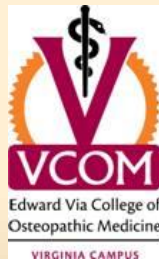


Reproductive and Developmental Toxicity of QACs

Toxics Use Reduction Science Advisory Board Meeting
January 14, 2021

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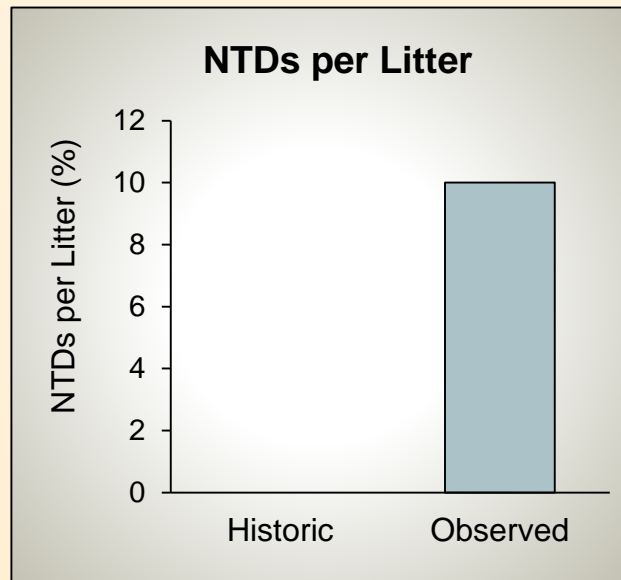


DISCLOSURE

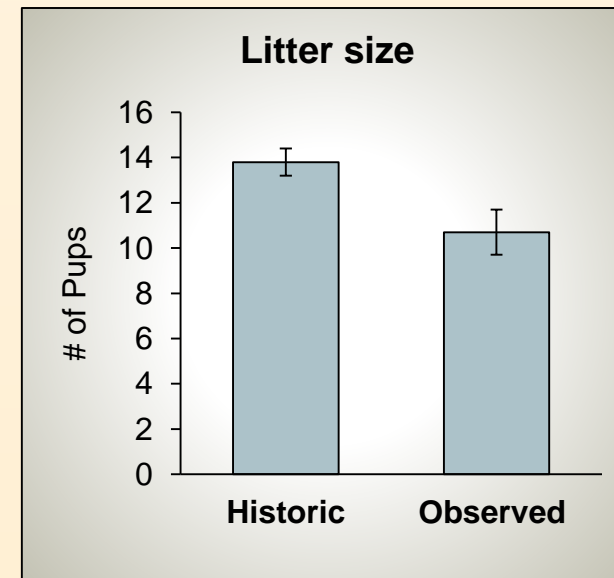
I have nothing to disclose; no financial or other ties which would pose a conflict of interest

Initial Findings – from a change in disinfectant

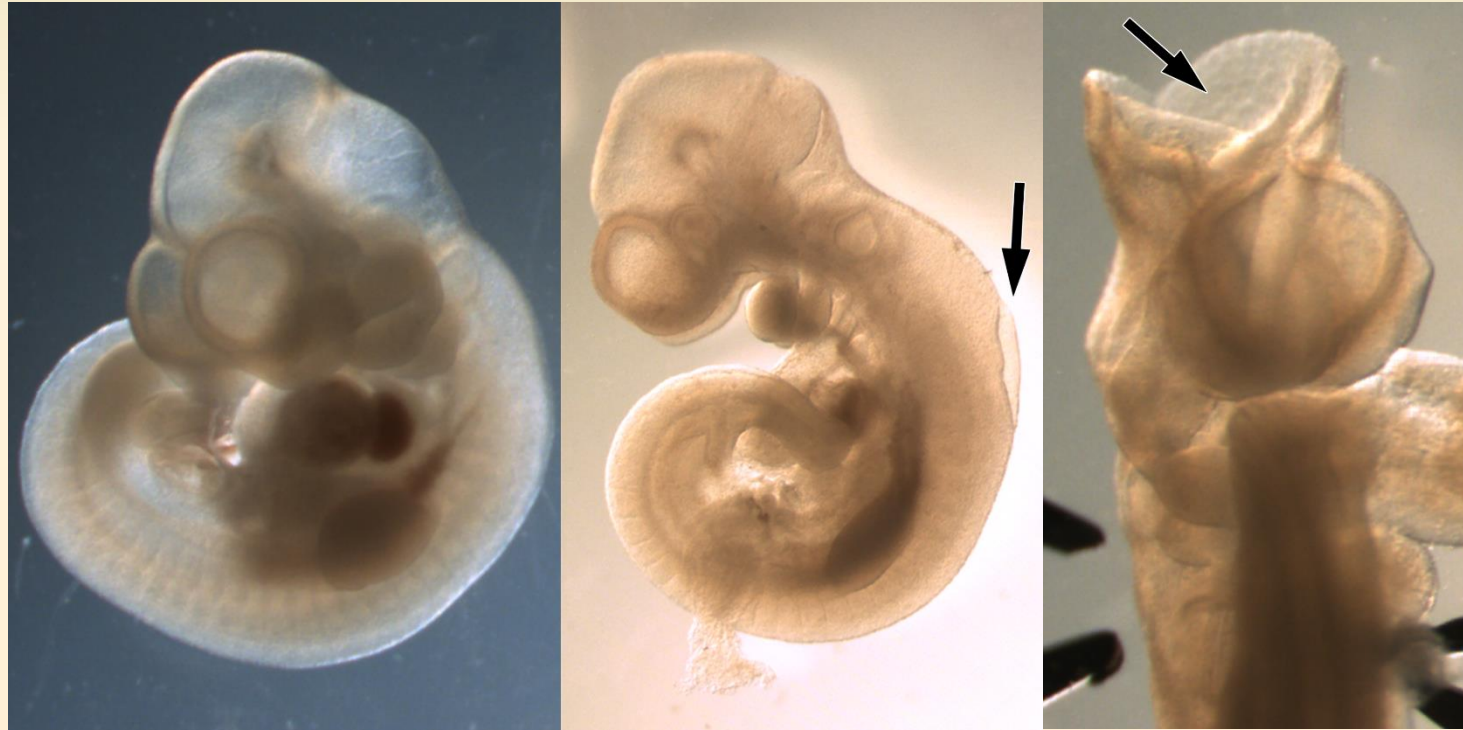
Control mice suddenly developed Neural Tube Birth Defects (NTDs)



Decrease in number of mouse pups born

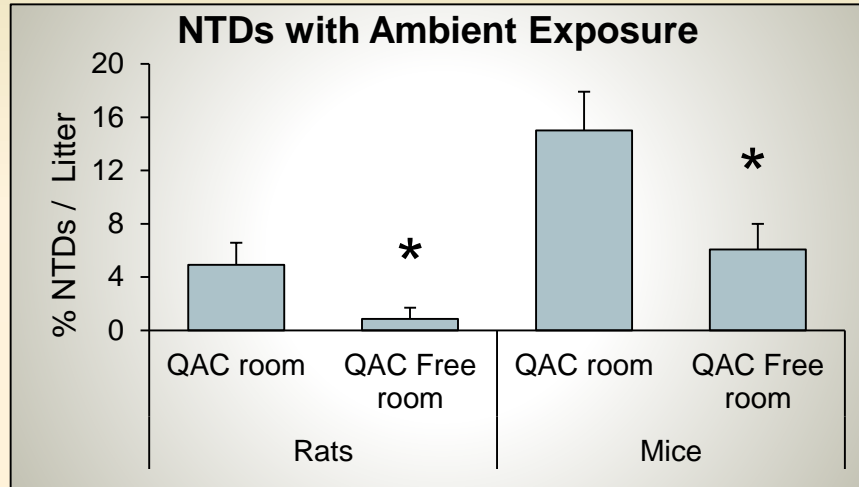


What is an NTD?



