Reproductive and Developmental Toxicity of Selected QACs: A Chemical Detective Story

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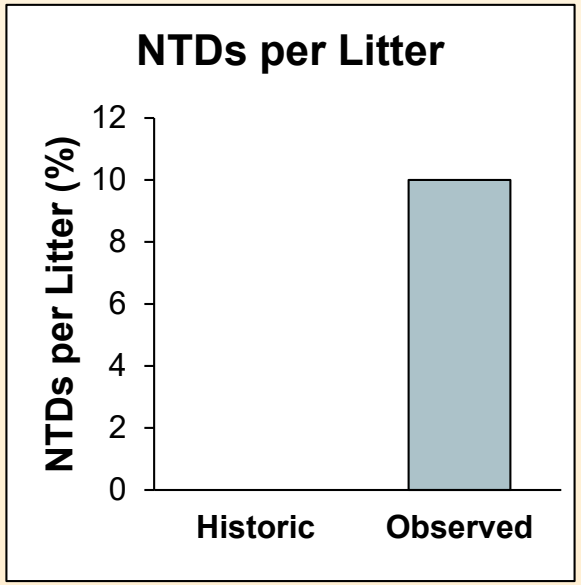
DISCLOSURE

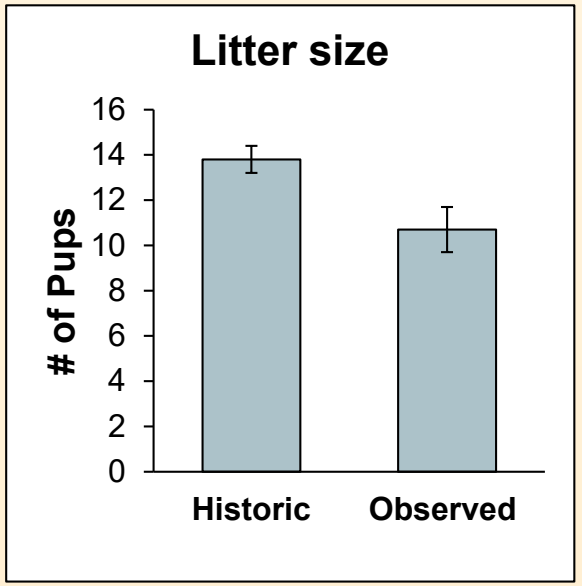
I have nothing to disclose; no financial or other ties which would pose a conflict of interest

Stage 1. “The Crime Scene”

Control mice suddenly developed Neural Tube Birth Defects (NTDs)



Also noticed a decrease in number of mouse pups born



Stage 2. “The Investigation”

- No change to animal husbandry, diet, source of mice, etc.
- Serology was negative for known mouse pathogens
- Toxicologic analysis of the food, bedding, enrichment materials was negative
- Rearing mice in a sterile environment had no effect

Stage 2. “The Investigation” continued

Further questioning of the animal care supervisor revealed that they recently switched to a new disinfectant in the mouse room

- Floors, walls, and racks are foamed once a week
- Floors are mopped daily
- Mouse boxes are sprayed before opening
- Hands are wetted with disinfectant prior to handling mice

Stage 3. “The Prime Suspect”

Quaternary Ammonium Disinfectant

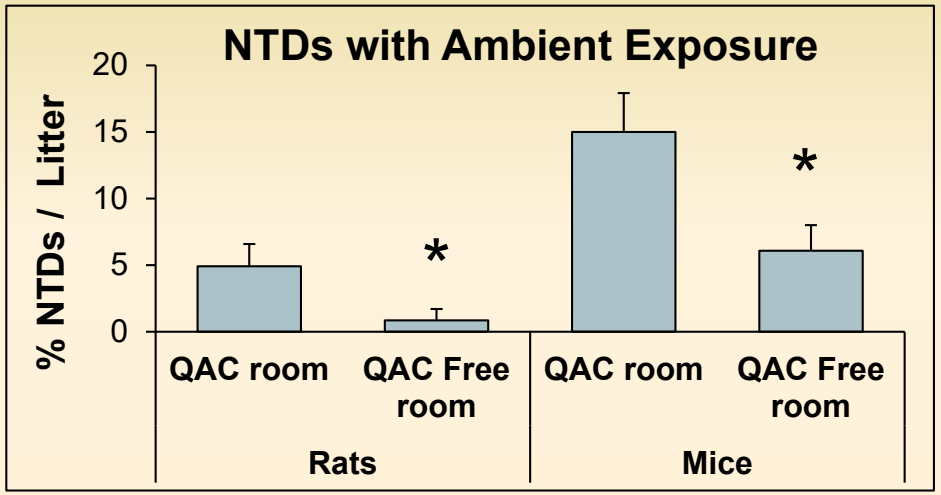
Specifically a mixture of:

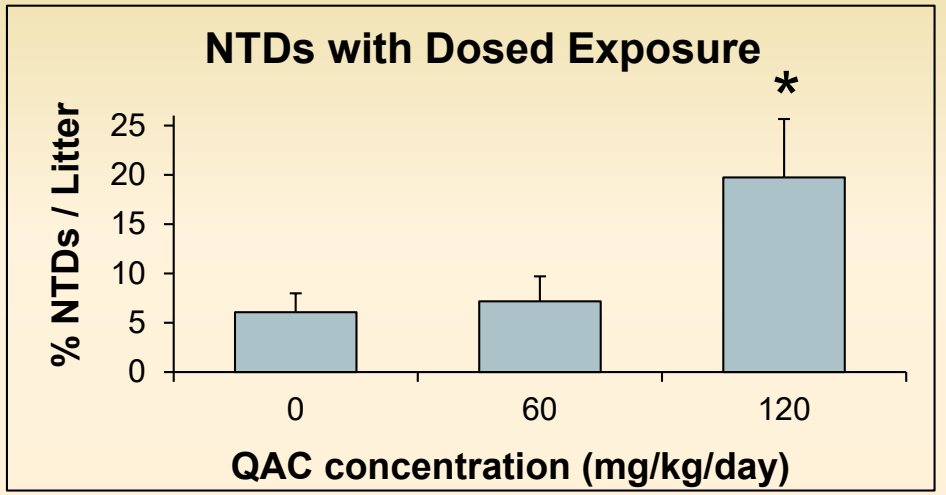
6.76% Alkyl dimethyl benzyl ammonium chloride (ADBAC, BAC) with 60% C-14, 25% C-12, 15% C-16 chain lengths

