



Letting our Defenses Down

A Trichloroethylene Metabolite Suppresses Innate Immune Defense against Microbial Infection of Gestational Tissues

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“Rising amounts of chemicals polluting our environment may affect the virulence of microorganisms and/or the susceptibility to infections among humans”

- Ilback and Friman, Crit Rev Food Sci Nutr, 47:499-519 2007

“The idea of incorporating infectious disease into the toxicological paradigm is exactly the kind of pioneering concept that can take environmental health to the next level.”

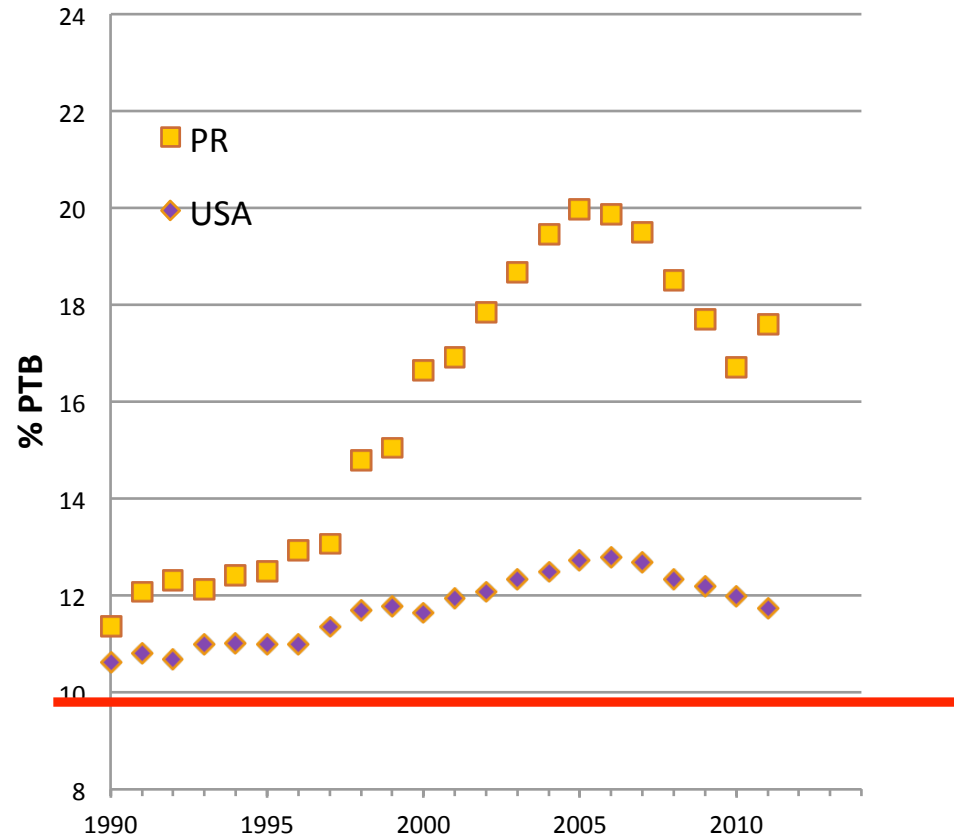
- Birnbaum and Jung, Environ Health Perspect 118:a327-a328, 2010

Preterm Birth is Prevalent



Preterm Birth in Puerto Rico

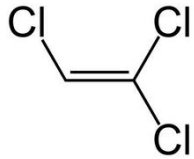
- Puerto Rico has the highest preterm birth in the US (17.6%) and one of the highest rates in the world
- Average preterm birth rate in US is 11.7%



Blencowe et al., 2012; NCHS, 2012

Toxicants

Trichloroethylene



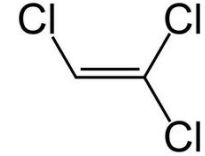
Pathogens

Group B Streptococcus



Adverse Birth
Outcomes ?