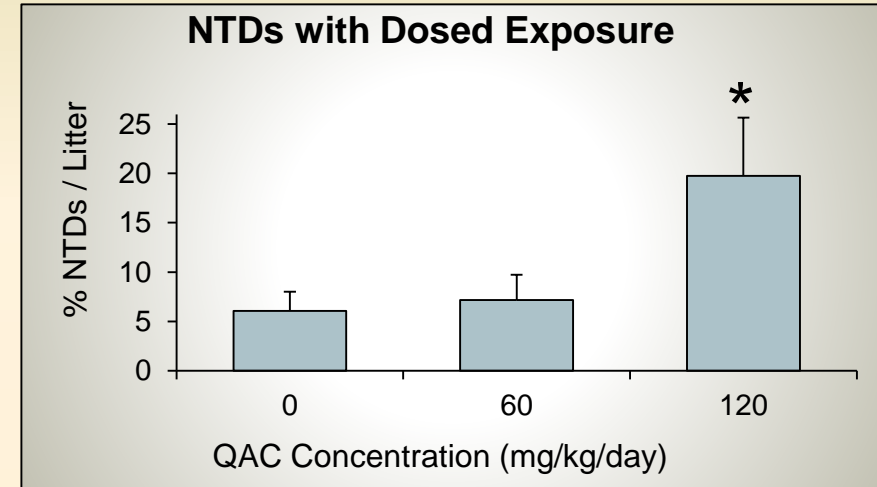
In Humans, NTDs cause Anencephaly and Spina Bifida

Testing the Disinfectant

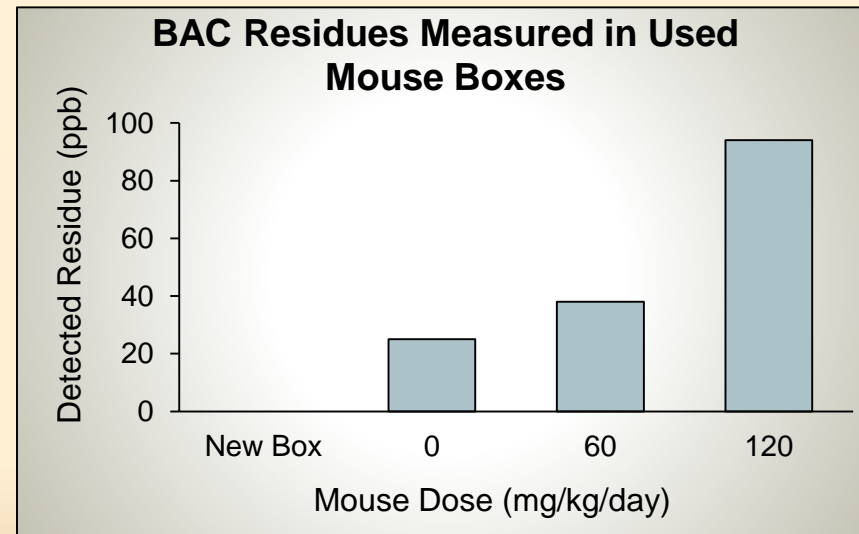


10-12 litters per treatment

* Significantly different



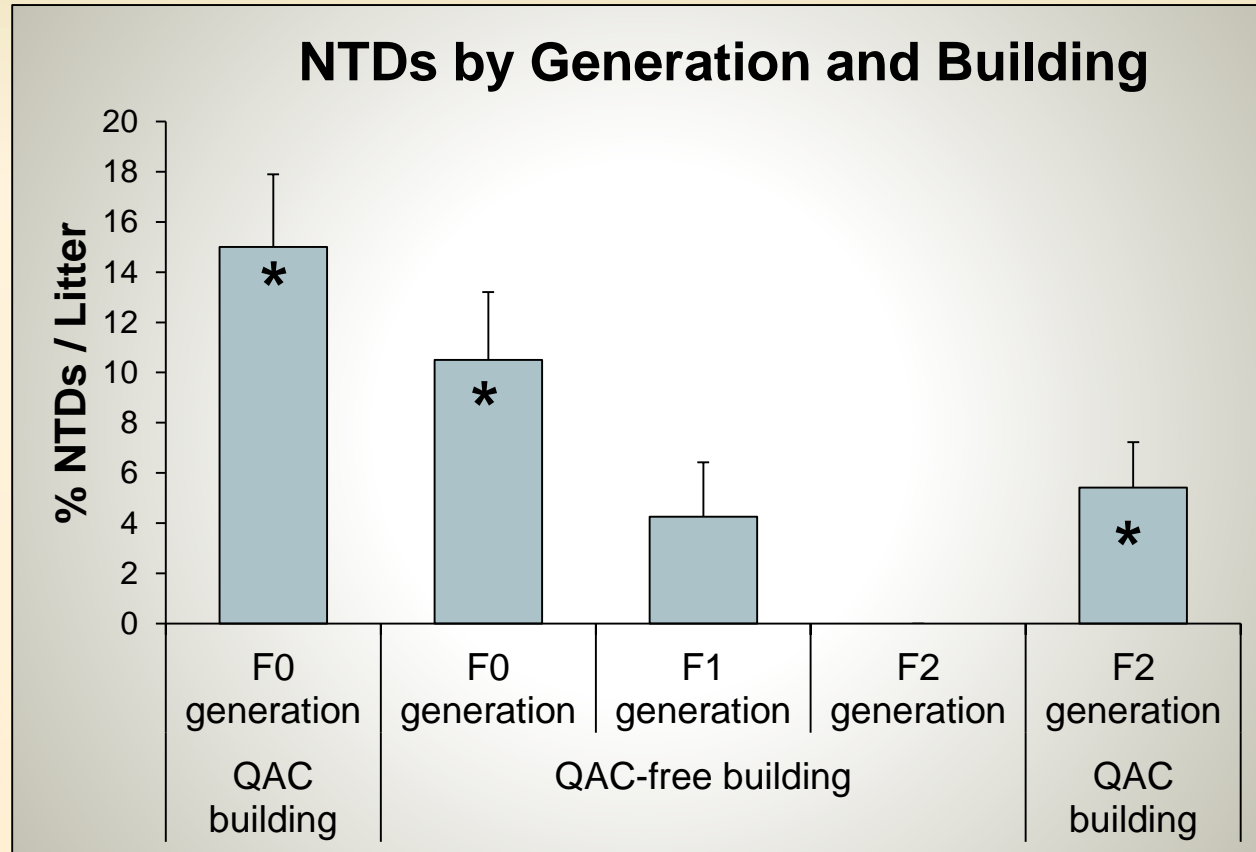
Dosed in the feed



5 boxes per group

- Moving to a QAC-free room helped, but we still saw NTDs
- Even in the QAC-free room, boxes became contaminated after 1 week