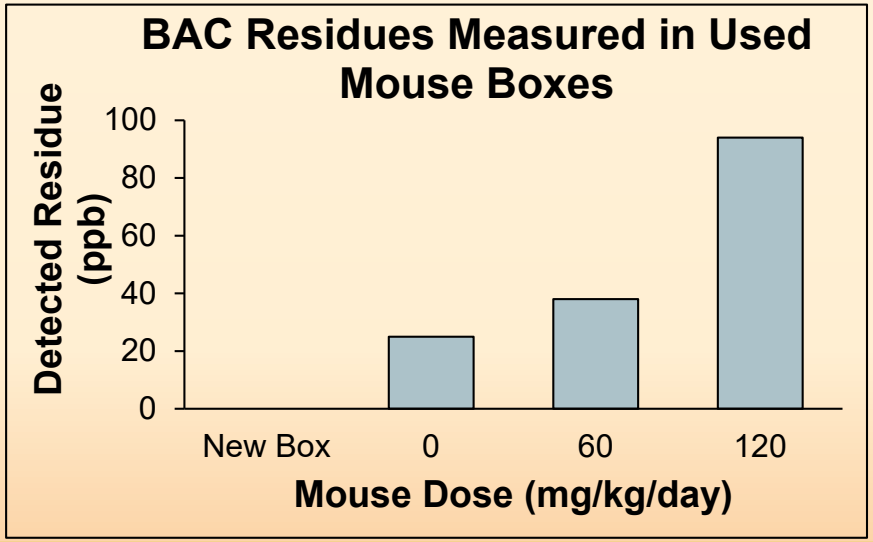
and

10.1% Didecyl dimethyl ammonium chloride (DDAC)

Stage 4. “Building the Case”