Trichloroethylene (TCE)



Common industrial solvent

Common drinking water contaminant

Known human carcinogen

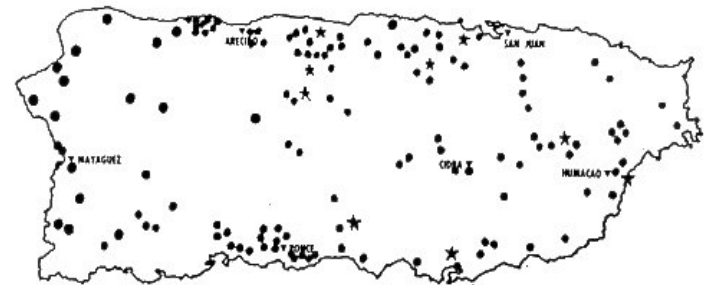
Immunotoxicant

- Increased bacterial counts and mortality in mice co-treated with TCE and *S. zooepidemicus* (Selgrade, et al. 2010)
- Autoimmune diseases (Cooper, et al. 2009)
- Altered cytokines (Iavicoli, et al. 2005)

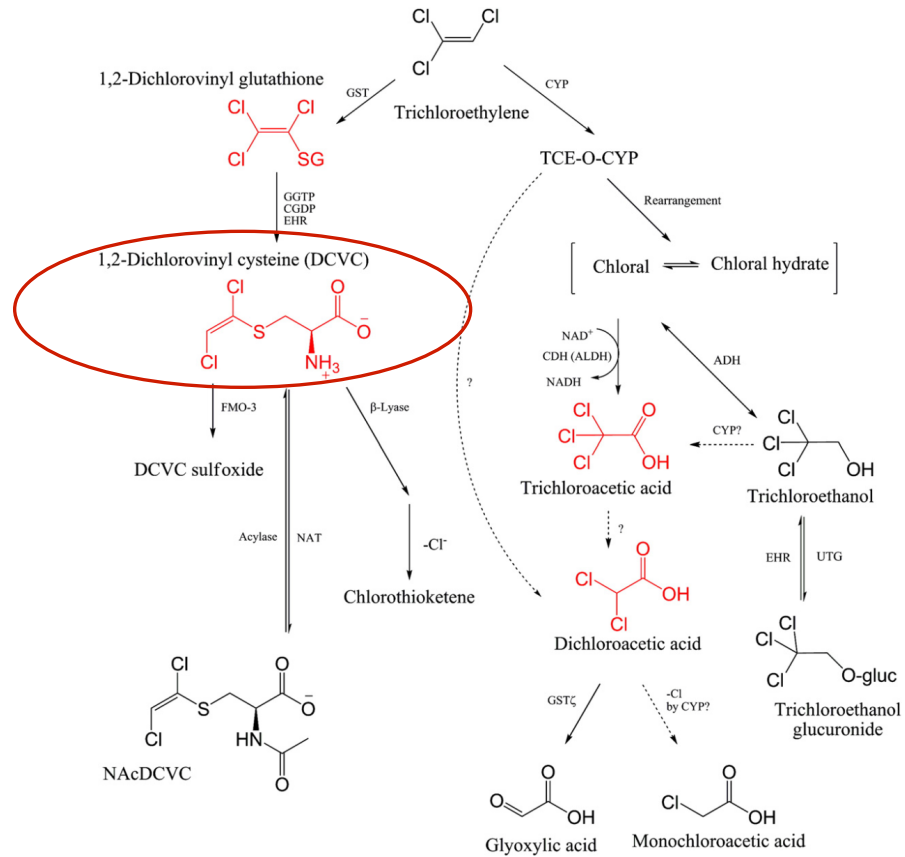
Developmental toxicant

- Neural tube defects (Bove, et al. 2002)
- Cardiac defects

Superfund and Hazardous Waste Site Contaminant

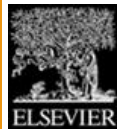