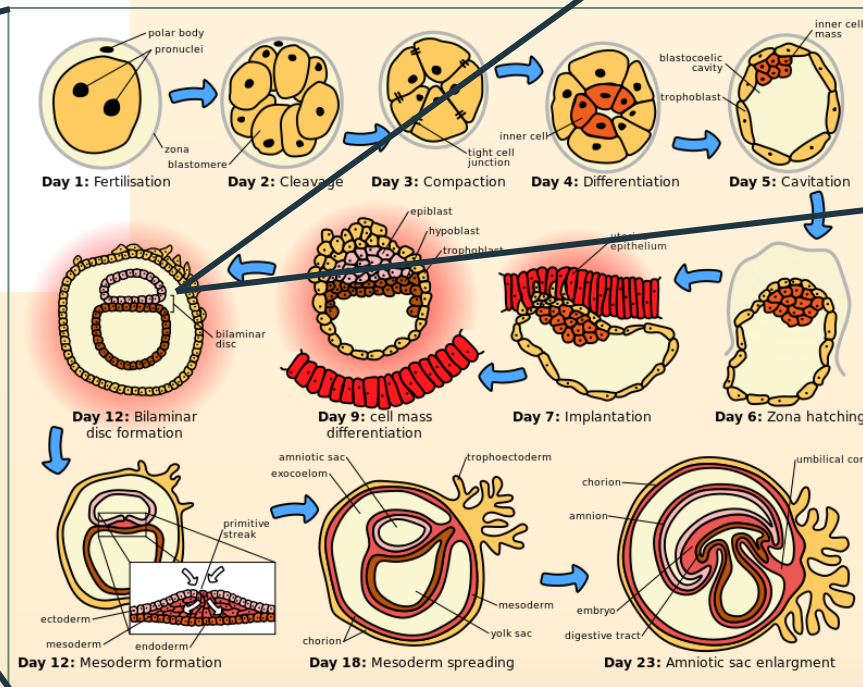
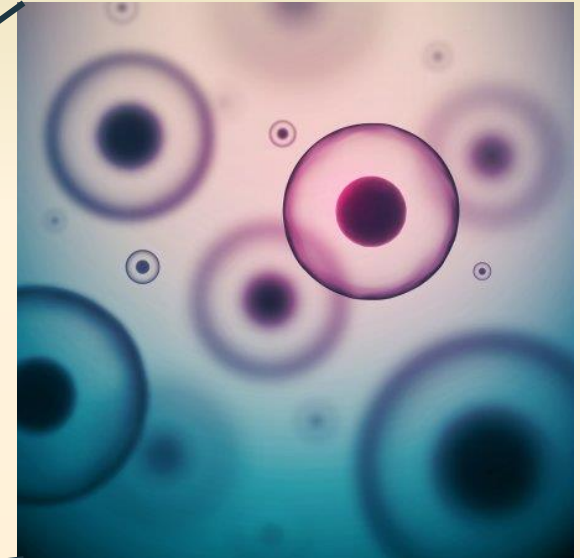
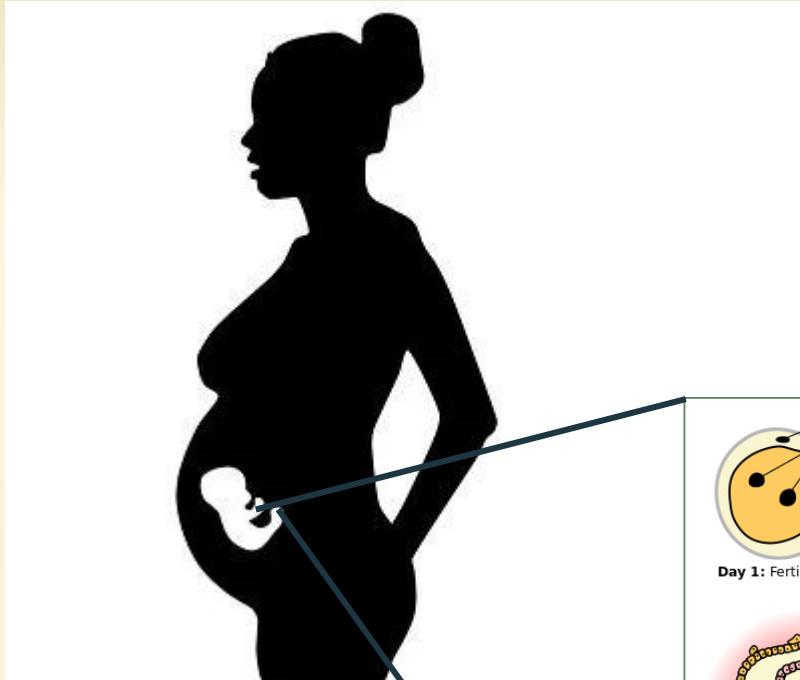
Finding the Negative Control



Ambient Exposure

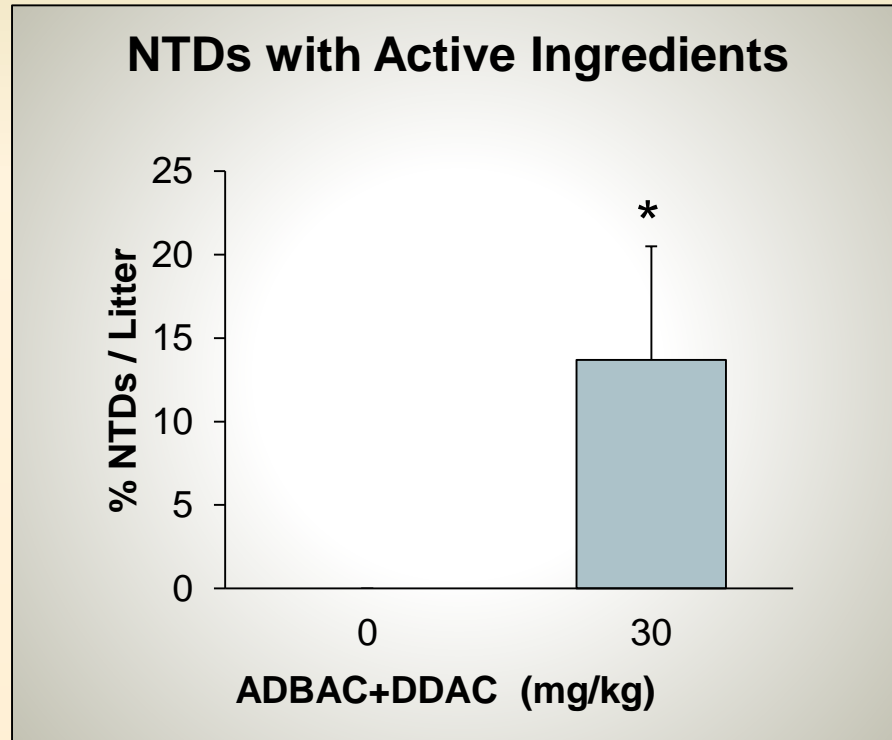
NTDs persisted until the offspring of the F2 generation

Why Did it Take 2 Generations?



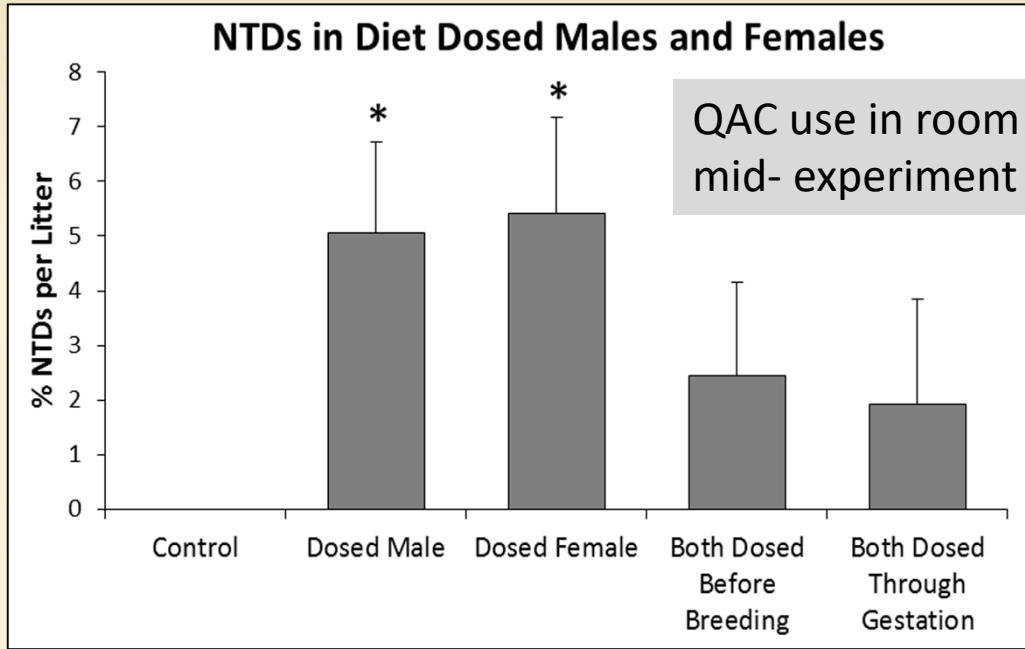
Male and Female germ cells (stem cells for next generations egg and sperm) are formed 12 days after fertilization when the entire embryo is only 500 cells

