

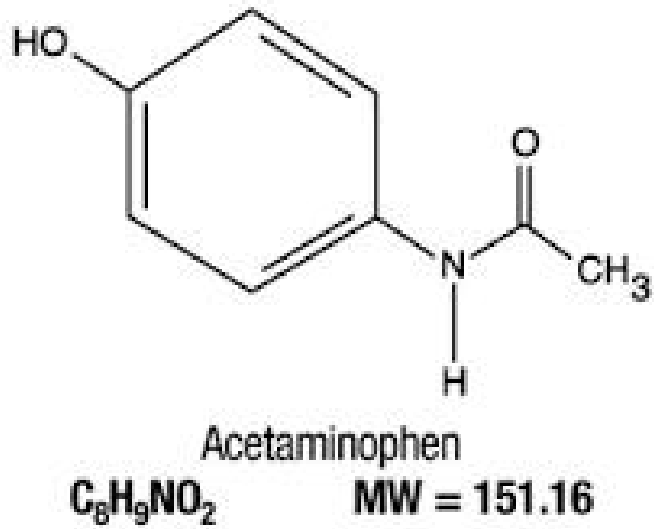
Exploring Multifactorial
Contributors to Disease Outcomes:
The Possible Role of
Acetaminophen in Asthma and
Autism

CHE Partnership Call June 7, 2016

Part 3: Ann Bauer

Acetaminophen (APAP) as a risk factor

- N-acetyl-para-aminophenol, Paracetamol, Tylenol
- Crosses blood brain barrier and placenta
- May be toxic at therapeutic doses



Aniline converts to APAP

- 5.6 million metric tons- 2016
- Biomonitoring indicates ubiquitous and high human exposure to APAP