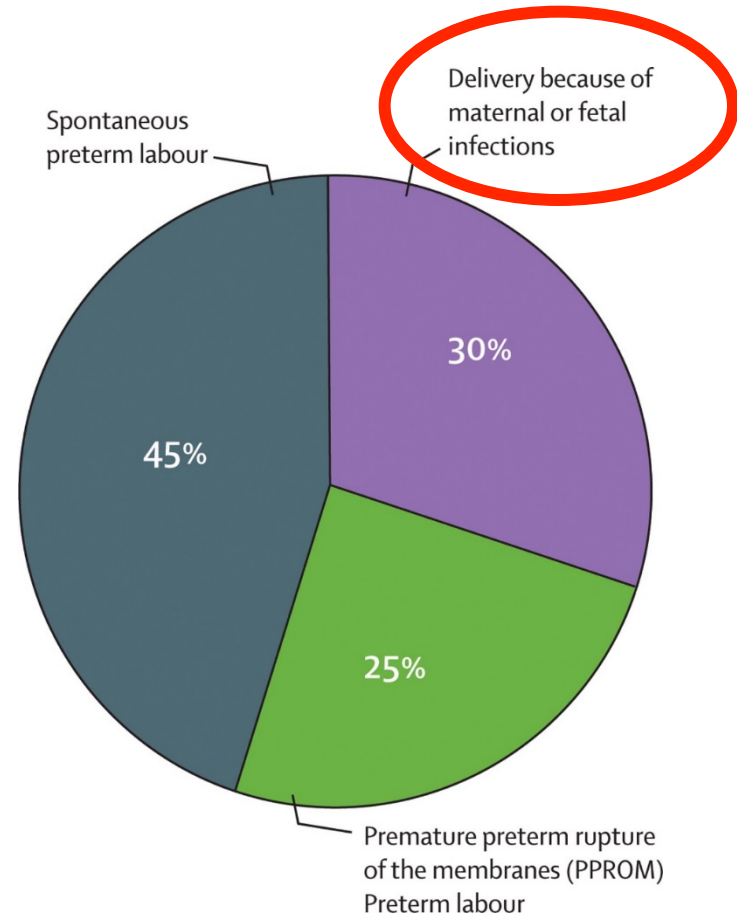


TCE Metabolism



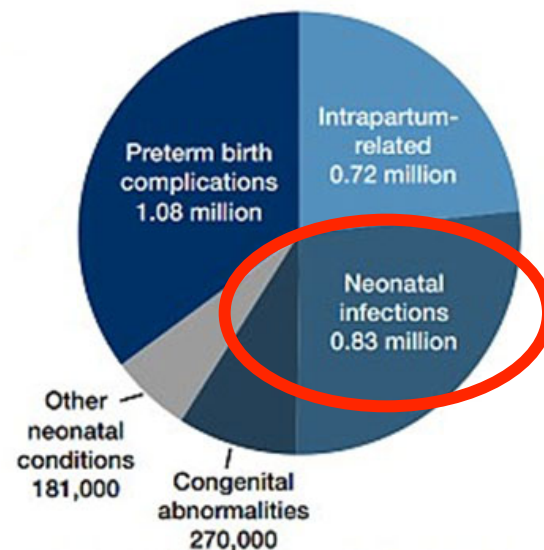
<http://rusynlab.unc.edu/publications/2009/Kim%20et%20al%202009%20TAP.pdf>

Infections Contribute to Preterm Birth



Infections Contribute to Neonatal Death

Figure 2.1: Estimated distribution of causes of 3.1 million neonatal deaths in 193 countries in 2010



**Preterm birth is a risk factor for neonatal and postneonatal deaths
At least 50% of all neonatal deaths are preterm**

Source: Updated from Lawn et al., 2005, using data from 2010 published in Liu et al., 2012.

