

It would be easy to miss large adverse effects

Consider a prospective study of 10,000 pregnant women

- **Assume an ectopic pregnancy rate = 5 per 1,000**

If none were DES exposed 50 ectopic pregnancies would be expected

Unless DES was under study, a 10-fold increase in risk could be missed,

- **Assume DES increases risk of ectopic pregnancy 10-fold = 50 per 1,000**
- **Assume 1% (100) women were DES exposed**
- **55 ectopic pregnancies would be expected**

Unless DES was under study in relation to ectopic pregnancy

This 10-fold increased risk in DES-exposed women would have been missed

Classical Epidemiology

First alert	Health problem in humans (DES, DBCP)
What is studied	Does a (single) exposure cause a (single) outcome
Exposure	Isolated (or few)
Level	Moderate/high
Prevalence	Rare/uncommon
Route	Single
Outcome	Isolated (or few)
Type	Severe; dichotomous (e.g. cancers, malformations)
Prevalence	Rare/uncommon
Cofactors	Confounding or effect modification by variables (e.g. age, race) separately

“Environmentally Sensitive” Epidemiology

First alert	Abnormalities in wildlife (or screening test)
What is studied	Multiple exposures (pattern): multiple endpoints (pattern)
Exposure(s)	Multiple (pattern)
Level	Very low/low
Prevalence	Variation is important because exposure is ubiquitous
Routes	Multiple (food, air, water, dermal)
Outcomes	Multiple (pattern)
Type	Array of continuous variables and their pattern (e.g. semen quality, cognitive function)
Prevalence	Must be redefined to reflect variation in patterns
Co-factors	Modification (interactively) by genetics, infectious and environmental agents

Conducting Environmentally Sensitive Epidemiology

- **Let toxicology and ecotoxicology drive hypotheses (find human analogues)**
- **Use true *Multivariate Analysis* (the study of multiple endpoints and their interactions)**
- **Define *patterns of disruption* (testicular dysgenesis syndrome, genital dysmorphology)**
- **Incorporate *feedback systems* in causal models**
- **Explore mathematics of *complex systems* (Complexity Theory, nonlinear dynamics)**

Default assumptions

- **All irreversible developmental changes result from *Alterations of Endocrine Signaling Systems***
- **Small shifts in individual development can cause larger effects *at the population level***
- **All exposures producing irreversible developmental changes in experimental systems produce *analogous changes in human and wildlife populations (Precautionary Principle)*.**