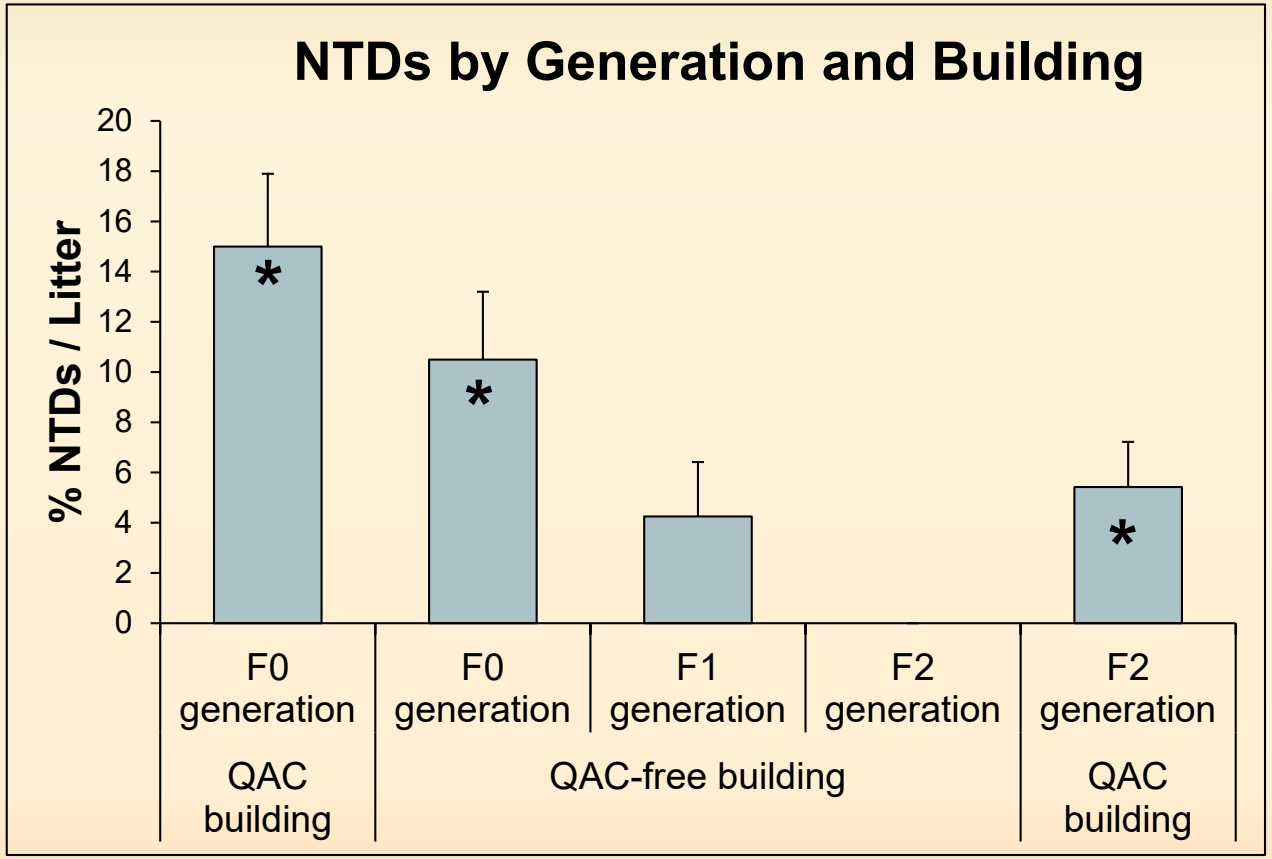


N = 10-12 litters per treatment
5 boxes per treatment

* Denotes significantly different

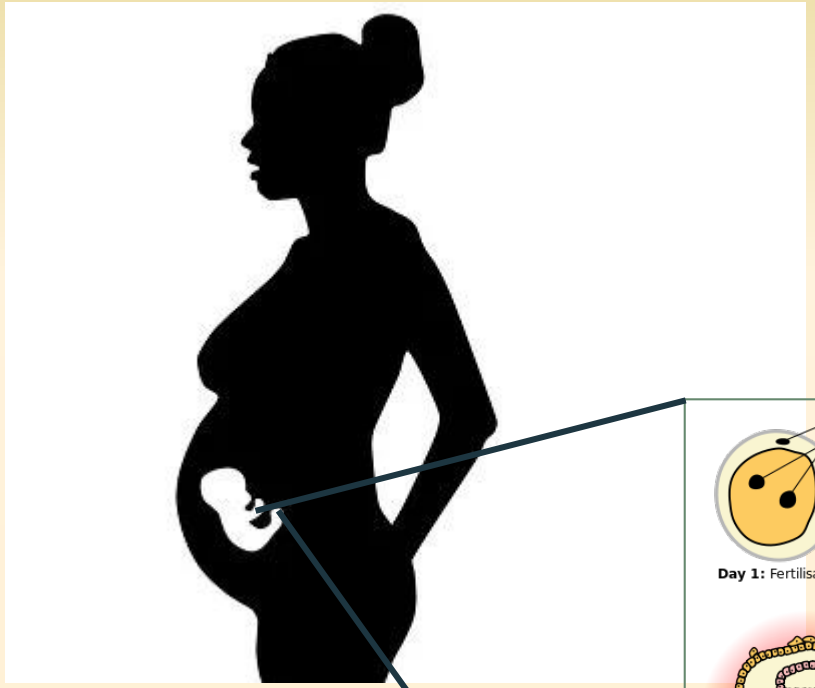
Stage 4. “Building the Case” continued

- NTDs persist until the offspring of the F2 generation

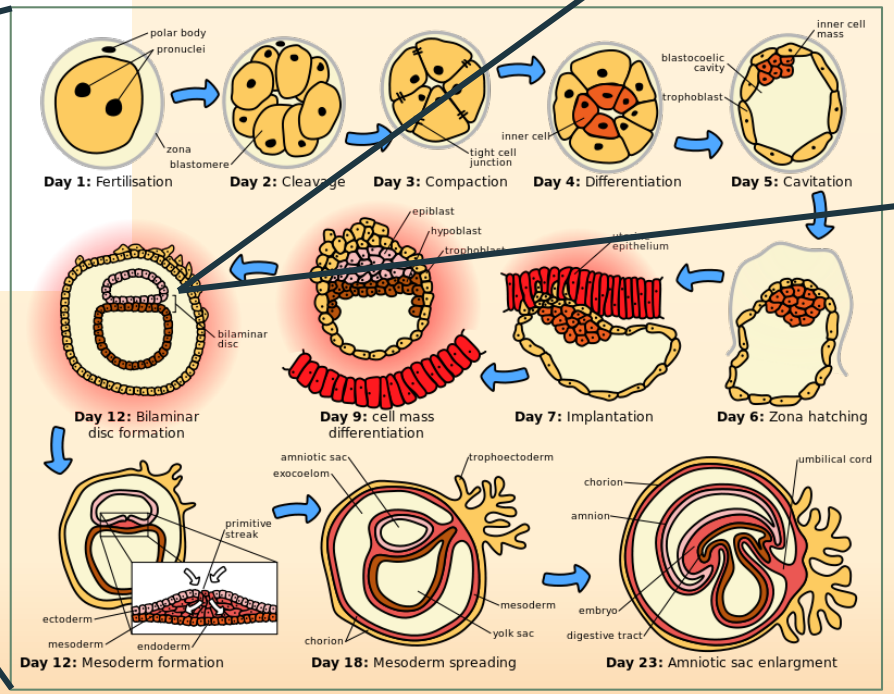


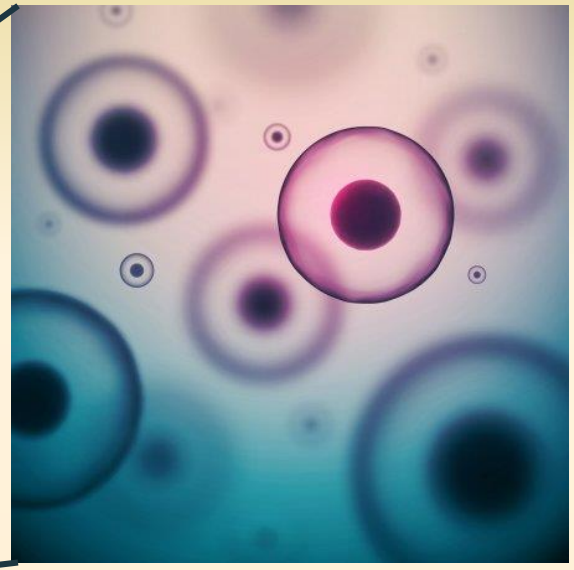
Ambient Exposure

Stage 4. “Building the Case” continued



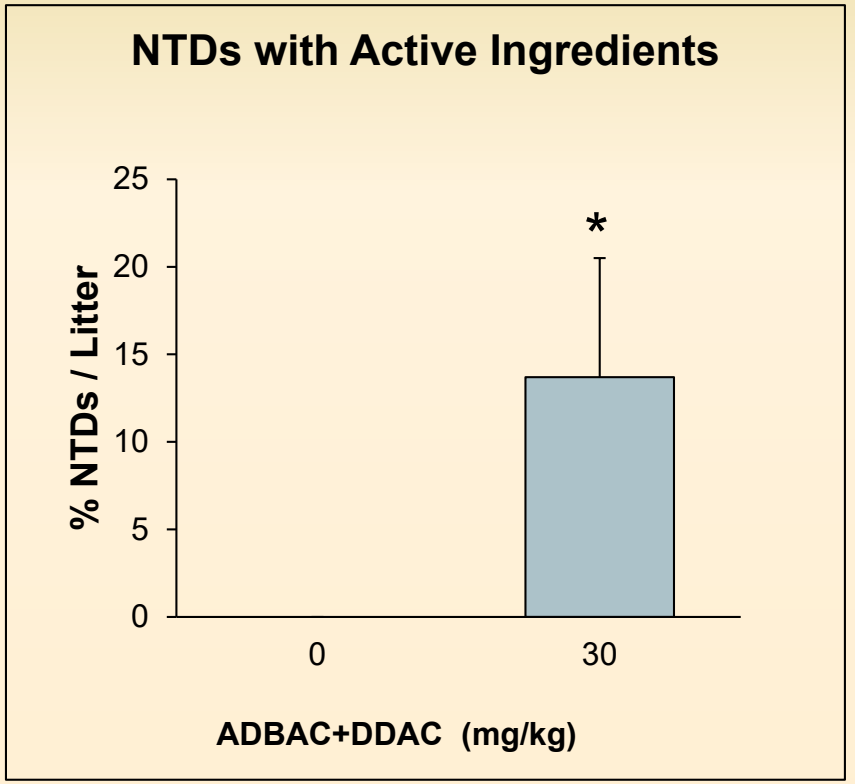
About 500 cells at this stage





Male and Female germ cells, stem cells for next generation egg and sperm, are formed by day 12 of development

