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# The Impact of Phthalates on Women's Reproductive Health: Current State-of-the-Science and Future Directions

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# BACKGROUND

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- A dramatic increase in exposure of women to environmental toxicants
- A particular group called « endocrine disruptors »
- Endocrine system: essential to development and reproduction
- Adverse health effects in an intact organism, its progeny , and also in subsequent generations
- i.e. natural and synthetic hormones, plant constituents, pesticides, compounds used in the plastics industry and in consumer products, and other industrial by-products

# Phthalates

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- A group of **man-made** chemicals used as plasticizers,
- High-volume production and **ubiquitous** environmental presence,
- Greater than **95% of a general population** sample had measurable levels of phthalate metabolites in their urine (NHANES-USA)
- **Exposure in women is greater than in men** due to behaviour, lifestyle and occupation factors



# Behavioral determinants of women's exposure to phthalates

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## Occupational exposure:

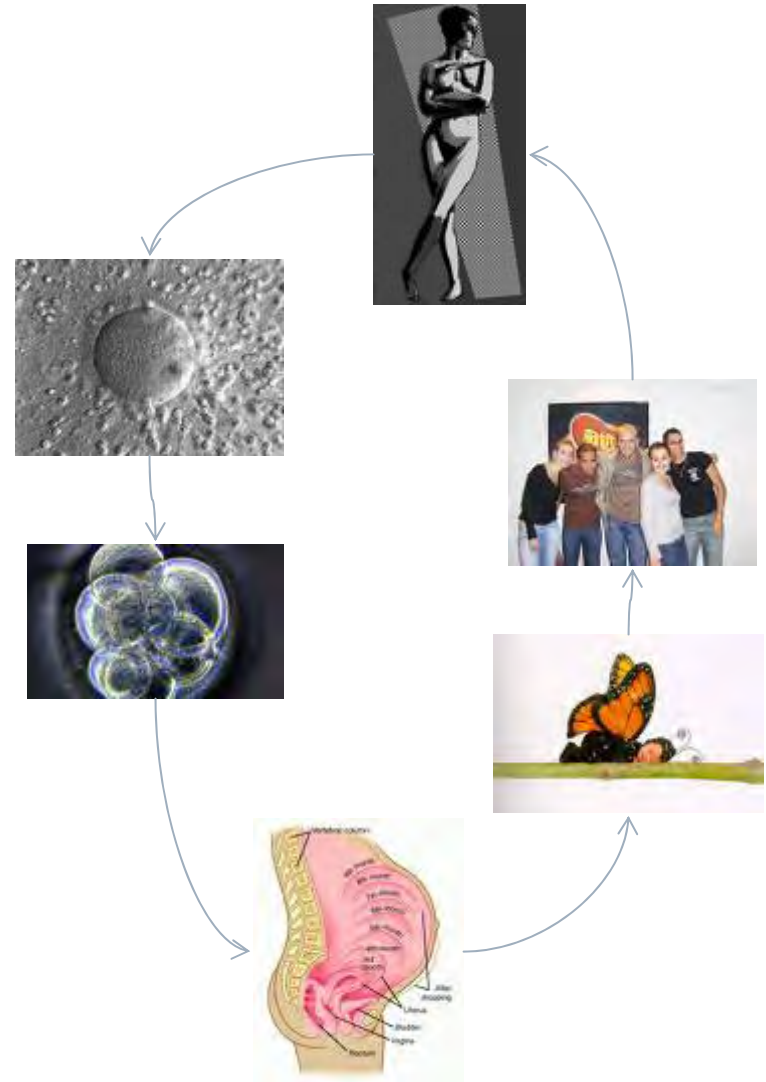
- Segregation of tasks by sex
- The way protective equipment is used (e.g. personal protective clothing and gear are normally designed for men sizes) (Arbuckle, 2006).
- Certain occupations are predominantly staffed by women. (e.g. cosmetologists)

