIVE HEALTH ENDPOINTS



This diagram shows scenario of exposure to pesticides and potential reproductive health endpoints for the female.

Pesticides can interfere with female reproductive function by multiple mechanisms and through various pathways, including altered hormonal balance, direct damage of the female gamete, interference with fertilization and implantation, abnormal reproductive tract development/function.

Refs:

- Bretveld RW, Thomas CMG, Scheepers PTJ, Zielhuis GA, Roeleveld N. Pesticide exposure: the hormonal function of the female reproductive system disrupted? *Reproductive Biology and Endocrinology*. 2006, 4:30.
- Sanborn M et al. Pesticides Literature Review: Systematic Review of Pesticide Human Health Effects. Ontario. *The Ontario College of Family Physicians*. 2004.

Image: Bretveld et al. Pesticide exposure: the hormonal function of the female reproductive system disrupted? Reproductive Biology and Endocrinology. 2006, 4:30. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

EVIDENCE FROM HUMAN STUDIES WORLDWIDE

- ❖ **Denmark:** Association between exposure to pesticides and reduced fecundity
- ❖ **Netherlands:** spontaneous abortion
- ❖ **Italy:**
 - Reduction in fecundity
 - Spontaneous abortion
- ❖ **Canada:** spontaneous abortion
- ❖ **USA:** Disturbances of age at menarche (earlier) and menstrual cycles (shortened)
- ❖ Prenatal exposures to some pesticides are being linked to decreased IQ & attention disorders.



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37

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Exposure to pesticides and resulting female reproductive health effects have been documented around the world. The universal use of pesticides and long term contamination potential in the environment indicates that populations globally may be affected by these environmental contaminants.

Refs:

- Abell A, Juul S, Bonde JP. Time to pregnancy among female greenhouse workers. *Scand J Work Environ Health*. 2000; 26:131–136.
- Denmark: This study examined the possibility that work in greenhouses with potential exposure to pesticides entails a risk for reduced fecundity in terms of increased time to pregnancy. Methods. Among 1767 female members of the Danish Gardeners' Trade Union, telephone interview data were obtained on the 492 most recent pregnancies of women employed when they stopped contraception to get a child (the starting time). The pregnancies were classified according to job characteristics at the starting time. The ratio between the likelihood of pregnancy during a month for the exposed persons versus the referents (the fecundability ratio) was estimated by discrete proportional hazards regression. Results. The adjusted fecundability ratio for workers in flower greenhouses versus other union members was 1.11 [95% confidence interval (95% CI) 0.90-1.36]. Among workers in flower greenhouses the handling of cultures many hours per week, the spraying of pesticides, and the nonuse of gloves was related to reduced fecundability [adjusted fecundability ratio 0.69 (95% CI 0.47-1.03), 0.78 (95% CI 0.59-1.06), and 0.67 (95% CI 0.46-0.98), respectively]. Conclusions. The findings suggest that female workers in flower greenhouses may have reduced fecundability and that exposure to pesticides may be part of the causal chain. Additional studies of fertility among women working in greenhouses are highly warranted.
- Bretveld RW et al. Reproductive Disorders Among Male and Female Greenhouse Workers. *Reproductive Toxicology*. 2008; 25(1):107-114.
- Netherlands: The aim of this study was to evaluate reproductive disorders in male and female greenhouse workers. In 2002, data were collected from 4872 Dutch greenhouse workers and 8133 referents through postal questionnaires with detailed questions on reproductive disorders of the most recent pregnancy, lifestyle habits, and occupational exposures (e.g. pesticides) prior to conception. Different reproductive outcome measures were compared between 957 male and 101 female greenhouse workers and 1408 referents by means of logistic regression analyses. The analyses of primigravitous couples showed a slightly elevated risk of prolonged TTP (OR_{women} = 1.9; 95% CI: 0.8–4.4) and an increased risk of spontaneous abortion among female greenhouse workers (OR_{women} = 4.0; 95% CI: 1.1–14.0). A decreased risk of preterm birth was found among male greenhouse workers (OR_{men} = 0.1; 95% CI: 0.03–0.5). This study may offer some evidence for the hypothesis that pesticide exposure affects human reproduction leading to spontaneous abortion and possibly to prolonged time-to-pregnancy.