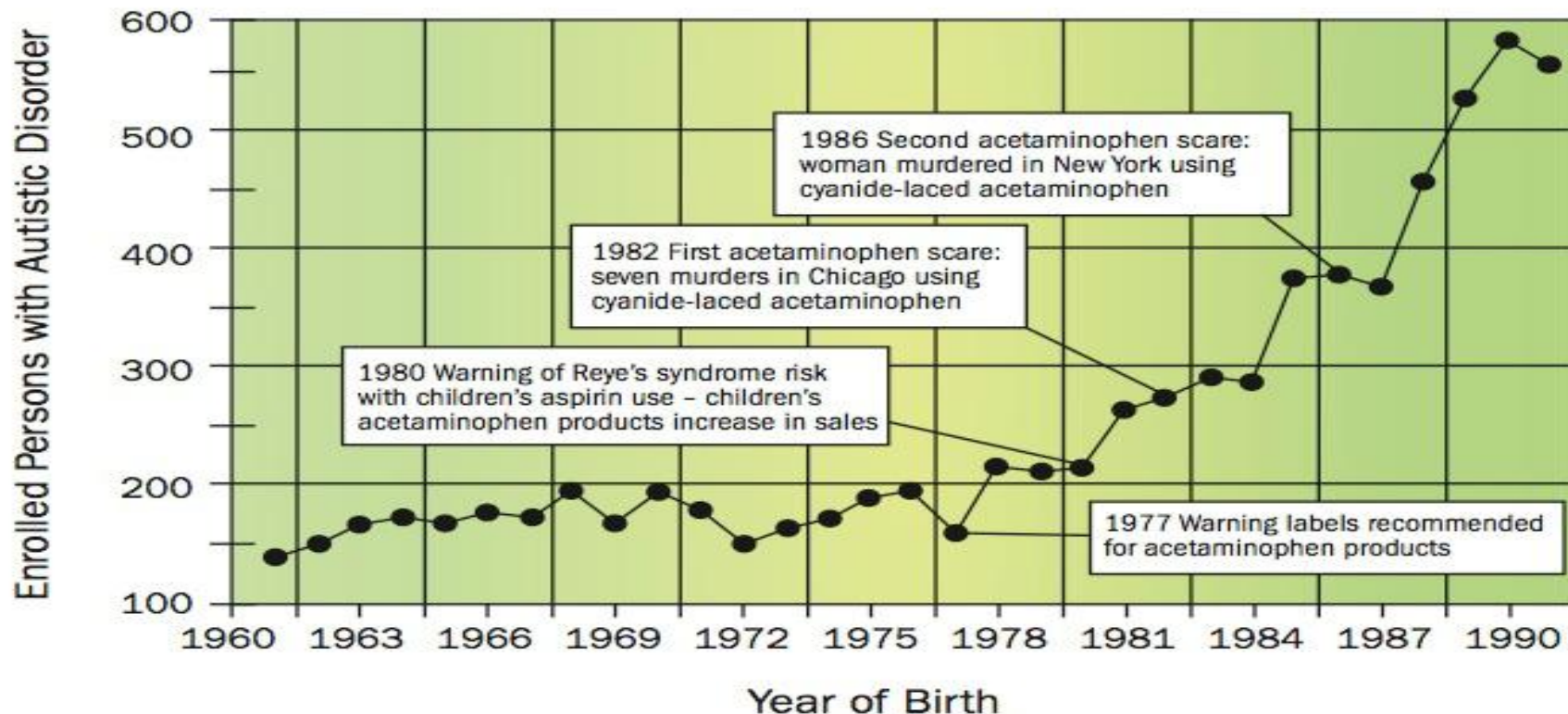


(Holm et al. 2015)

This is what started my investigation