## Outside of the work environment:

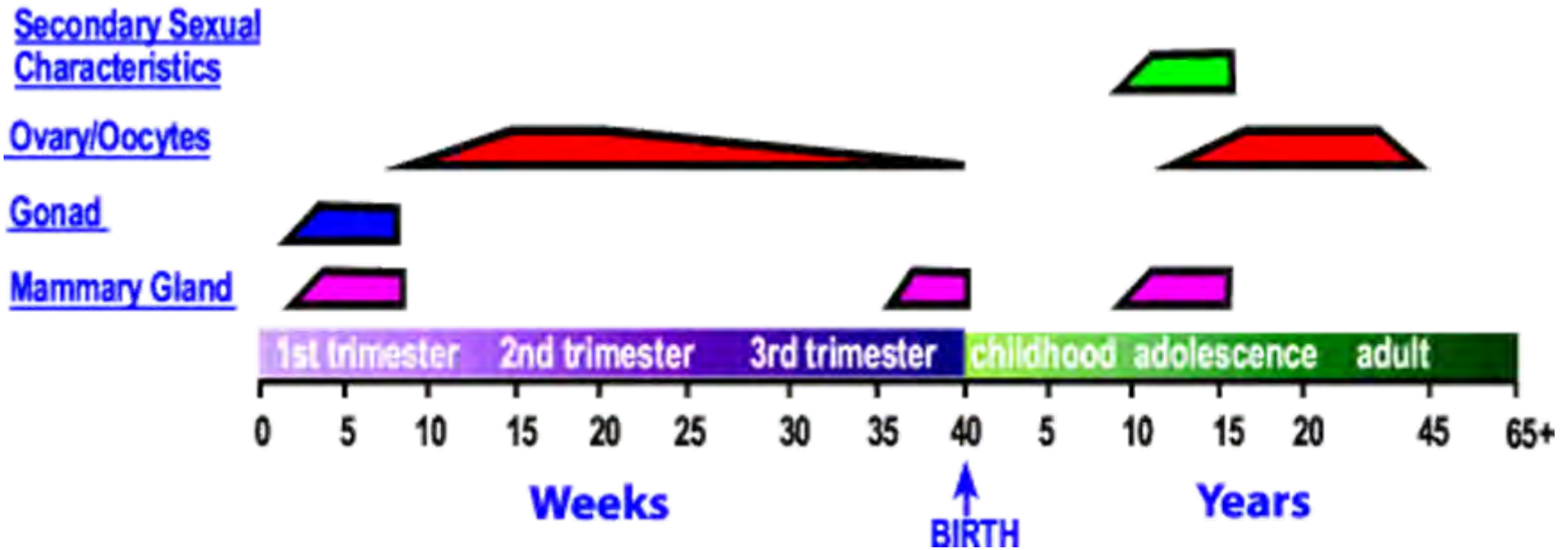
- Cosmetics
- Household products

# Phthalates

- Possible association with adverse developmental and reproductive health outcomes
- These two processes are interrelated in the life cycle encompassing the production of sperm and eggs, fertilization, prenatal development of the offspring, birth, postnatal development, sexual maturity, followed again by production of sperm and eggs.