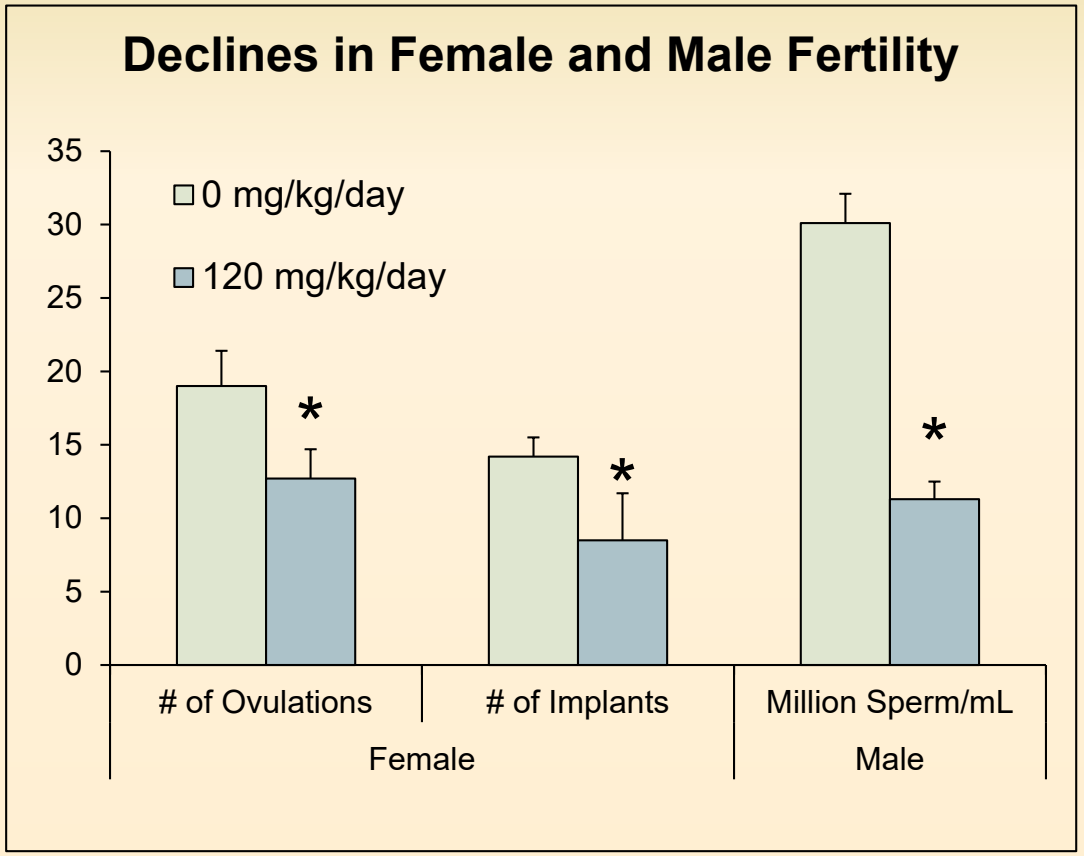
Stage 4. “Building the Case” continued



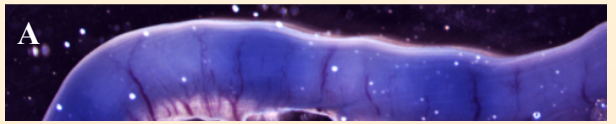
Stage 5. "Testing the Hypothesis"

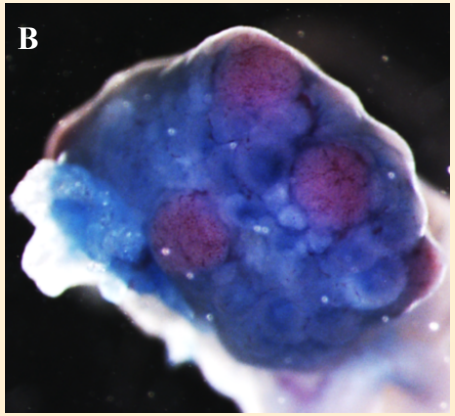
Test	Result
Facilities using QAC disinfectant vs. those not using QAC disinfectant	Reproduction and Development return to normal in the Non-QAC facility
Ambient exposure vs. oral dose	No difference in result, or slight increase in dosed over ambient
Dose with cleaning product vs. a combination of the individual active ingredients (in the same proportion)	No difference in response
Oral gavage vs dose in the feed vs. dose in the water	Gavage >> in feed > in water
Male exposure vs. female exposure	Both are affected. Male only exposure still causes NTDs

Stage 5. Fertility



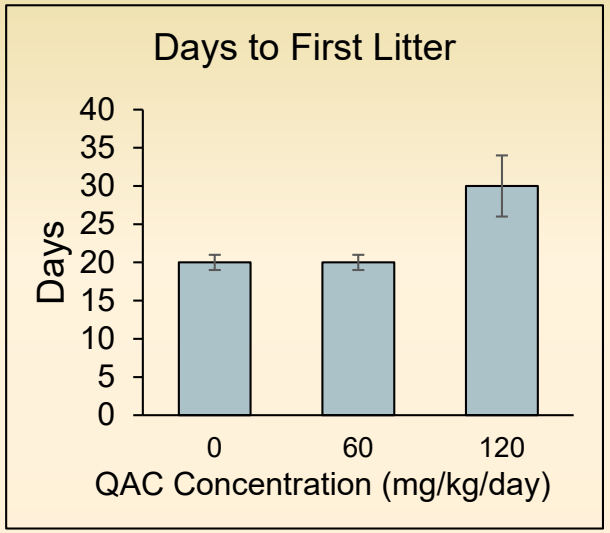
- Significant declines in both male and female fertility
- Significant declines in blood concentrations of reproductive hormones FSH, LH