Confirming the Active Ingredient

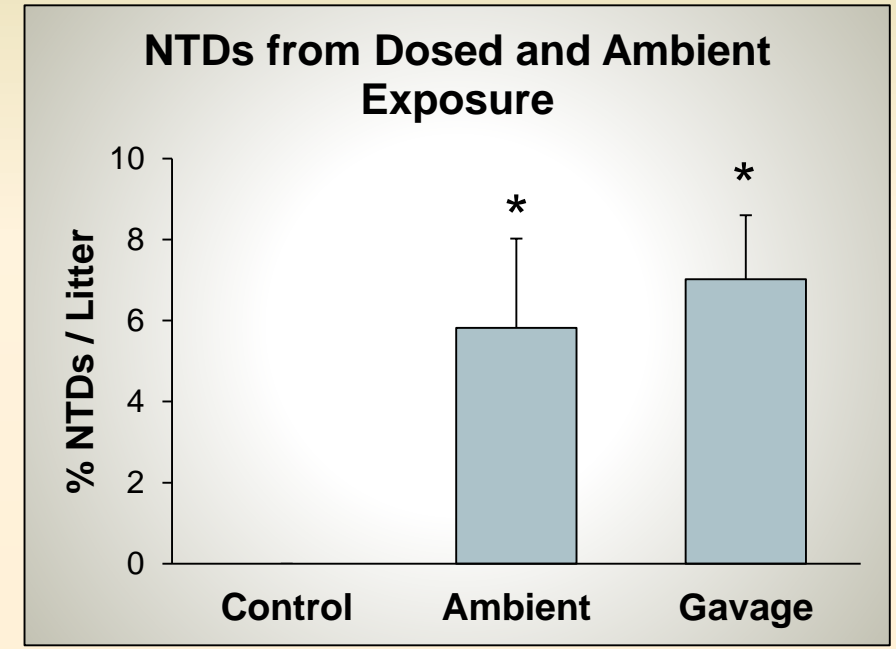


- The active ingredient in the disinfectant caused NTDs
- Shows that it is not some other property of the disinfectant

Characterizing Exposure



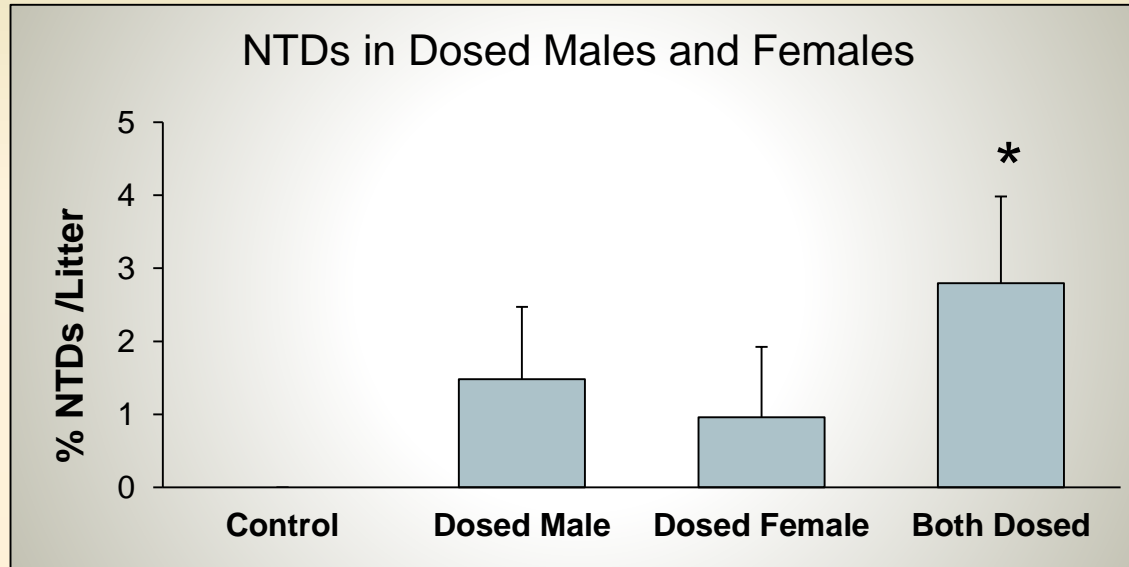
120 mg/kg/day for 8 weeks



Males received 7.5 mg/kg every other day for 10 days prior to breeding
Females received one dose of 7.5 mg/kg on day 8 of gestation
Both groups received ambient exposure

- Exposure to EITHER males or females causes NTDs
- Ambient exposure more important than dose exposure
- Only need to dose at “critical time periods”

Male and Female Exposure



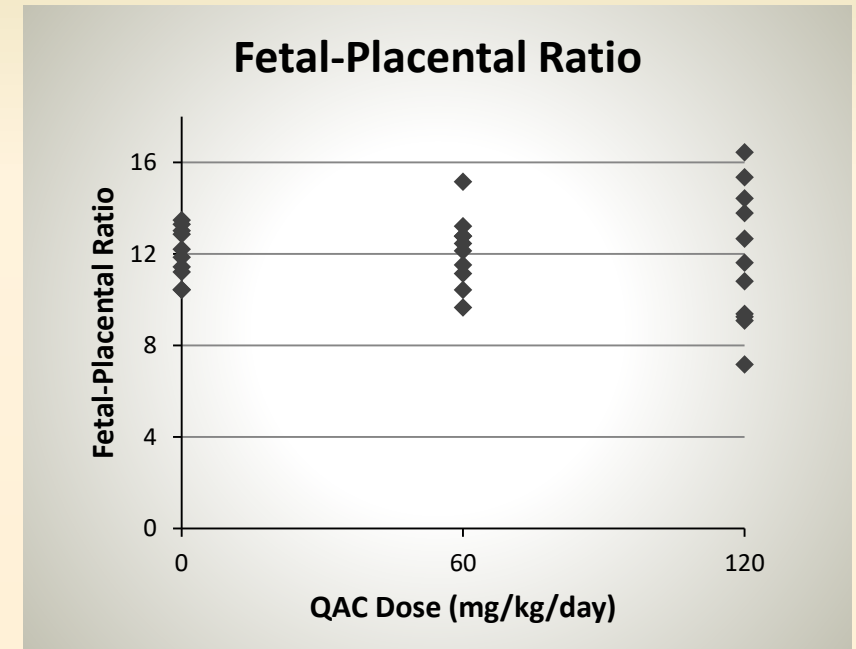
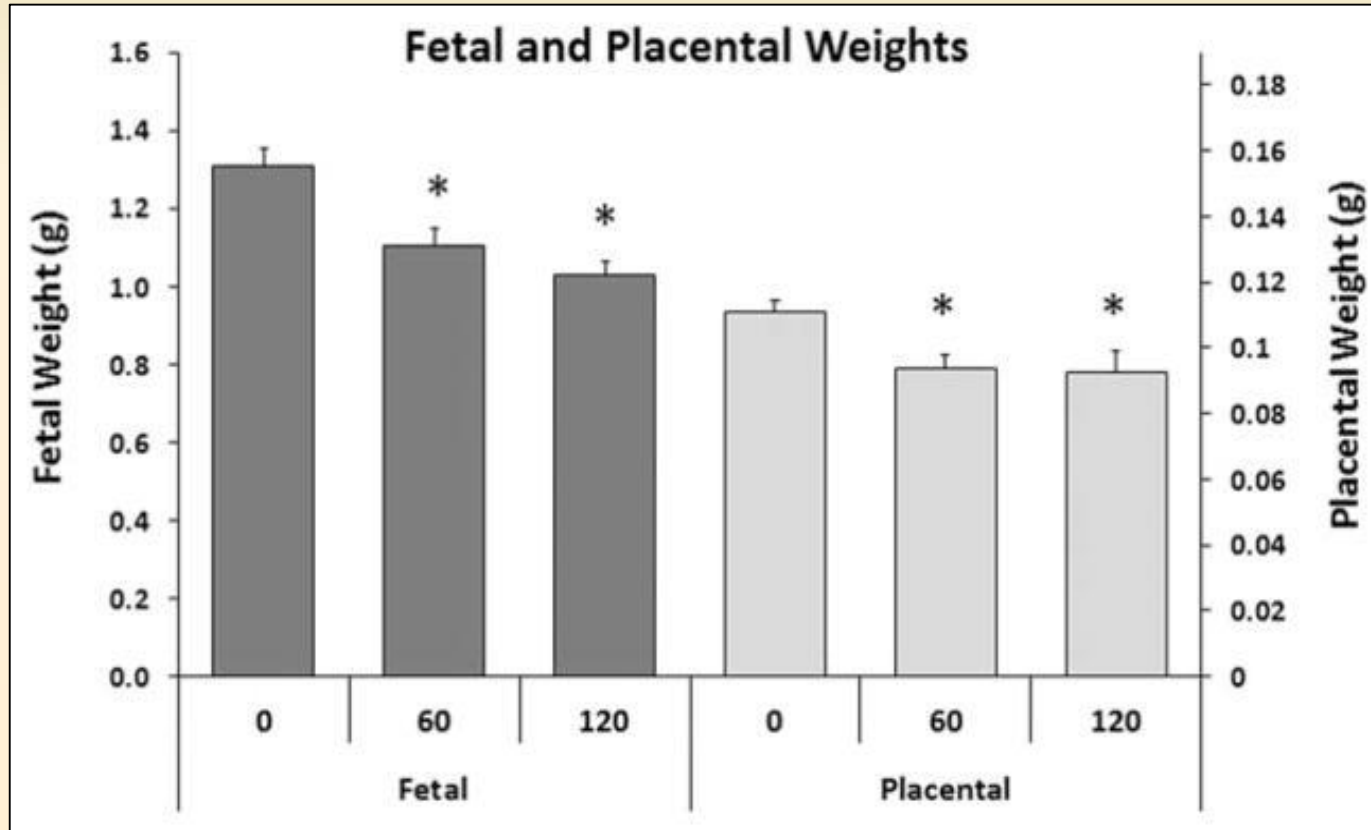
- Confirmed that exposure to EITHER males or females causes NTDs
- Effect is additive
- With no ambient exposure, a higher oral dose can be used

