



Anilin og paracetamol

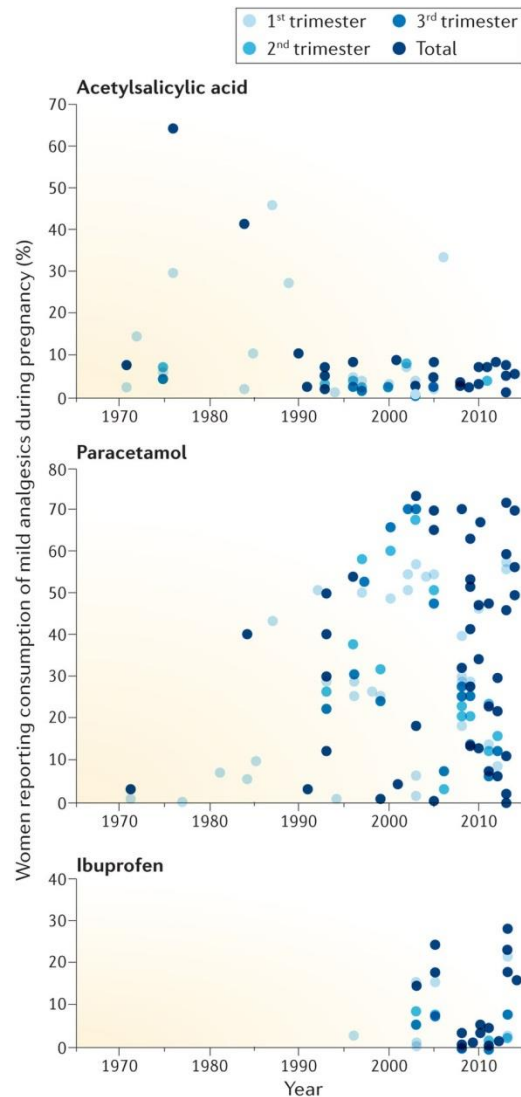
Når eksponeringen flyder sammen

**Seniorforsker,
David M. Kristensen PhD,
Rigshospitalet,
Københavns Universitet**



Gilbert 2006.

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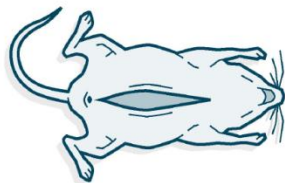
Mange gravide bruger paracetamol

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Paracetamol forstyrrer den mandlige udvikling!

Ex vivo

Caesarean section of pregnant rat dams at e14.5



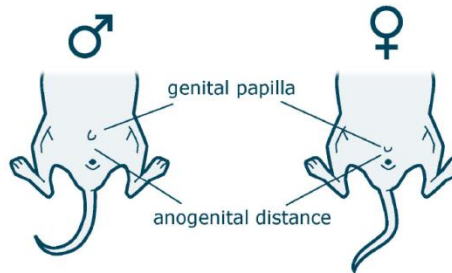
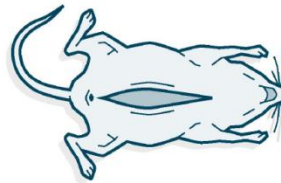
Dissection of testes and mesonephros



Exposure and measurement of testosterone and prostaglandin after 24, 48, and 72 h

In vivo

Caesarean section of pregnant rat dams at e21 after gavage with compounds from e13-e21



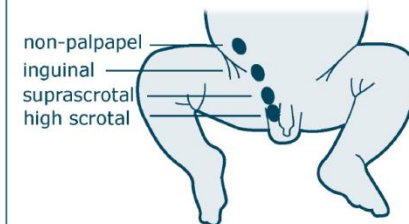
Measurement of anogenital distance and dissection of testes