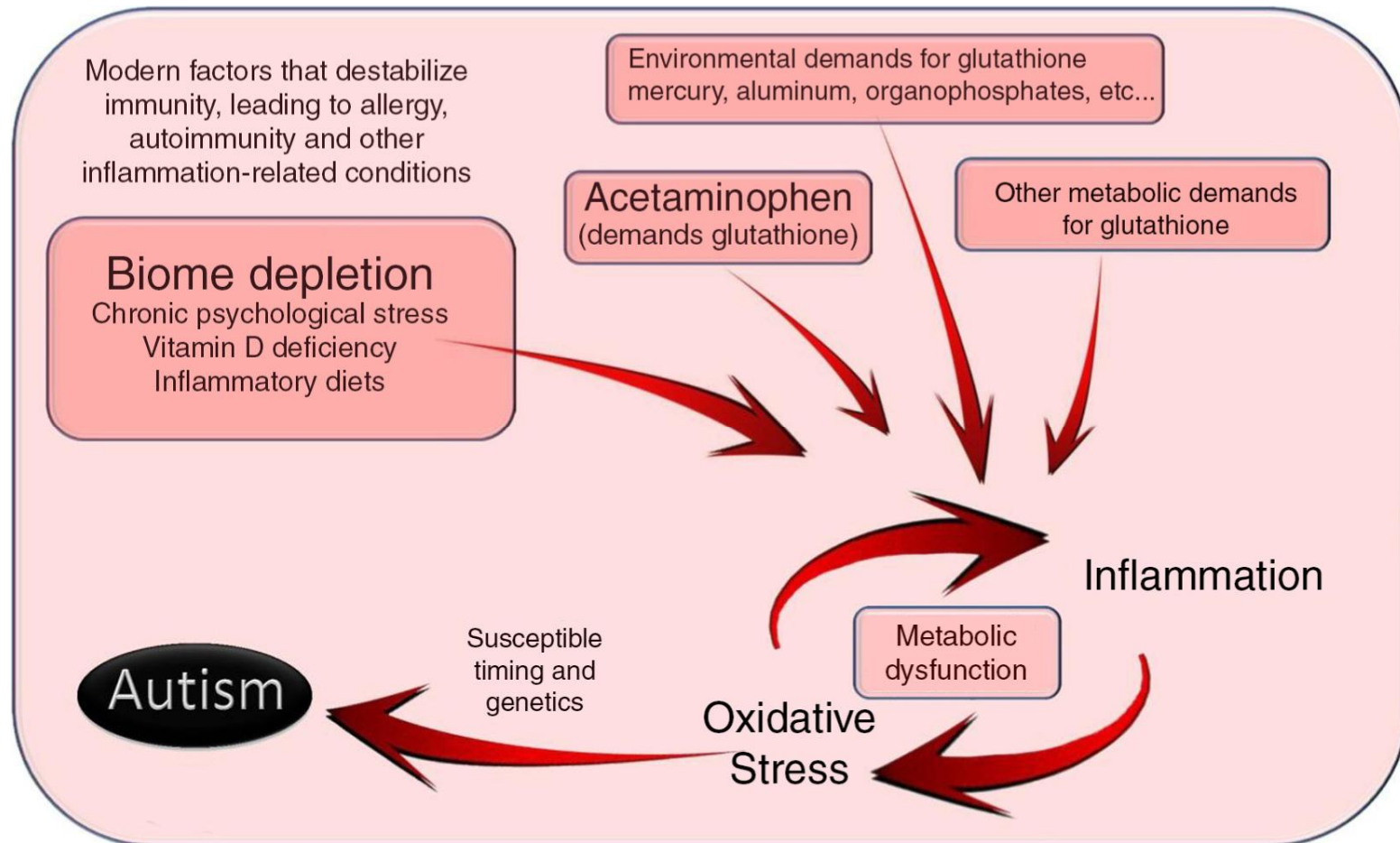
Similar trend found for asthma and autism- 5 populations