Males received 30 mg/kg every other day for 10 days prior to breeding

Females received one dose of 15 mg/kg on day 8 of gestation.

There was no ambient exposure

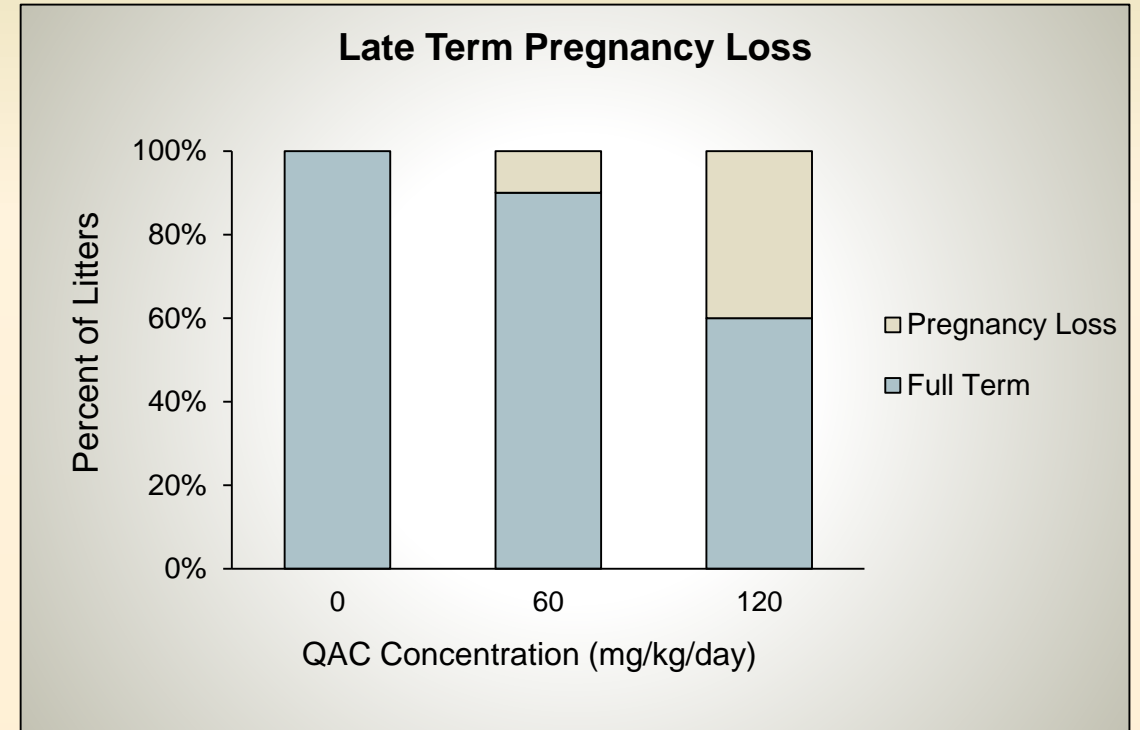
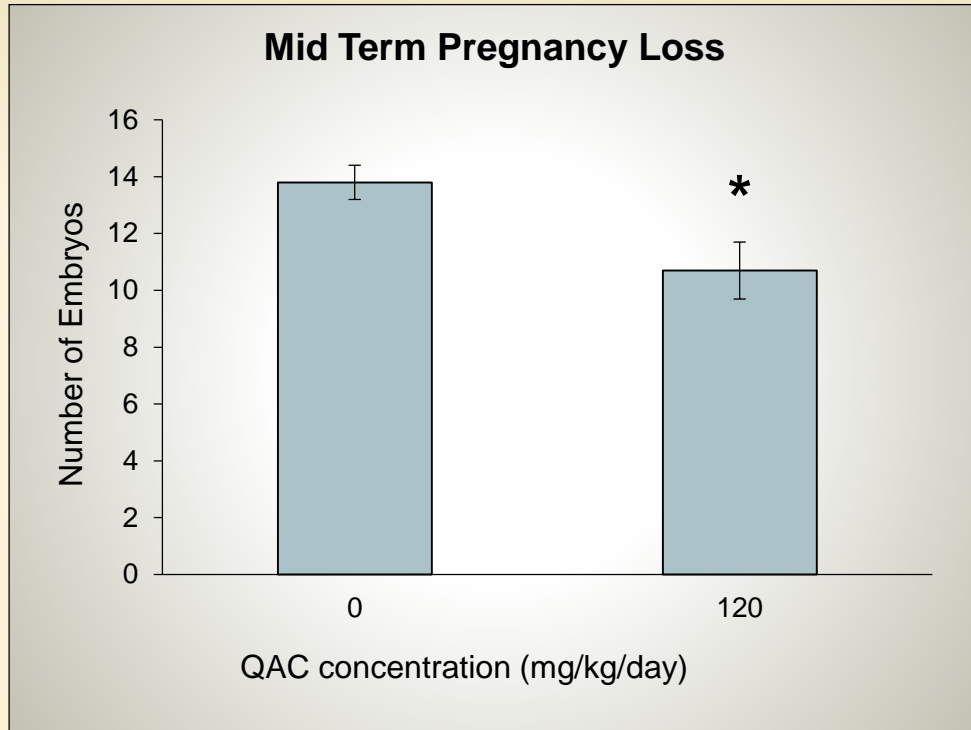
Later in Development: The Placenta



Fetal placental mismatch can cause:

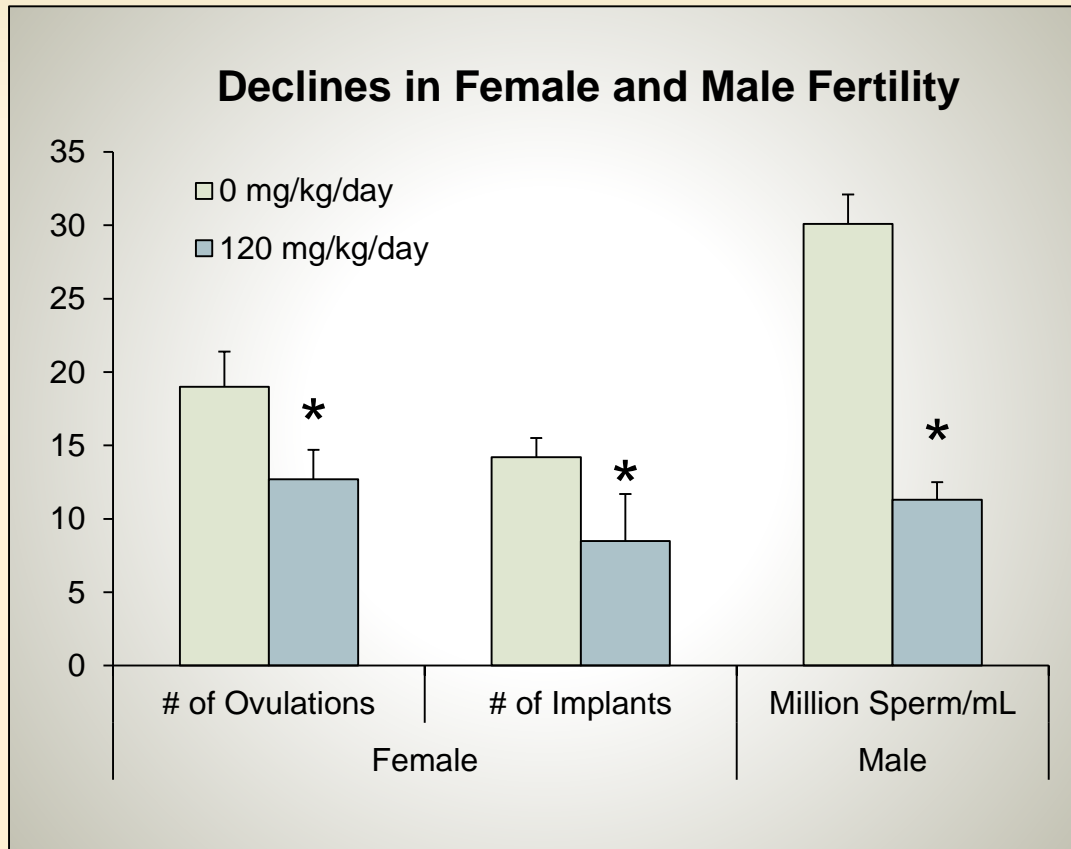
- Fetal death
- Low birth weight
- Preterm labor