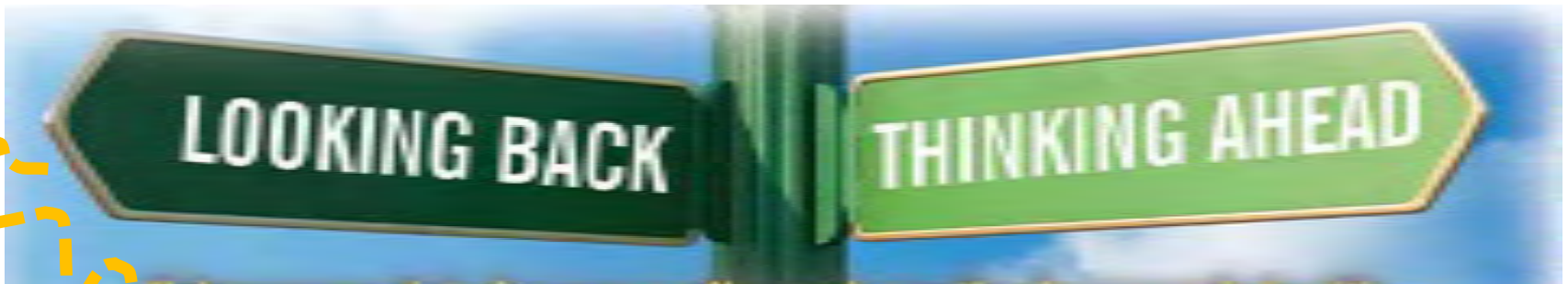
# CRITICAL WINDOWS OF SENSITIVITY TO ENDOCRINE DISRUPTORS



<http://www.emcom.ca/EM/windowsfr.shtml>

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# Phthalates



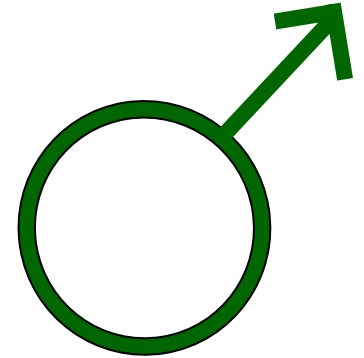
Literature review on the potential developmental and reproductive effects of phthalates in the life cycle

# Perinatal period

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- Decreased Anogenital Distance (AGD)
  - Disbalance in testosterone production
  - Leydig cells differentiation



- Decreased AGD in 85 boys. Recently reproduced in 106 boys <sup>(1, 2)</sup>
- No correlation found by Huang et al in 33 Taiwanese boys <sup>(3)</sup>.
- Lower post-natal surge of reproductive hormones <sup>(4)</sup>



(1) Swan et al, 2005

(2) Swan et al, 2008

(3) Huang et al, 2009

(4) Main et al, 2006

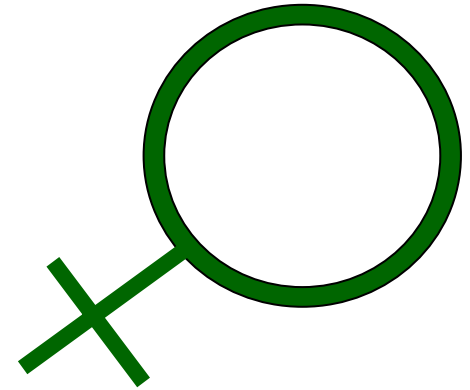


# Perinatal period

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Borch et al. reported increase in AGD after *in utero* exposure <sup>(5)</sup>



Huang et al <sup>(3)</sup>. found a significantly negative correlation between amniotic fluid Mono-Butyl Phthalate and AGD



(5) Borch et al, 2006  
(3) Huang et al, 2009

# Puberty

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Genetic factors

Nutrition

Climatic conditions

Intrauterine conditions

**MENARCHE**

**Stress**

Acute or chronic illnesses  
Adverse physical conditions  
Adverse psychological conditions

**Endocrine  
Disruptors**

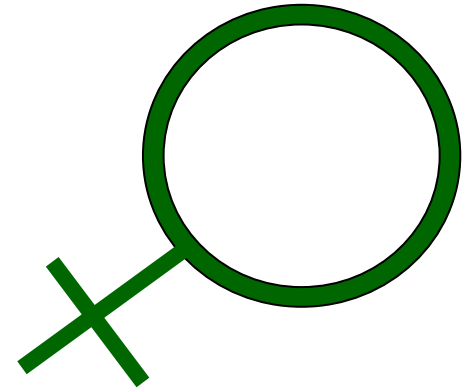
# Puberty

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- Ovaries:

- reduced serum estradiol levels and absence of ovulation



higher concentrations of several phthalate parent compounds in young girls who had experienced premature breast development (thelarche) <sup>(6)</sup>



(6) Colon et al., 2000 (Puerto Rico)

# Adulthood

## Endometriosis

- Higher plasma DEHP concentrations in 55 women diagnosed with endometriosis compared to 24 controls and 92.6% of them had detectable DEHP and/or MEHP in the peritoneal fluid (Cobellis et al., 2003).
- Infertile women with endometriosis (n=49) had significantly higher concentrations of Di-n-butyl phthalate (DnBP), Butyl benzyl phthalate (BBP), Di-n-Octyl Phthalate (DnOP) and DEHP compared with 38 age-matched control women without endometriosis (Reddy et al., 2006).