Figure 2. Number of Enrolled Persons with Autistic Disorder in California by Year of Birth and Significant Events in the History of Acetaminophen Use



From: Schultz ST. *National Acetaminophen Sales and Autistic Disorder in California*.¹² Adapted by Schultz from: Changes in the population of persons with autism and pervasive developmental disorders in California's developmental services system: 1987 through 1998. A report to the legislature (California Department of Developmental Services, 1999). Used with permission.

Autism (ASD), ADHD and Asthma may be the result of Glutathione depletion



(Bilbo et al. 2015)

Guidelines suggest the use of APAP with the circumcision procedure



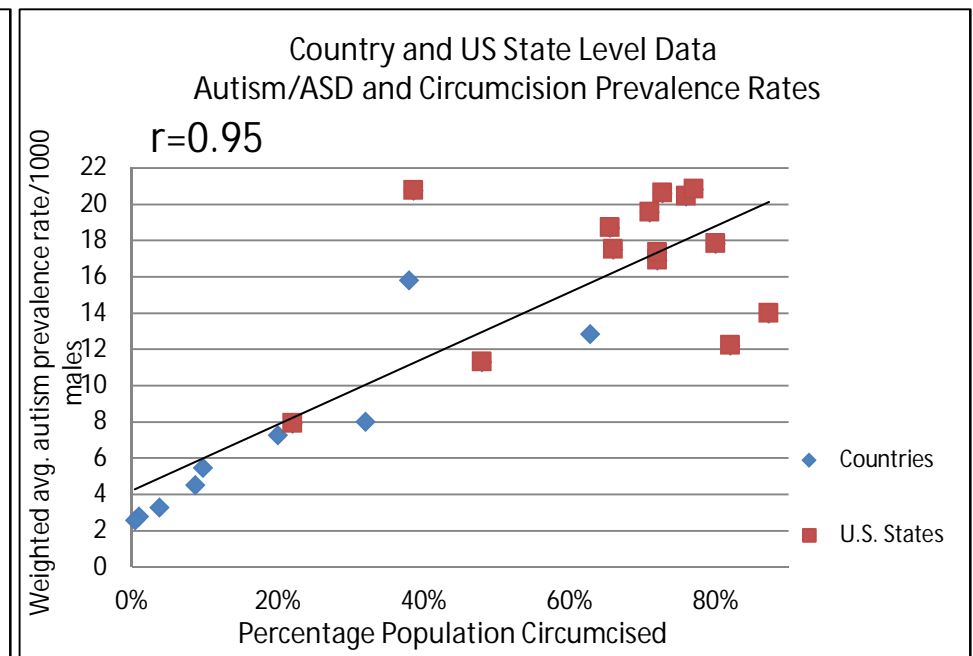
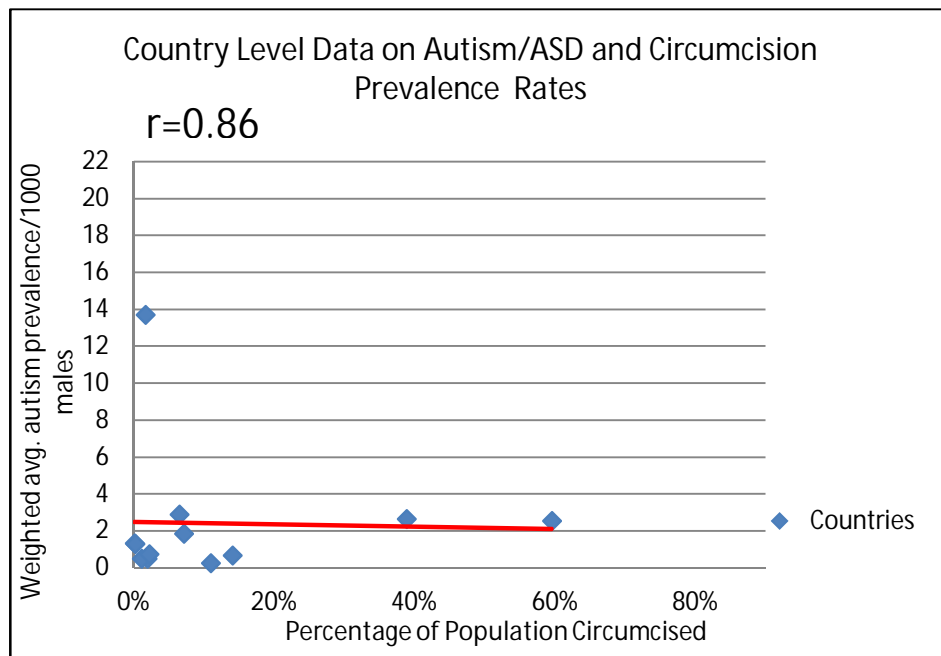
Could this be an important exposure?

Brain growth spurt (3rd trimester -2 years) is at it's peak at birth
Underdeveloped / Compromised non -toxic metabolic pathways

In an Ecologic study, ASD rates increase with the circumcision rates only after APAP guidelines

BEFORE APAP suggested

AFTER APAP suggested



(Bauer & Kriebel 2013)

In a Danish Cohort study of 347,877 boys, circumcision is associated with increased risk of ASD only after APAP guidelines

BEFORE APAP Suggested

AFTER APAP Suggested

Circumcision exposure and risk of ASD:
(Hazard Ratio= 1.15, 95% CI 0.75-1.77)

Circumcision exposure & risk of ASD:
(Hazard Ratio =1.80, 95% CI 1.25-2.60)

Circumcision exposure & risk of Infantile ASD:
(Hazard Ratio =2.06, 95% CI 1.36 -3.13)

(Frisch and Simonsen 2015)

4 cohort studies suggest prenatal APAP can have adverse effects on neurodevelopment

1) Norwegian MoBa Birth Cohort

- Utilizing a sibling control design (2919 same sex pairs), prenatal exposure to APAP for more than 28 days:
- Increased risk of adverse gross motor skills and behavioral outcomes by almost 70% in 3 year olds
- 50% increased risk of language problems

(Brandlistuen et al. 2013)

The only ASD specific cohort study

2) Danish National Birth Cohort

- 64,322 followed for an average of 12.7 years. Pregnancy use of APAP was associated with increased risk of:
- ASD w/ Hyperkinetic disorder –ever used
(HR=1.51, 95% CI 1.19-1.92)
- Infantile ASD w/ Hyperkinetic disorder – 3 trimesters
(HR=2.45, 95% CI 1.35-4.53)

(Liew et al. 2015)

2 ADHD and prenatal APAP Studies

3) Danish National Birth Cohort of 40,916 -7 years old.