From: DailyMail.com, 3 May 2012

Group B Streptococcus



Gram-positive bacterium

10-30% women colonized

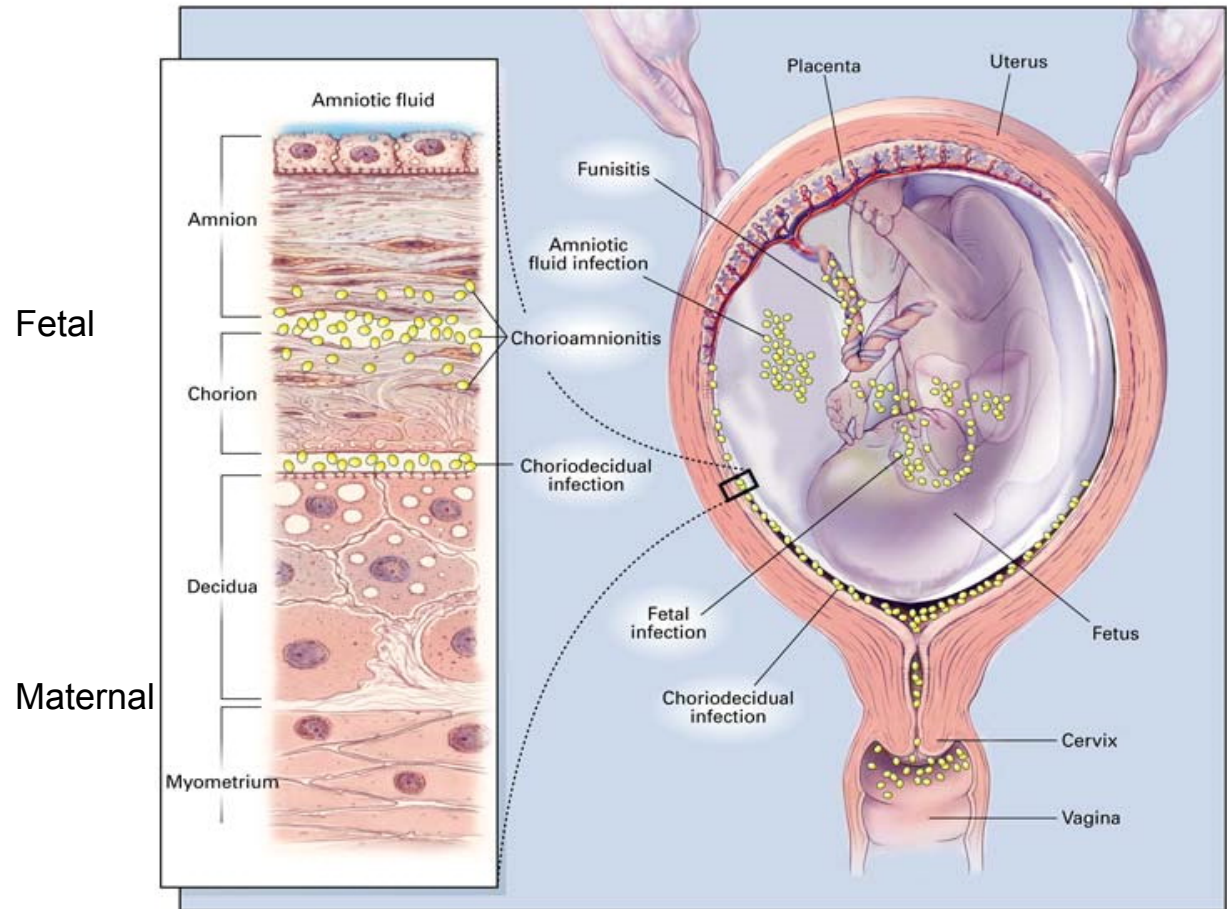
“Leading cause of infectious neonatal morbidity and mortality in the United States” (MMWR)

0.34-.037 cases per 1,000 live births (CDC)