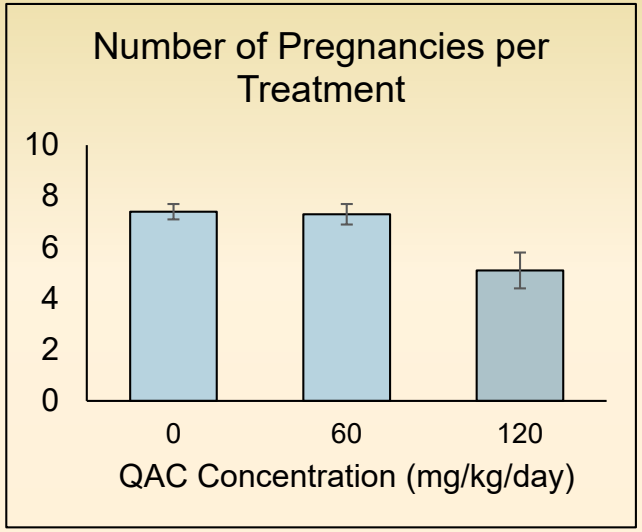


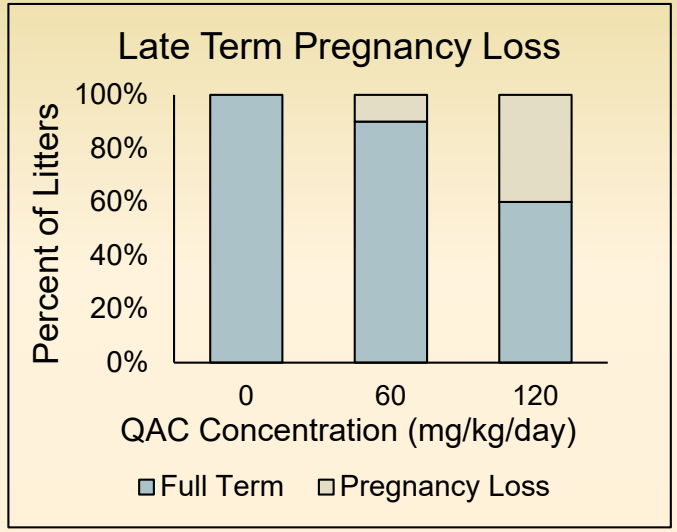


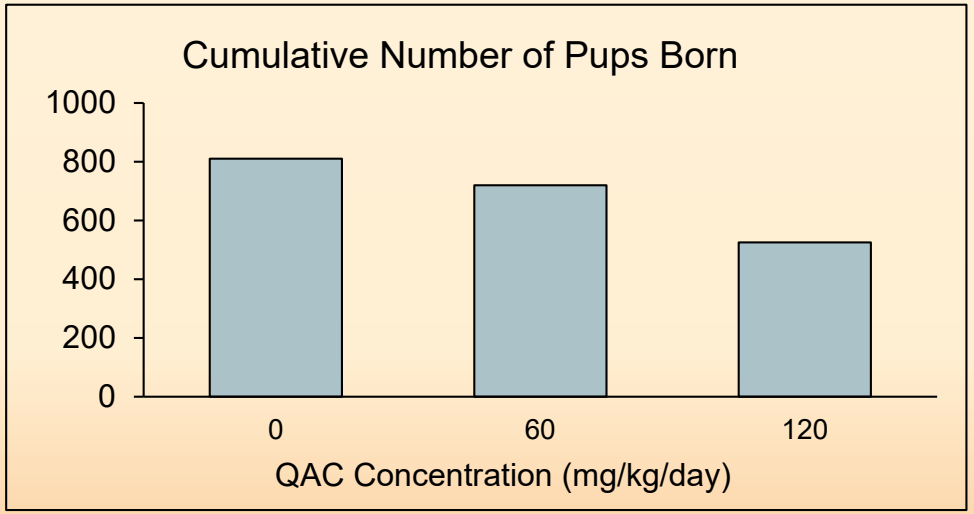
Dose
Exposure

Stage 5. Fertility continued



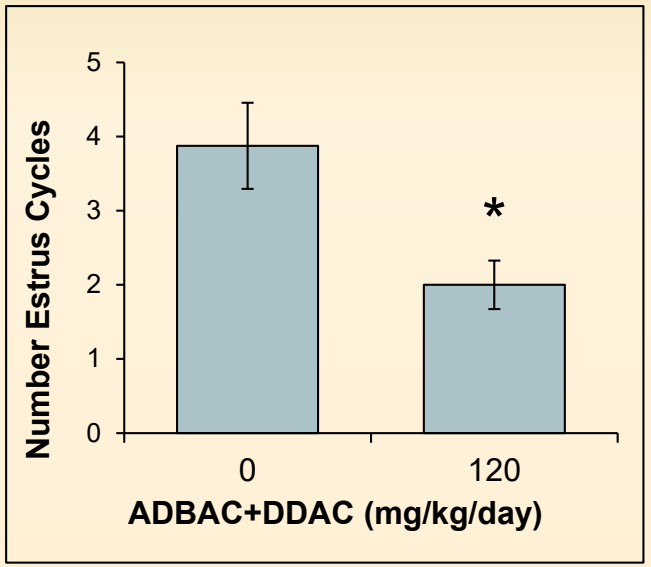


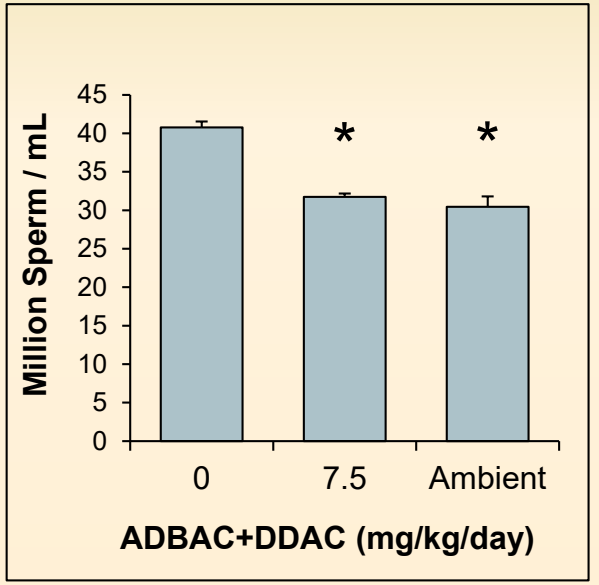


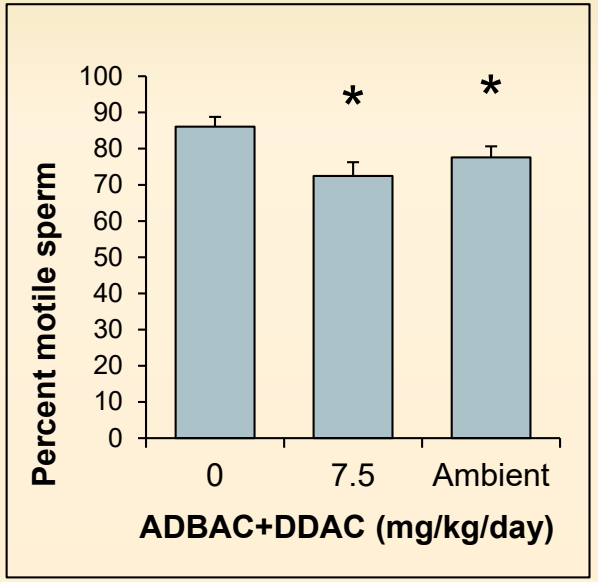