Those exposed had higher risk of :

Hyperkinetic disorder (HR=1.37 95% CI 1.19-1.59)

ADHD medication (HR=1.29, 95%CI 1.15-1.44)

(Liew et al. 2014)

4) Auckland Birth Cohort of 871 – 7 & 11 years.

Those exposed had modestly higher risk of:

ADHD related difficulties

(Thompson et al. 2014)

A Supportive Animal study

- APAP during a **critical neonatal period** of brain development can induce long-lasting effects on cognitive function in male mice. (Viberg et al 2014)

APAP may have endocrine disrupting properties

- Human and rodent studies find reproductive consequences:
 - Cryptorchidism (male congenital malformation)
 - Male infertility
 - Female infertility

4 Endocrine disrupting chemical mixtures and autism related gene expression

1) 8 Anti-androgenic chemicals mix

(di-n-butylphthalate, diethylhexylphthalate, vinclozolin, prochloraz, procymidone, linuron, epoxiconazole, and p,p'-DDE)

2) 4 Estrogenic chemicals mix

(bisphenol A, 4-methylbenzylidene camphor, 2-ethylhexyl 4-methoxycinnamate, and butylparaben)

3) APAP alone

4) All 13 Chemical mix

(Lichtensteiger et al. 2015)

All 4 mixtures had a strong , mixture-specific impact on genes

- Sex and region specific gene expression patterns were elicited in developing rat brains. Genes linked to:
 - increased risk of ASD
 - excitatory glutamatergic synapses
 - migration and pathfinding of glutamatergic and GABAergic neurons

(Lichtensteiger et al. 2015)

“APAP may have exerted an important influence”

- The effects of APAP alone on individual genes in the developing brain were almost identical to those of the All 13 Chemical Mix

(Lichtensteiger et al. 2015)

Conclusions

- The evidence suggests that it is plausible that APAP is a contributing causal factor in the diseases of ASD, ADHD, Asthma, as well, as infertility
- These emerging risks associated with APAP use may outweigh the potential benefits