Human studies (no experimental animal studies)

# Adulthood

## Thyroid function

- Experimental *in vitro* and *in vivo* studies
- In Taiwanese women, increased second trimester DnBP exposure was associated with decreased maternal thyroid hormone levels. (Huang, et al.2007).
- Association between MEHP and decreased thyroid hormone has been found in adult men (Meeker, Calafat, & Hauser, 2007).

# Pregnancy adverse effects

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Timing of labor

•Phthalates cord blood levels associated to preterm birth (Latini, 2003)

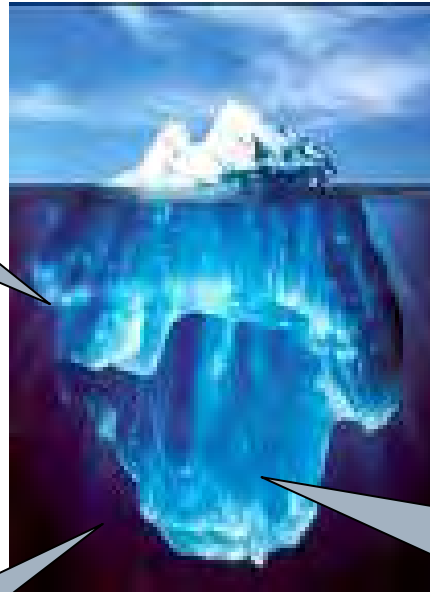


•Mothers phthalate levels in urine associated to longer mean length of gestation (Adibi, 2009)

# Conclusion

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biologically plausible  
effect on women's  
health

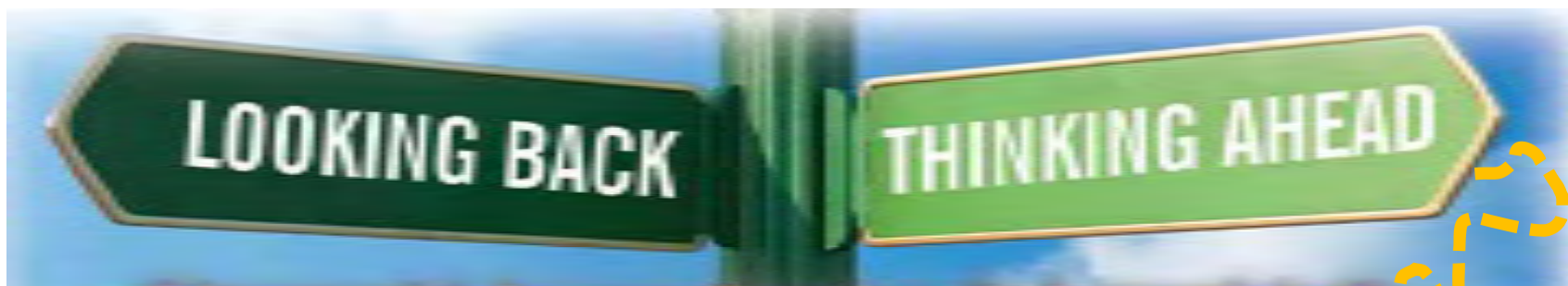


priority in the agenda  
of scientists,  
government regulators  
and policy makers.

Future research  
needs to focus on  
health outcomes  
in humans

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# Phthalates



Future directions



## Ongoing policies and programs

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- The European Union has banned a number of phthalates from cosmetics manufacture, children's toys, and childcare articles which can be placed in the mouth.
- United States: August 2008. Federal government signed a bill that bans toxic phthalates from children's products.
- In Canada: The Canadian Environmental Protection Act, 1999 (CEPA 1999).
- In 2002, recommendations on the use of Di(2-ethylhexyl) phthalate (DEHP) on medical devices
- In 2007, Health Canada's Consumer Product Safety Bureau proposed a consultation to prohibit the use of DEHP in the plasticized material of toys and products that are like to be mouthed for children under three years of age
- However, as of today, no phthalates have been banned from the market in Canada.