Over a 6 month breeding trial

Stage 5. Fertility continued







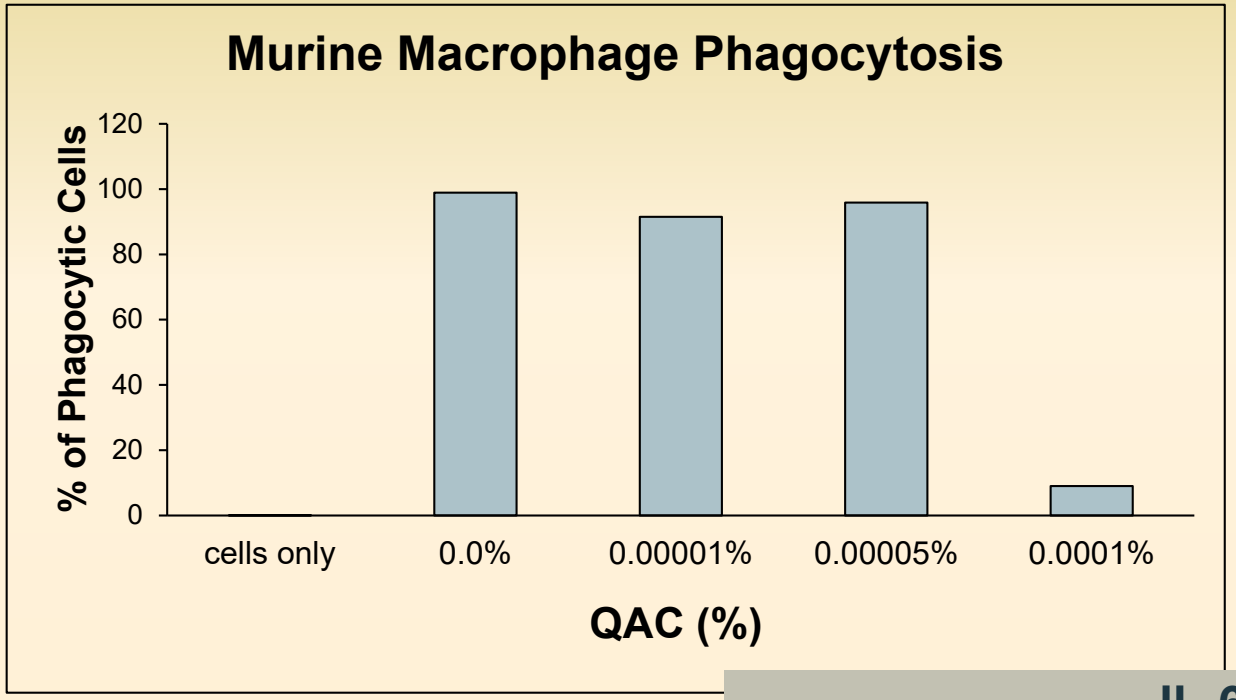
Number of estrus cycles per 3 week period

Sperm Count

Sperm Motility

Ambient and
Dose exposure

Stage 5. Immune Function



Antibody Response

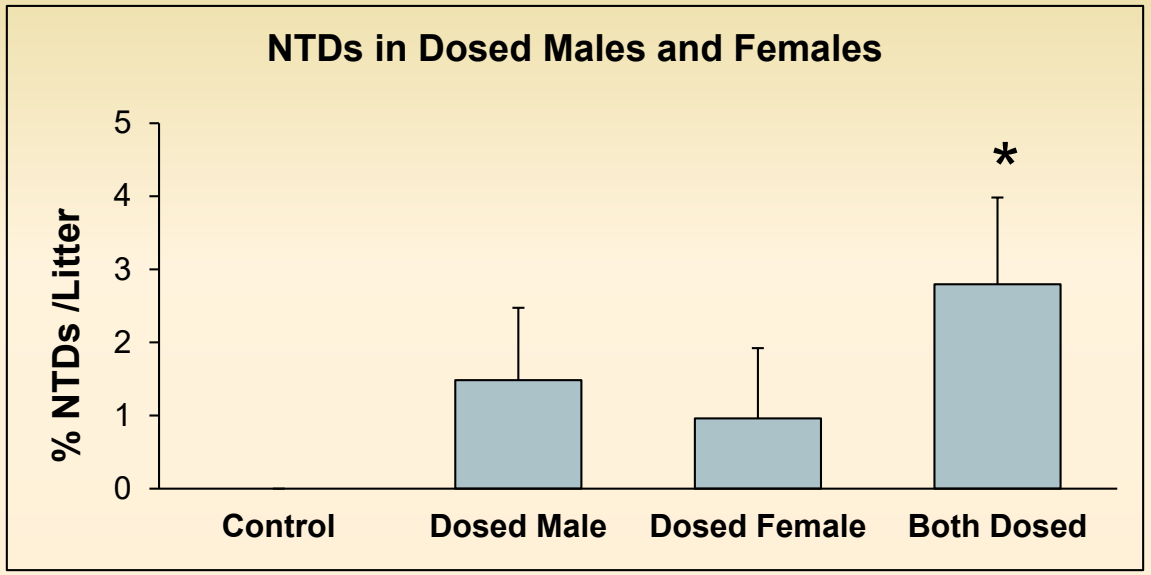
Prenatal exposure:

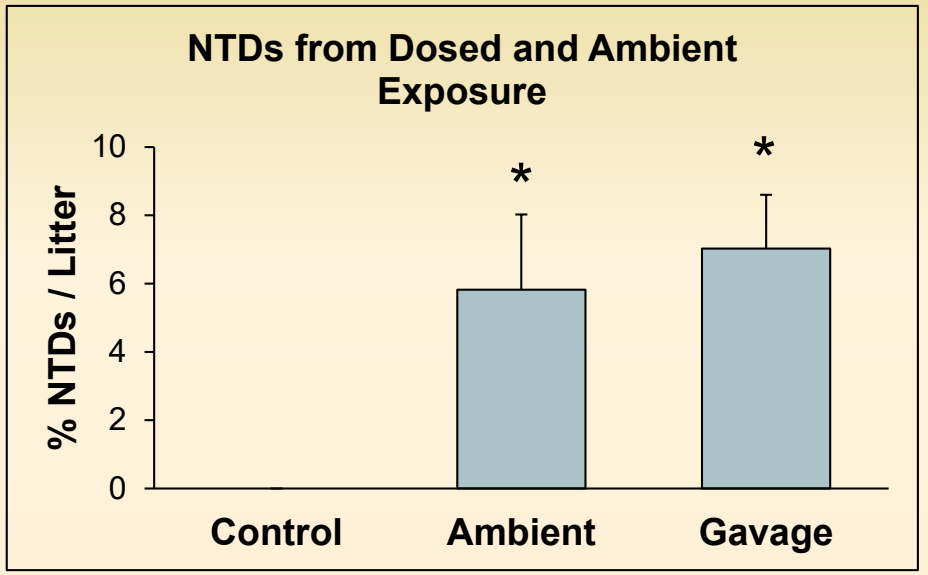
Decreased IgG response
Increased IgE response

Cytokine Production (pg/L)

	IL-6	TNF-α	IL-10
Cells alone	0±0	0±0	0.01±0.005
Stimulated Cells	8.36±0.16	7.05±0.58	0.32±0.04
Stimulated + QAC	13.9 ±0.23*	19.4 ±0.58*	0.15 ±0.02*

Stage 5. Development





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.