Conclusions

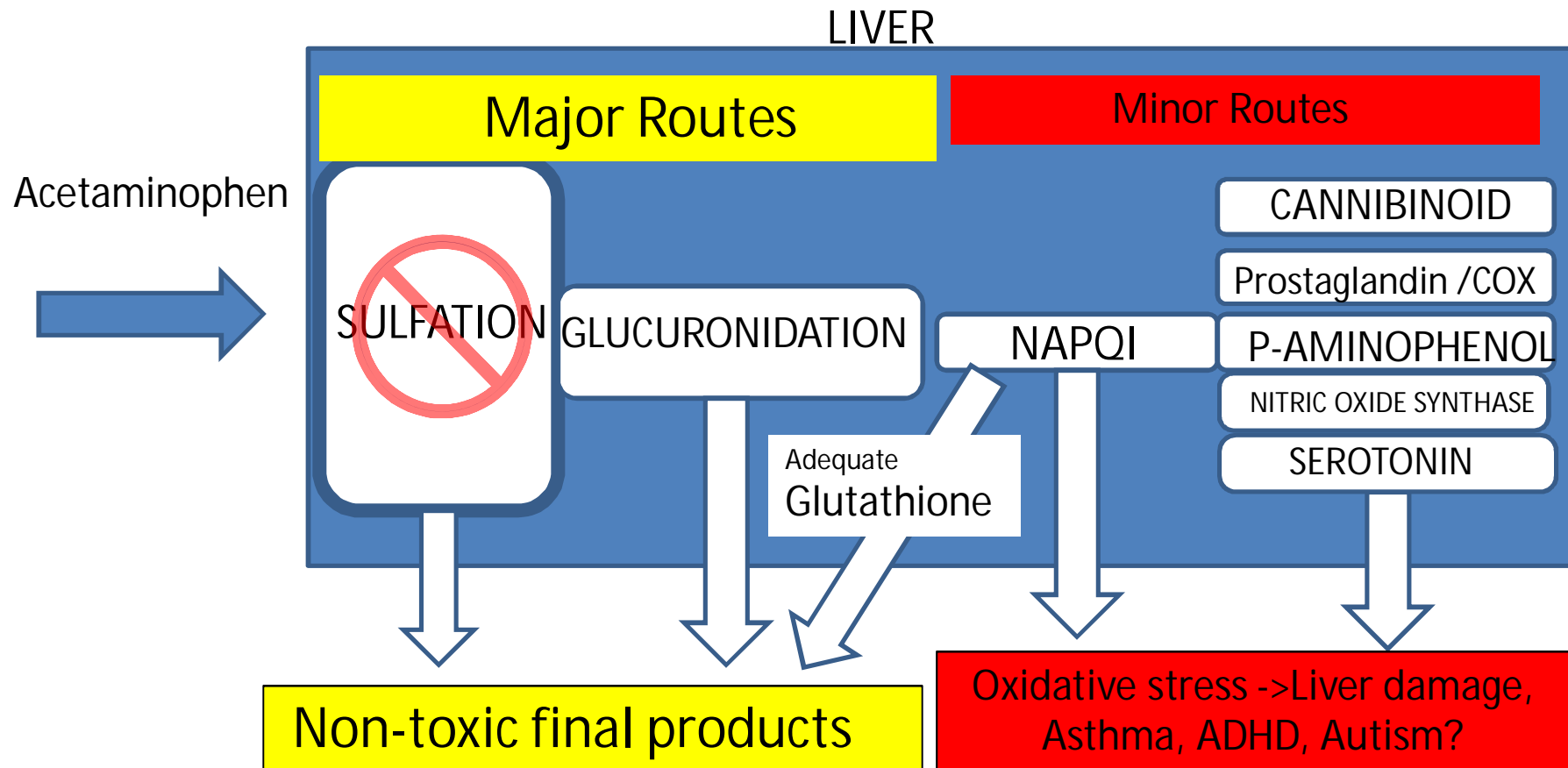
- More generally, there is likely no single cause of these diseases
- We need to develop integrative research methods that take into account:
 - Complex physiology and multifactorial nature of disease
 - Broad array of human exposures that may act in concert

The End

- Special thanks to Joel Tickner, David Kriebel, Martha Herbert, Lorelei Walker and Elise Miller

Acetaminophen Infant Metabolic Clearance Model

Reduced sulfation capacity often seen in autism



Vaccines

- Cochrane systematic review (Demicheli et al 2012) research on the MMR vaccine:
 - 6 self-controlled case series studies
 - 2 ecological studies
 - 1 case crossover trial
 - 5 time series trials
 - 17 case-control studies
 - 27 cohort studies and
 - 5 randomized controlled trials.
-
- More than 15 million children took part in this research. No one could find evidence that vaccines are associated with autism.
 - To read the article, visit <https://tinyurl.com/prnc9tc> ■

What is causing changing autism prevalence over time?

- Better diagnosis, more awareness, shifting diagnosis
- Studies suggest this accounts for some of the increase
 - Lui 2010 /Weintraub 2010 (40%)
 - Nevison 2014 (20-25%)
 - Hansen 2015 (60%)

 - all childhood immune disorders have been increasing in prevalence over similar time period

APAP's effects on reproduction and the brain may act through different mechanisms

- APAP displayed anti-androgenic effects on male REPRODUCTIVE end points
- APAP's effects on BRAIN gene expression differed from the anti-androgenic chemicals

- *“Suggesting cannibinoid and/or prostaglandin synthesis by APAP may have prevailed over inhibition of testosterone synthesis”*

(Lichtensteiger et al. 2015)

Cochrane Review of Newborns and Acetaminophen

*“Paracetamol (Acetaminophen) **should not be used** for painful procedures given its lack of efficacy and its potential for adverse effects”*

(Ohlsson and Shah 2015)