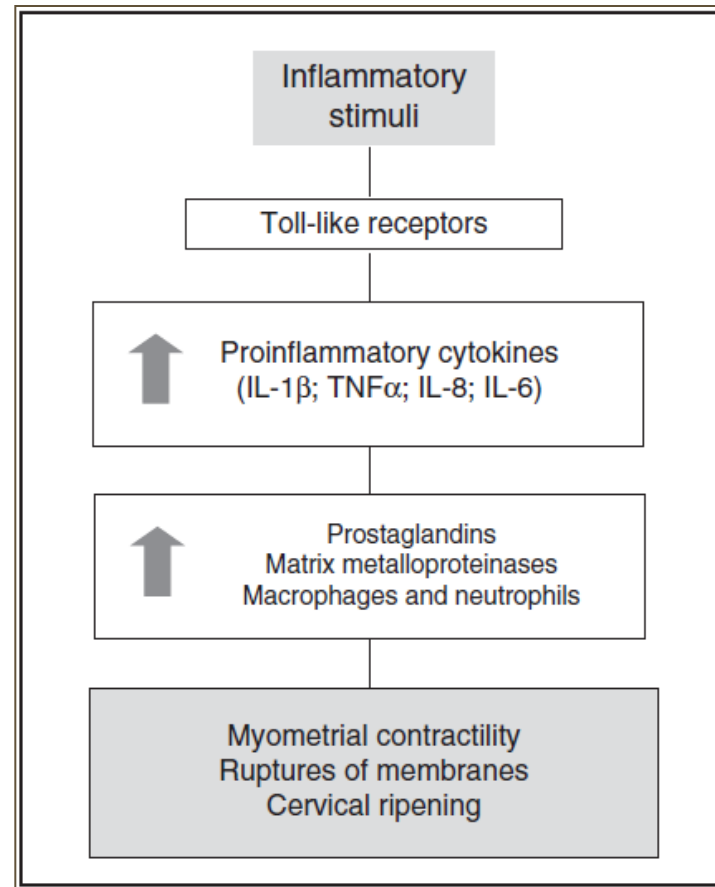
Associated with poor birth outcomes



Extraplacental
Membranes
Protect
Gestational
Compartment
from Microbial
Infection



Inflammation & Parturition



Challis, JR et al., Reprod Sci 16, 206-215, 2009

Hypothesis

The TCE metabolite DCVC decreases innate immune response of gestational membranes, thereby increasing host susceptibility to infection

Experimental Design

Acquire tissues from non-laboring cesarean section deliveries

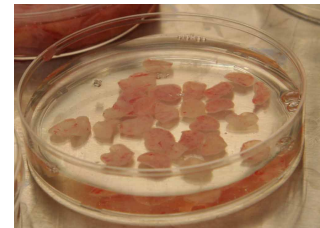
Tissue Punch Cultures

- Blunt dissect choriodecidua (CD) from amnion
- Float 12 mm CD tissue punches in media

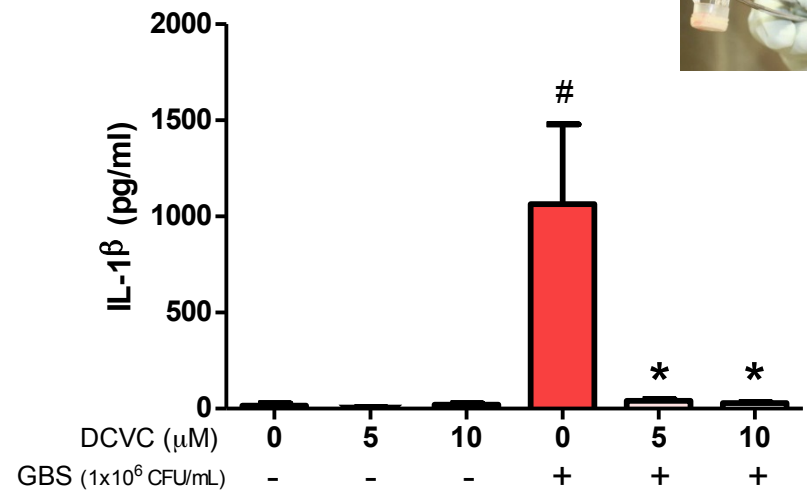
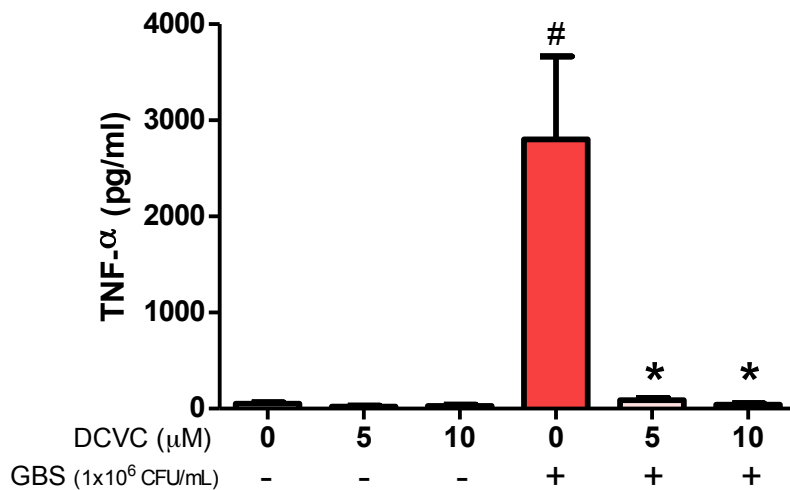
Transwell Cultures