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After conducting this literature review on the impact of phthalates on women reproductive health, several data gaps were identified. The authors recommended that the following actions be conducted:

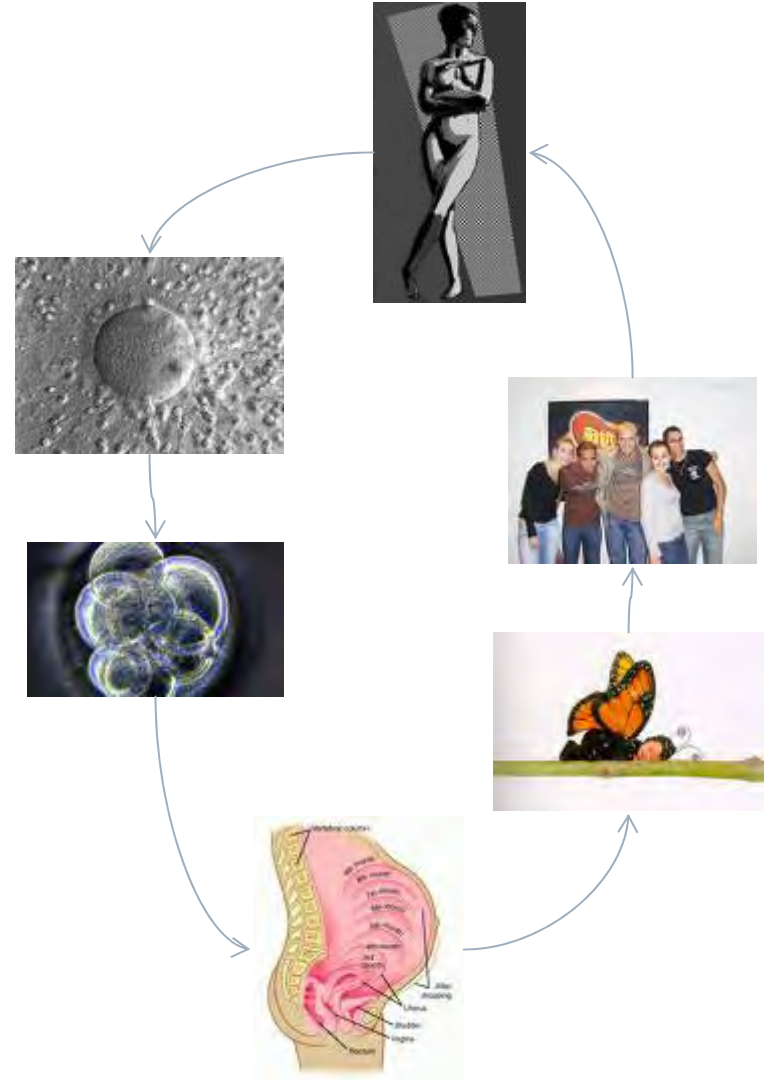
# Longitudinal studies in human

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1. Support population based longitudinal studies to obtain better data on phthalates toxicity during the various stages of life.
2. Promote prospective pregnancy cohort studies, starting periconceptionally until the postpartum period for assessing reproductive and developmental toxicity of phthalates.

# Longitudinal studies in human

3. Expand the scope of these studies to include other aspects of women's reproductive health (e.g. puberty, the menstrual cycle, ovarian and endometrial diseases, menopause, etc).
4. Promote *intergenerational studies* to account for the impact of parental phthalates exposure on future generations.



# Longitudinal studies in human

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5. Promote research in specific settings that may pose higher risks of phthalates exposure to vulnerable population through medical devices (e.g., high risk obstetric services, neonatal and pediatrics intensive care units).
6. Conduct international collaborative studies that would develop and link registries and databases to increase the power of epidemiological studies.
7. Develop guidelines for the assessment of a broad range of developmental and reproductive end points.