Measurement of testosterone after 3 h

Epidemiology

Interview during third trimester asking about maternal use of mild analgesics

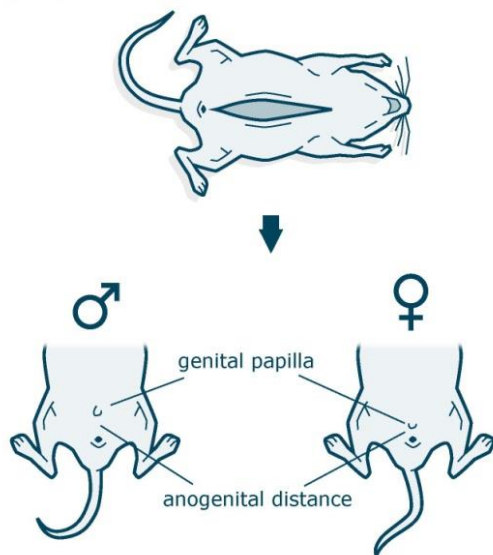


Clinical examination by pediatricians for cryptorchidism at birth

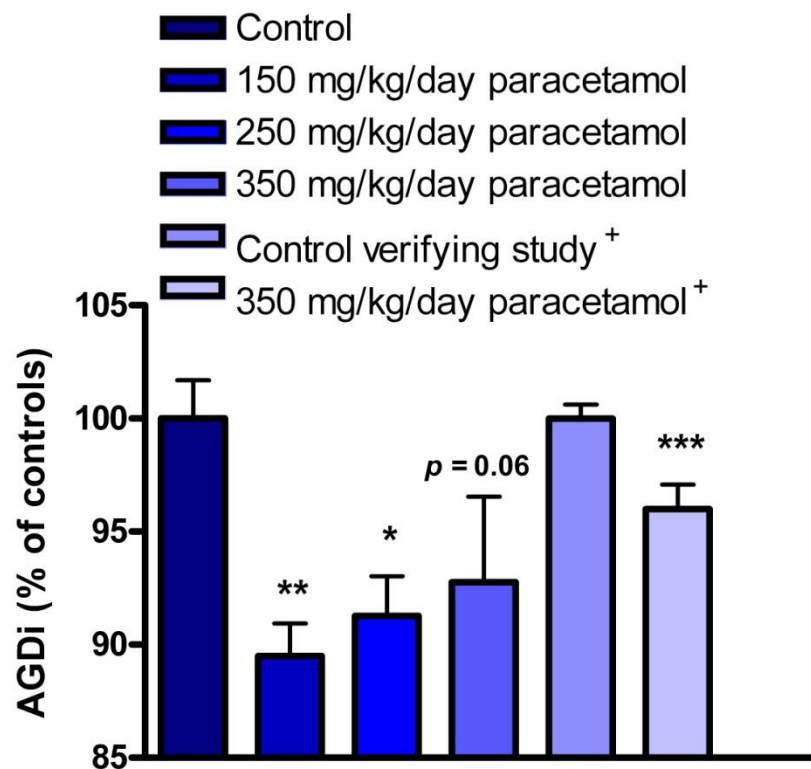
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In utero

Caesarean section of pregnant rat dams at E21 after gavage with compounds from E13-E21



Measurement of anogenital distance and dissection of testes

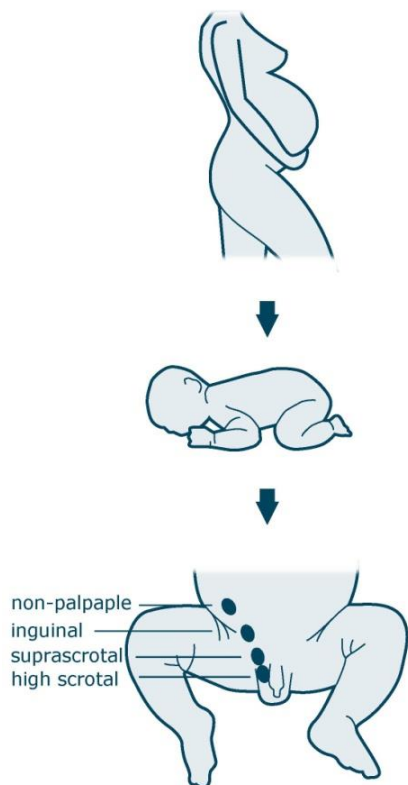


Kristensen *et al.* 2011 HumRep.