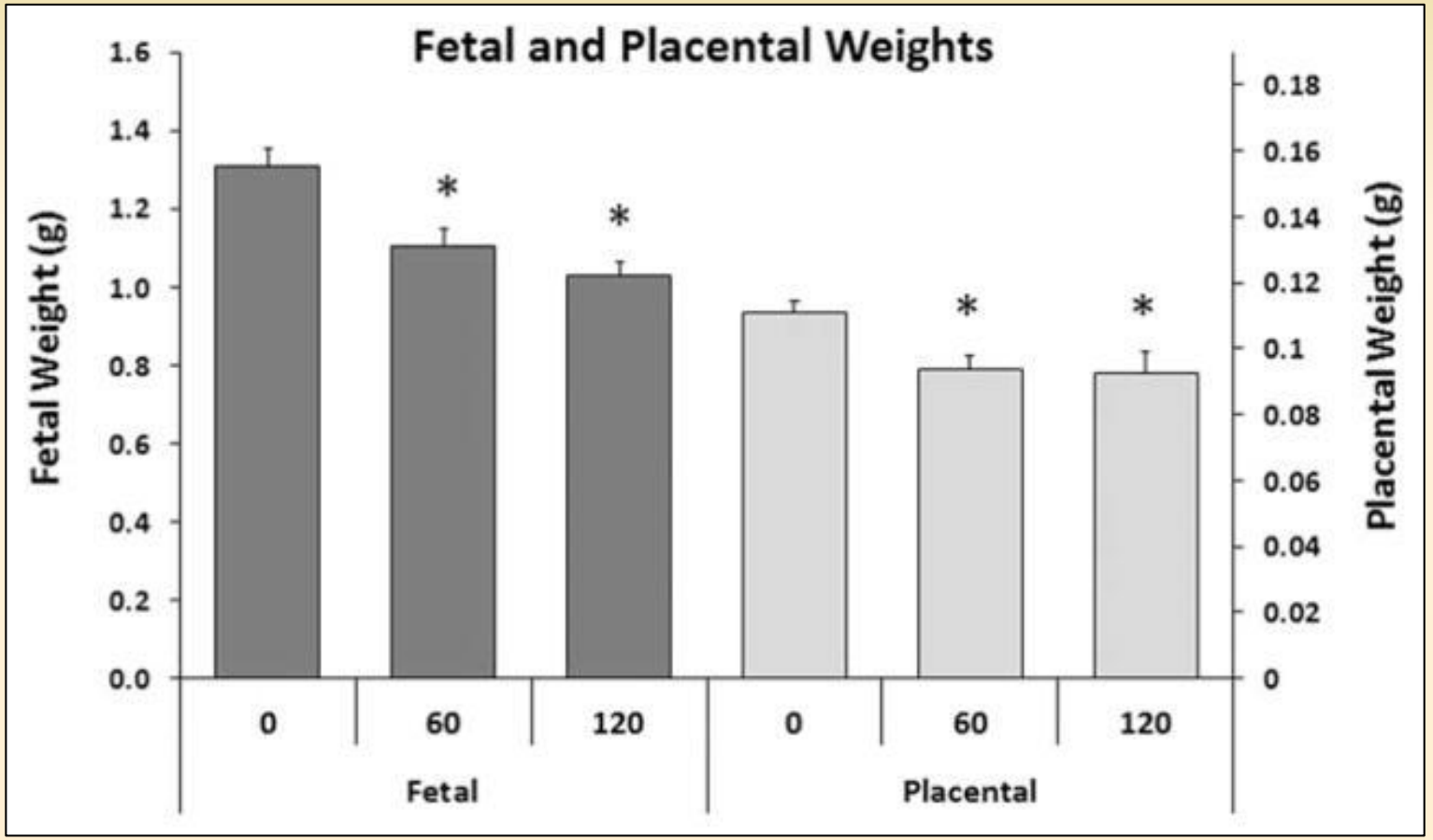
There was no ambient exposure

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

Mice received ambient exposure

Stage 5. Development



Stage 6. QACs in Humans

EXPOSURE is UBIQUITOUS

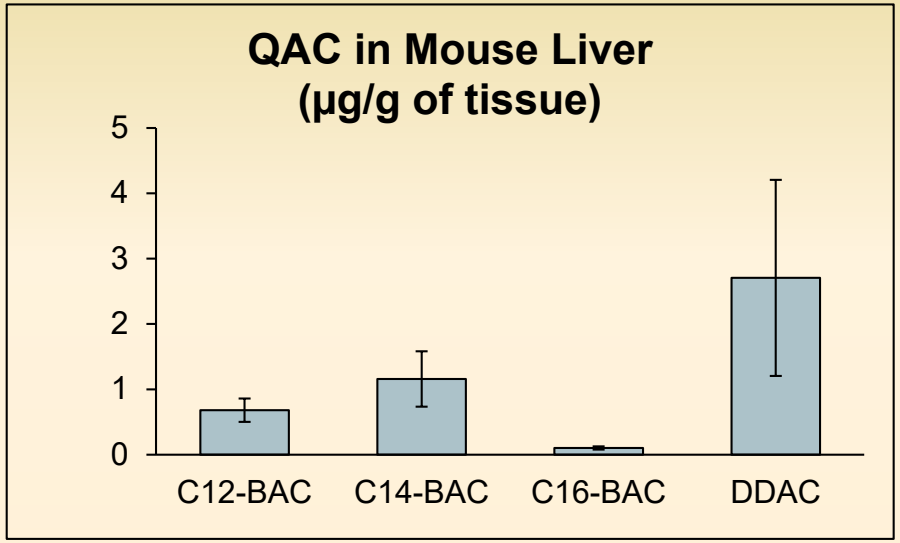
- 50% of first year medical students had QAC residues on their hands (based on a one point in time assessment)
- 80% of random participants had detectable QACs in their blood (N=43, QAC screening trial)
- Over 5,000 household products contain a QAC (based on publically available household product databases)

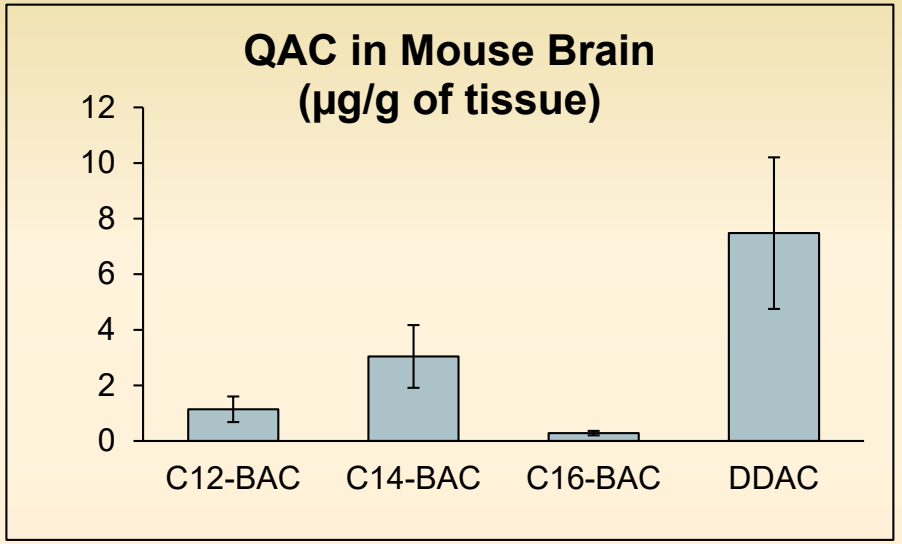
Stage 6. QACs in Humans

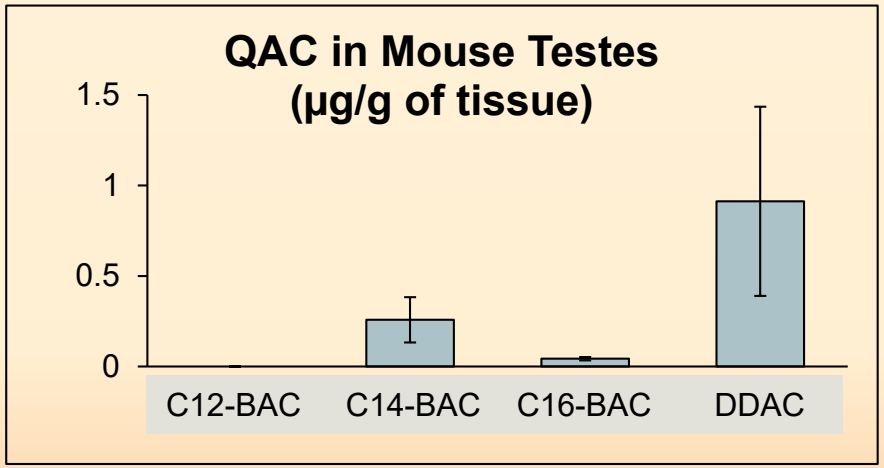
QAC Screening Trial

- 43 random participants from a rural college town were enrolled
- 2/3^{rds} students, 1/3rd non-students (based on visual estimation of age)
- 80% contained ADBAC 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

Stage 5. Implications







Numerous patents for use as contraceptives since the early 1970s

Licensed for use as a spermicides in Canada and Europe

Stage 7. 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

It behooves us to institute a biomonitoring program to better understand exposure and risk

SUMMARY

In Rodents	In Humans
❑ QACs cause birth defects	❑ Affects blood measurements of inflammation, mitochondrial function and cholesterol synthesis
❑ QACs alter immune function (also in-vitro)	
❑ QACs can accumulate in the tissues and cross the blood brain and blood testis barrier in rodents	
❑ QACs impair reproductive function	

Due to the adverse findings outlined in this presentation and others, monitoring exposure is a prudent first step