Later in Development: Fetal Loss

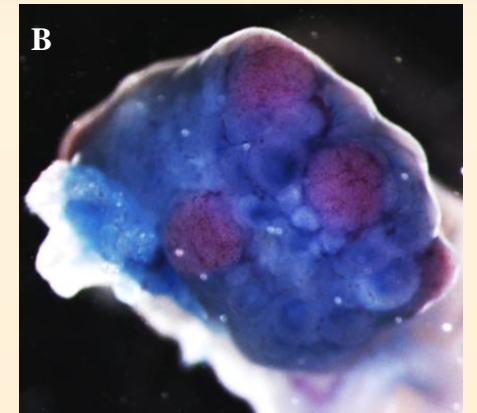


QAC Exposure caused fetal loss, both mid and late gestation

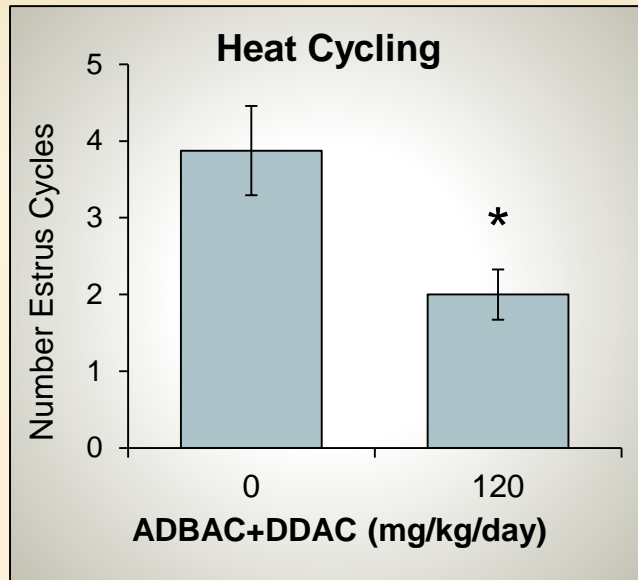
Fertility



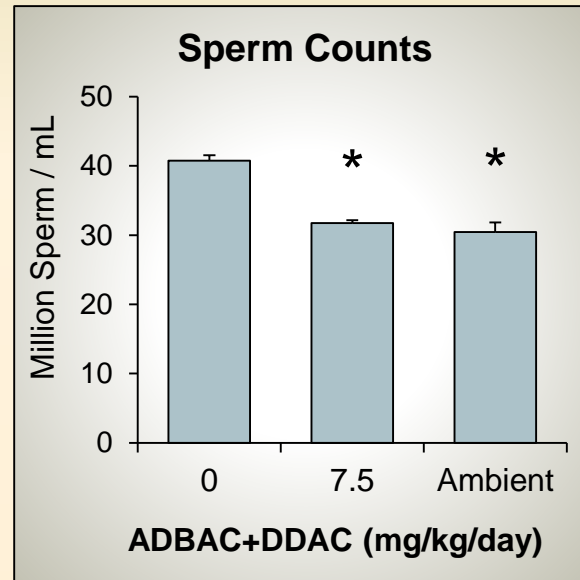
8 Week Dose Exposure



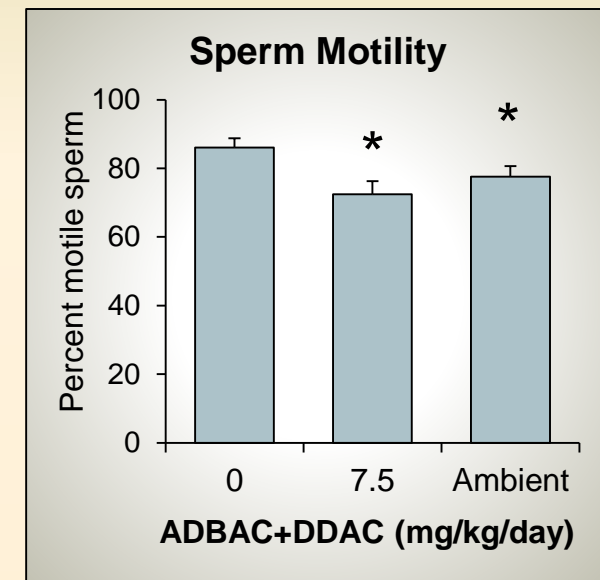
Fertility continued



Cycles in 3 weeks – Dose exposure

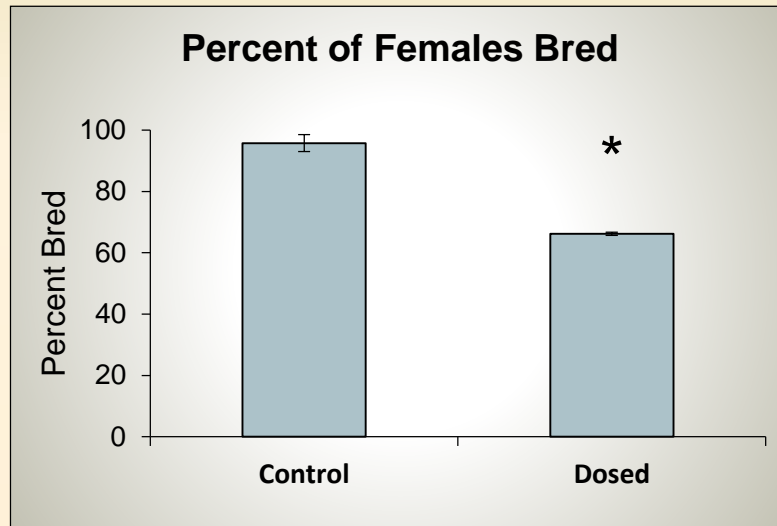


Ambient and Dose exposure

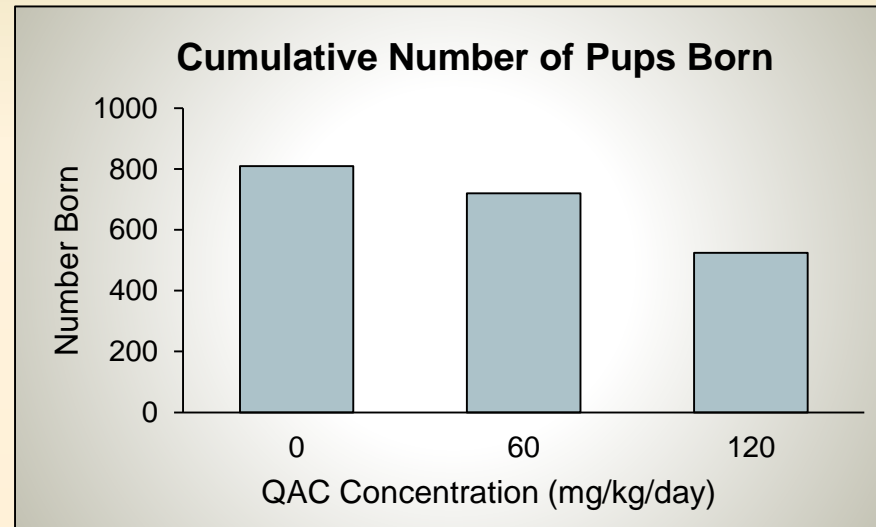


- Significant declines in both male and female fertility
- Effects seen with dose and ambient exposure

Fertility continued



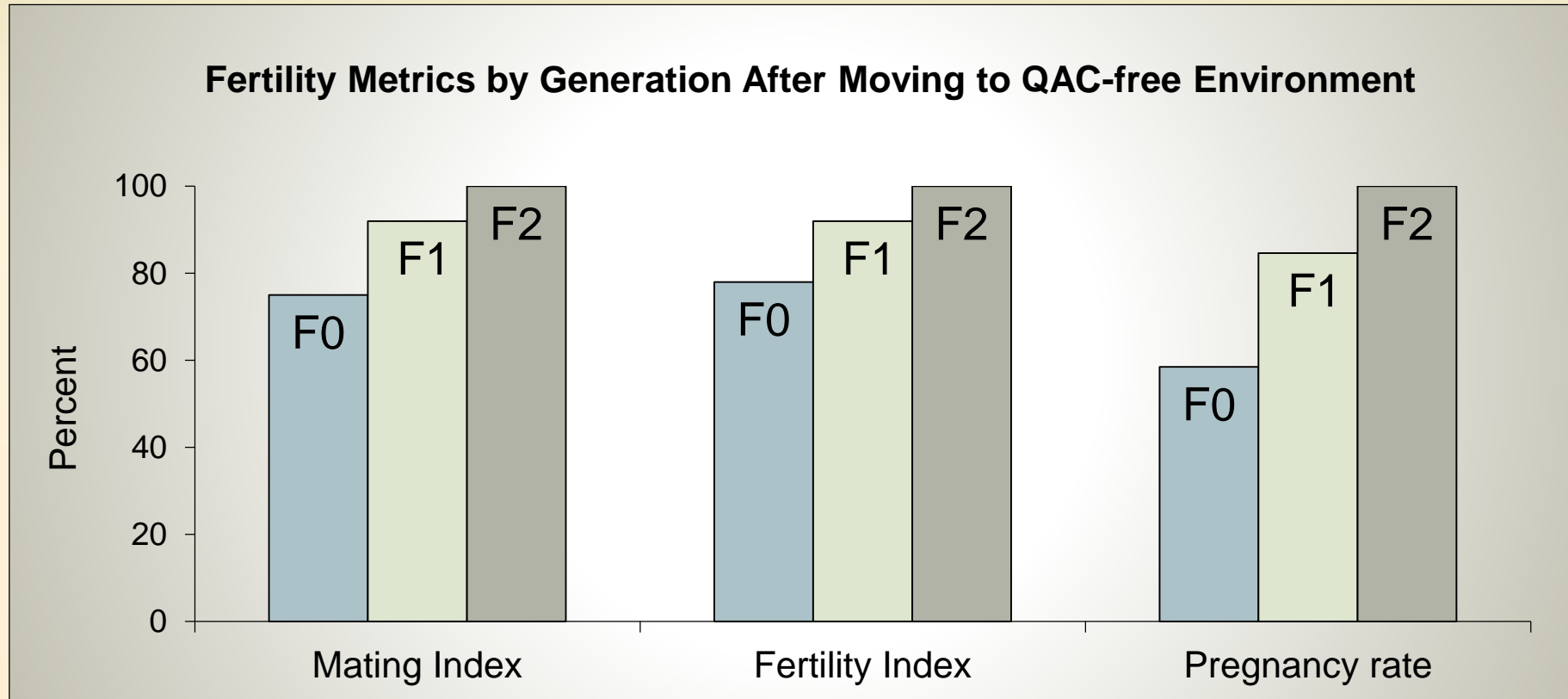
Males dosed with QAC, transferred to QAC-free room for 10 days, then bred to QAC-free females. N = 8 males, with 4 females/male.



Over the 6 month breeding trial

The end result from all the insults to reproduction is a dramatic decrease in the total number of pups born

Fertility continued



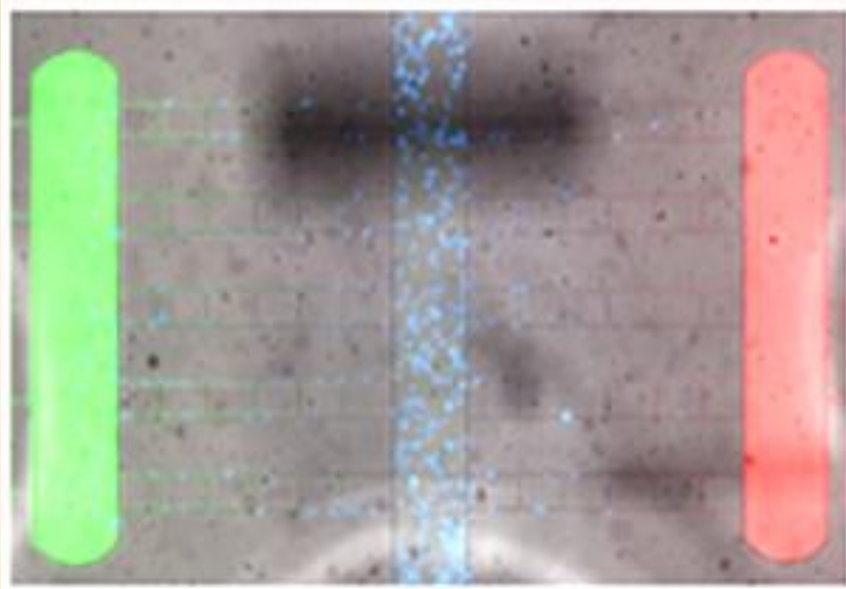
Mating index = $\# \text{ bred} / \# \text{ cohabited}$