# Biomonitoring and analysis techniques

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8. Continue to support biomonitoring programs in the general population (e.g. the Canadian Health Measures Survey and biomonitoring), as well as others focused on susceptible populations such as pregnant women and their offspring (e.g. the Maternal Infant Research on Environmental Chemicals- MIREC Study) being conducted under the Government of Canada's Chemicals Management Plan.

# Biomonitoring and analysis techniques



## MIREC

Maternal-Infant Research  
on Environmental Chemicals

- A National study of *In Utero* and Lactational Exposure to Environmental Contaminants.
- 2,000 pregnant women and their offspring from the first trimester of pregnancy through delivery and up to 6 months after birth.

• <http://www.mirec-canada.ca>



Health  
Canada

Santé  
Canada



Ontario



CIHR IRSC  
Canadian Institutes of Health Research  
Institut de recherche en santé au Canada  
L'Institut de recherche

# Biomonitoring and analysis techniques

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9. Sponsor the collection and storage of body fluids (e.g. blood, urine, breast milk, amniotic fluid, and meconium), as well as human tissues such as placenta and amniotic membranes. This will allow for future analysis when new techniques become available. Also, intergenerational studies will benefit from comparison between samples that have been stored from the parent's generation.
10. Expand research on biological markers of exposure.
11. Validate and standardize tests for measuring phthalate exposures in women.



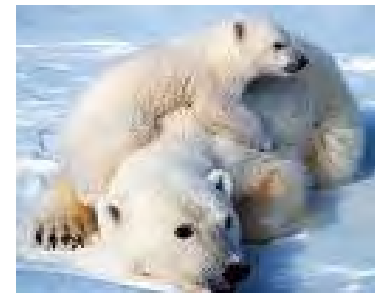
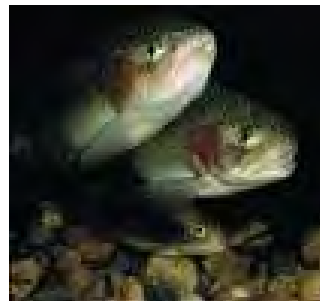
# Animal studies

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12. Develop **animal models** to explore the effects, as well as the underlying mechanisms of effects, of phthalates on female-specific diseases (e.g. endometriosis).



13. Evaluate the impact of phthalates in **wildlife**.

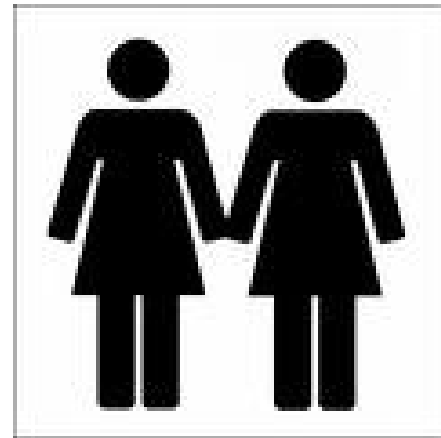


# Genetic susceptibility

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14. Support epidemiological studies that specifically address **gene and gene-environment interactions** specifically for phthalates.

15. Conduct research to determine if there are **gender differences in protective mechanisms** and how those mechanisms contribute to threshold for adverse effects during sensitive periods.

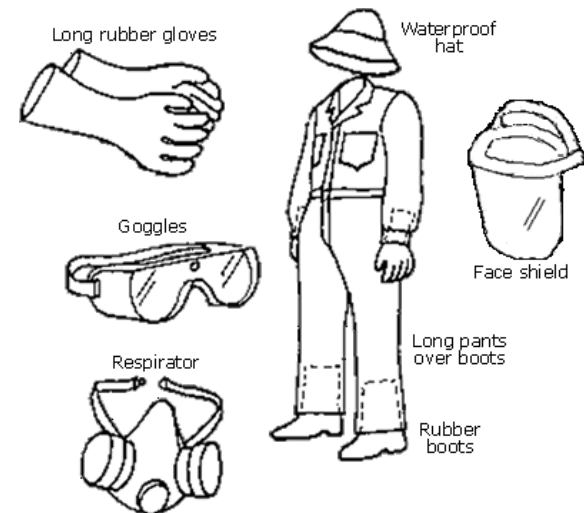


# Workplace conditions

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16. Develop regulations to protect women from the risk of exposure to phthalates in the workplace, especially in small businesses.