Italy:

- Petrelli G, et al. Spontaneous abortion in spouses of greenhouse workers exposed to pesticides. *Environ Health Prevent Med*, 2003, 8:77–81.
- Settini A et al. Spontaneous abortion and maternal work in greenhouses, *Am J Ind Med*, 2008, 51:290–295.

Ontario:

- Arbuckle TE, Lin Z, Mery LS. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population, *Environ Health Perspect*. 2001, 109:851–857

USA:

- Ouyang MJ et al. Age at menarche, and abnormal menstrual cycle length, *Occup Environ Med*, 2005, 62:878–884.

Although dichlorodiphenyltrichloroethane (DDT) exposure is known to affect human endocrine function, few previous studies have investigated the effects of DDT exposure on age at menarche or menstrual cycle length.

A cross sectional study was conducted to study the effects of DDT exposure on age at menarche and menstrual cycle length among 466 newly married, nulliparous female Chinese textile workers aged 20-34 years enrolled between 1996 and 1998. Serum was analysed for DDT and its major metabolites. Multivariate linear regression was used to estimate DDT exposure effects on age at menarche and multivariate logistic regression was used to estimate DDT exposure effects on odds of experiencing short or long cycles.

Relative to those in the lowest DDT quartile, the adjusted mean age at menarche was younger in those in the fourth quartile (-1.11 years). Modeled as a continuous variable, a 10 ng/g increase in serum DDT concentration was associated with an adjusted reduction in age at menarche of 0.20 years. Relative to those in the lowest DDT quartile, odds of any short cycle (<21 days) in the previous year were higher for those in the fourth quartile (odds ratio = 2.78; 95% CI 1.07 to 7.14). There were no associations between serum DDT concentrations and odds of experiencing a long cycle (>40 days). Results suggest that DDT exposure was associated with earlier age at menarche and increased risk of experiencing a shortened menstrual cycle

- Bouchard MF et al. Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year-Old Children. *Environ Health Perspect*. 2011, 119(8)

Image: WHO

CLINICAL INTERVENTIONS

- ❖ Clinicians are called to “Recognize, Diagnose and Report” potential health effects of chemical exposures
 - Especially for pregnant women
- ❖ Provide guidelines for patients, examples include:
 - Protect yourself from occupational exposure
 - Do not take the workplace home (e.g. wash, change clothes and shoes)
 - Minimize unnecessary use of pesticides and chemicals in the home
 - Use the safest pest control alternatives possible



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38

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<<NOTE TO USER: Adapt clinical intervention advice most directly applicable to the local situation in your region.>>

Refs:

WHO. Dioxins and their effects on human health. Fact sheet 225. Geneva, Switzerland, World Health Organization, 2010. Available at www.who.int/mediacentre/factsheets/fs225/en/index.html - accessed 14 July 2010.

Woodruff T. Reproductive Health And Pesticides. 2008. *Program on Reproductive Health and the Environment*. Available at www.arhp.org/uploadDocs/RH08_Woodruff.pdf - accessed 25 March 2010.

Image: WHO

POINTS FOR DISCUSSION

<<NOTE TO USER: Add points for discussion according to the needs of your audience.>>

ACKNOWLEDGEMENTS

WHO and its partners are grateful to the US EPA Office of Children's Health Protection and the UK Department of Health for the financial support that made this project possible.

First draft prepared by a working group at Johns Hopkins Bloomberg School of Public Health (Halshka Graczyk, MPH, with the lead of Dr. Lynn Goldman) and WHO (Marie-Noel Bruné, MSc)

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Last update: November 2011

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