- Mount tissue pieces on Transwell insert that lack synthetic membrane

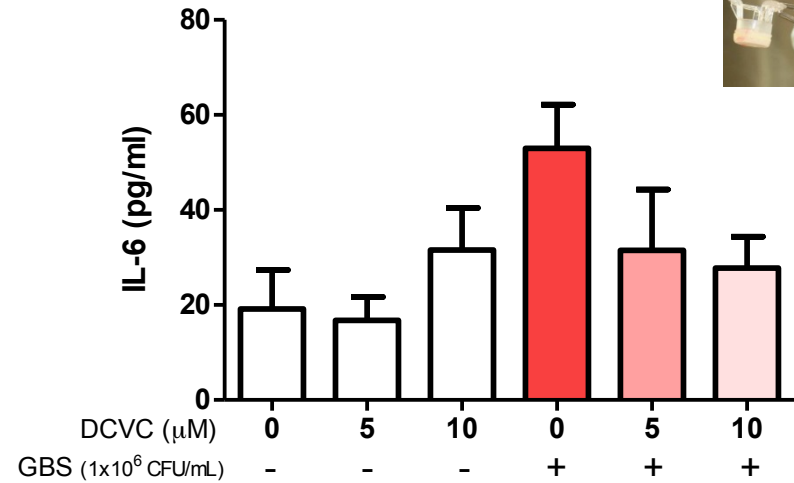
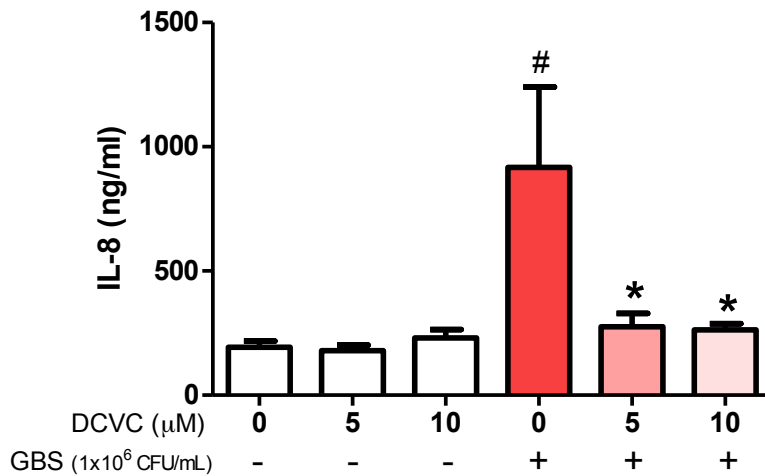
After 24 h acclimation, add GBS (strain A909) (1×10^6 CFU/mL)



DCVC Blocks GBS-Stimulated TNF- α and IL-1 β Release from Human Extraplacental Membranes