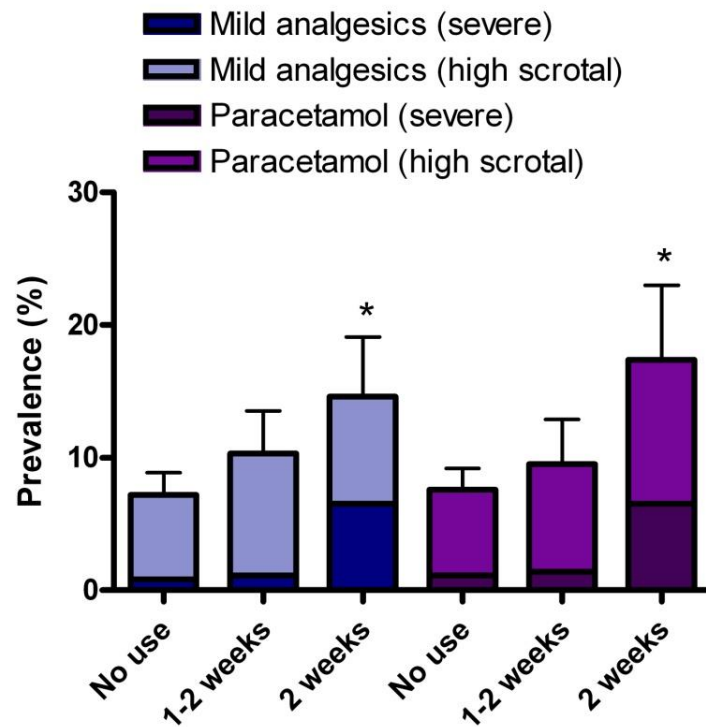
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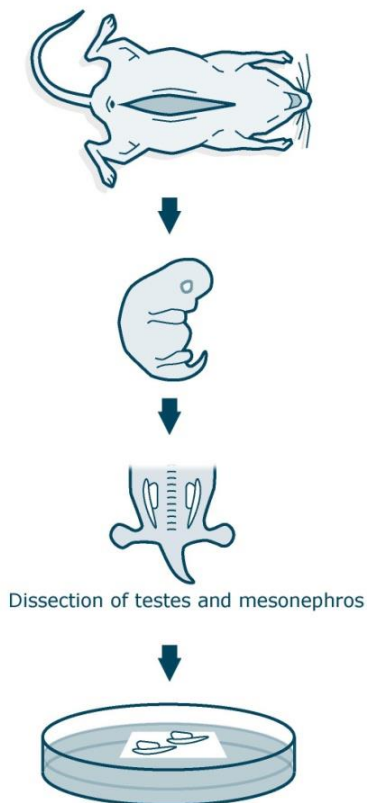


Kristensen *et al.* 2011 HumRep.

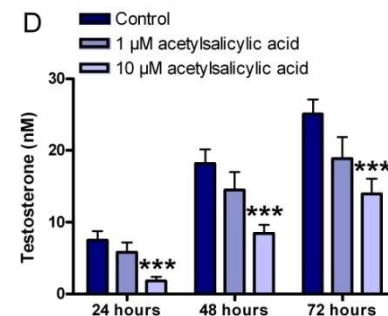
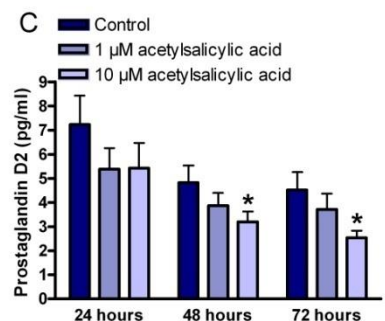
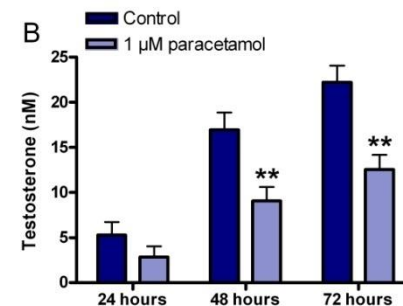
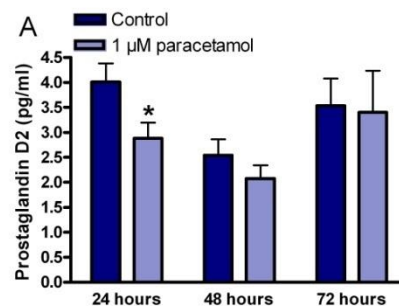
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Ex vivo