17. Place more emphasis on research for appropriate protective equipment for women workers.



# Working with stakeholders

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17. Require stakeholders to label phthalates in commercial products, especially personal day care products, packaging, cleaning agents, and medical devices.

18. Labels designed specifically for pregnant women and their babies should be added to personal day care products.



**Le 25 novembre 2008, la Ministre de la santé Mme Roselyne Bachelot a annoncé plusieurs mesures relatives à l'utilisation de cosmétiques pendant la grossesse:**

la Ministre souhaite faire étudier la possibilité d'apposer, sur les produits reprotoxiques, un logo indiquant qu'ils ne sont pas recommandés aux femmes enceintes et aux jeunes enfants.

# Working with stakeholders

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19. When other alternatives to medical devices containing phthalates are available, medical devices without phthalates should be used, particularly in vulnerable populations such as pregnant women, newborns, infants and young children.





# Education

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23. Introduce in the early school years the importance of an adequate management of plastics in daily life.

24. Include a course on endocrine disruptors, among them the phthalates, for medical students.



# Education

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25. Support conferences to inform the public about the impact of phthalates on health, as well as inform them about the gaps on actual knowledge.

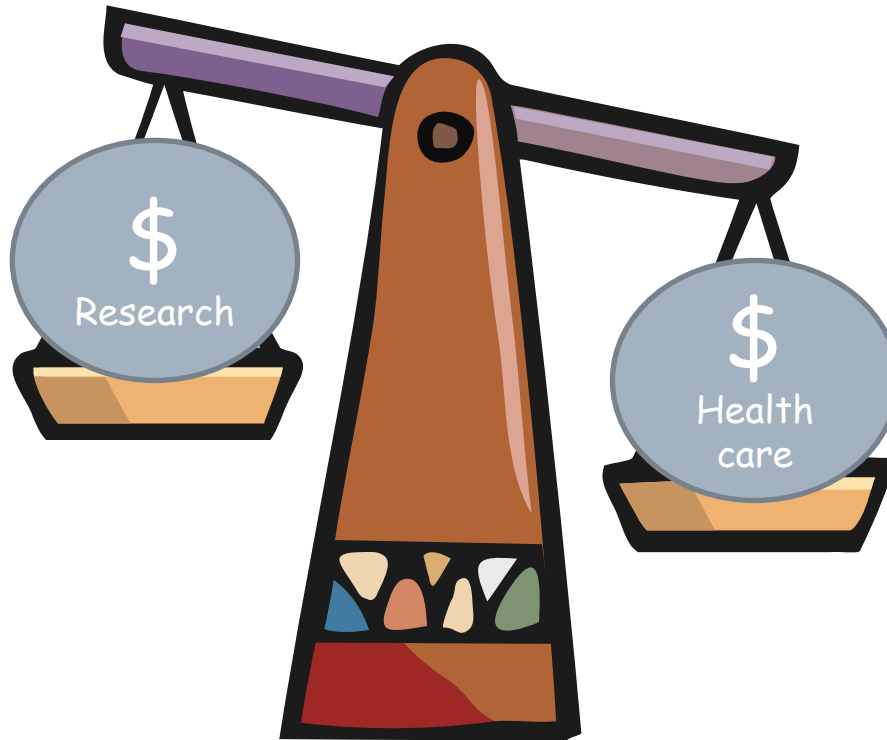




# Conclusions

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- Longitudinal studies in human
- Biomonitoring and analysis techniques
- Animal studies
- Genetic susceptibility
- Knowledge Transfer



- Reproductive tract developmental abnormalities
- Precocious puberty
- Thyroid diseases
- Testicular cancer in young men
- Endometriosis
- Reproductive failure in women
- Preterm birth

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# Thank you !



National Network on  
Environments and Women's Health

Réseau pancanadien sur la santé  
des femmes et le milieu



Health  
Canada

Santé  
Canada