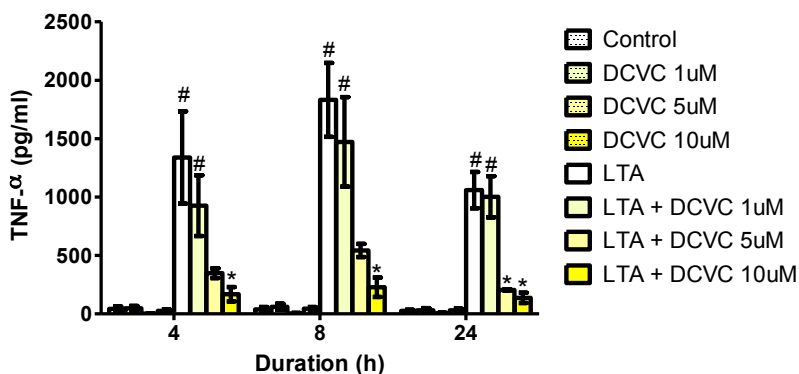


DCVC Blocks GBS-Stimulated IL-8 but not IL-6 Release from Human Extraplacental Membranes

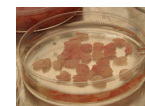
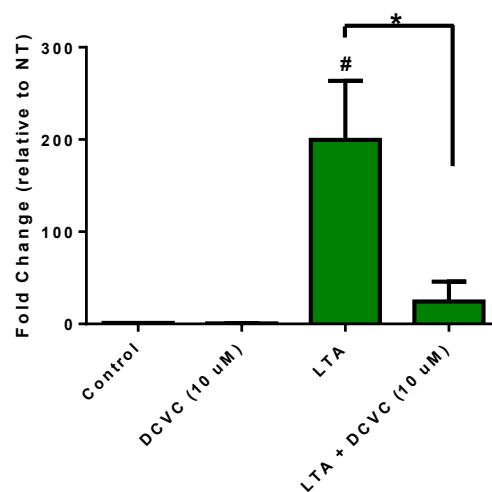


Lipoteichoic acid (LTA) is a gram-positive cell wall component that was used as a surrogate for GBS infection

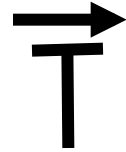
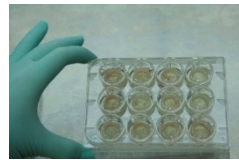
DCVC inhibited LTA-stimulated release of TNF- α from human gestational membranes at the lowest DCVC concentration (1 μ M) and the shortest exposure duration tested (4 h).



DCVC (10 μ M for 4 h) inhibited LTA-stimulated TNF- α mRNA expression



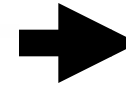
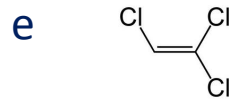
Group B Streptococcus



DCVC



Trichloroethylen



Adverse Birth Outcomes ?

- ↓ TNF- α
- ↓ IL-1 β
- ↓ IL-8

Acknowledgements

Publication

Boldenow E, et al. The trichloroethylene metabolite S-(1,2-dichlorovinyl)-l-cysteine but not trichloroacetate inhibits pathogen-stimulated TNF- α in human extraplacental membranes in vitro. *Reprod Toxicol*. 2015 Apr;52:1-6. PMID: 25653212.

Lab Members

- Sarah Jones
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Related Publications

- Boldenow E, et al. Role of cytokine signaling in group B Streptococcus-stimulated expression of human beta defensin-2 in human extraplacental membranes. *Am J Reprod Immunol*. 2015 Mar;73(3):263-72. PMID: 25263616
- Boldenow E, et al. Antimicrobial peptide response to group B Streptococcus in human extraplacental membranes in culture. *Placenta*. 2013 Jun;34(6):480-5. PMID: 23562109
- Korir ML, et al. Association and virulence gene expression vary among serotype III group B streptococcus isolates following exposure to decidual and lung epithelial cells. *Infect Immun*. 2014 Nov;82(11):4587-95. PMID: 25135682

Gestational Membranes Kill GBS (Strain A909)