Fertility index = $\# \text{ pregnancies} / \text{number bred}$

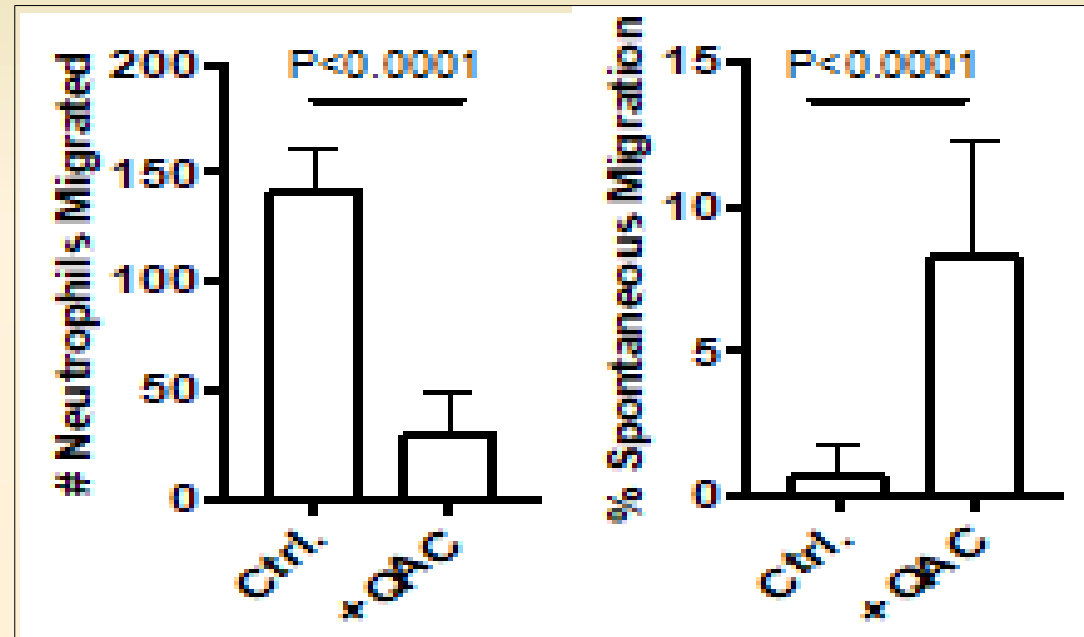
Pregnancy rate = $\# \text{ pregnancies} / \# \text{ cohabited}$

Fertility returned to normal after 2 generations

Immune Function: Neutrophils



Microfluidic device



N=12

Decision making in neutrophils isolated from ambiently exposed mice is altered

- Directional Migration is decreased (movement toward an attractant)
- Spontaneous Migration is increased (movement without attractant)
- Both are bad

QACs in Humans

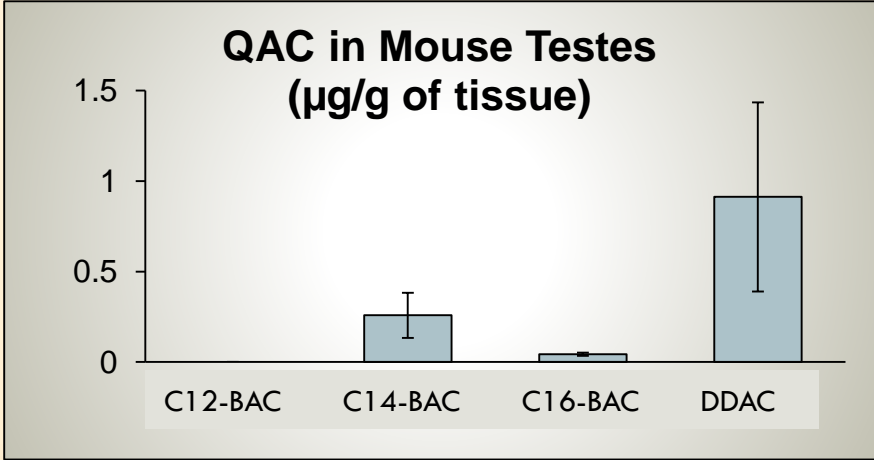
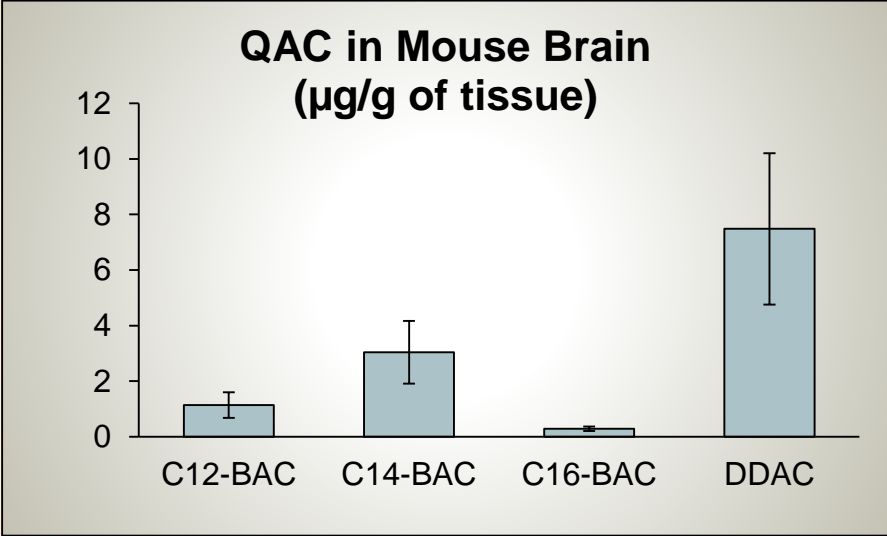
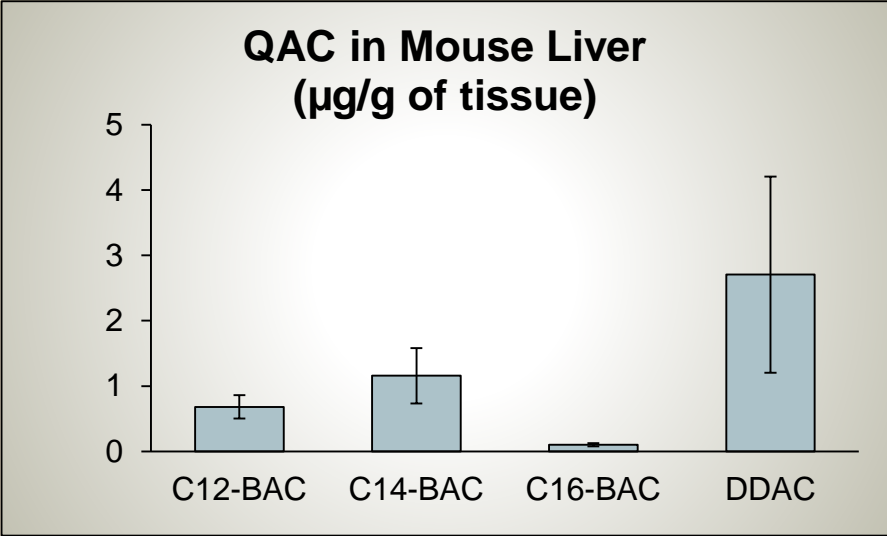
EXPOSURE is UBIQUITOUS

- 50% of first year medical students had QAC residues on their hands
(based on a one point in time assessment)
- Over 5,000 household products contain a QAC (based on publically available household product databases)

QACs in Human Screening Trial

- 43 participants enrolled in a screening trial
- 80% contained BAC and DDAC in their blood
- All four QACs measured (C12-BAC, C14-BAC, C16-BAC, DDAC) were detected in the blood
 - Increased markers of inflammation
 - Decreased mitochondrial function
 - Altered cholesterol synthesis

Implications



Numerous patents for use as contraceptives since the early 1970s

Licensed for use as a spermicide in Canada and Europe

Implications continued

I am not saying QACs are implicated in any disease

However, the possibility exists

- QAC use has increased dramatically in the last 30 years and will likely continue
- This rise in use follows the same trends as:
 - **Increases in**
 - Obesity
 - Diabetes
 - Autoimmune disorders
 - Asthma
 - Allergy
 - Autism
 - **Declines in**
 - Male and Female Fertility
 - Sperm counts
 - These disorders are characterized by
 - Increased inflammation
 - Mitochondrial dysfunction
 - Alterations in cholesterol homeostasis