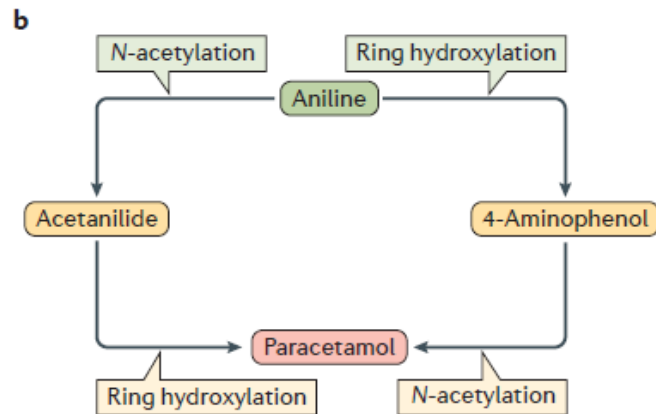
Caesarean section of pregnant rat dams at E14.5



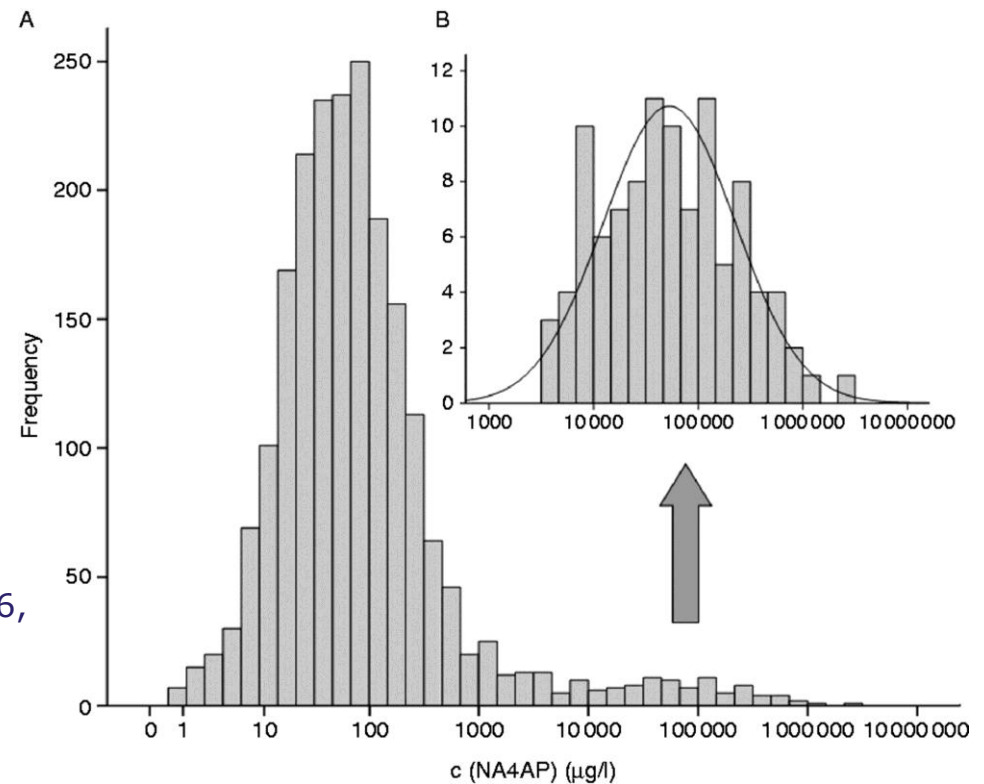
Exposure and measurement of testosterone and prostaglandin after 24, 48, and 72 h



Alle danskere, tyskere og amerikanere har har paracetamol i blodet



Kristensen, Mazaud-Guittot, Jégou *et al.* 2016,
Nature Rev. Endo.



Modick *et al.* 2014 & Nielsen *et al.* 2015.

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Hvor meget anilin bruges der?

Table 2.1 Market data and use pattern of aniline for the sum of USA, Western Europe for 1988

	BUA (1995) 1988 use	Srour (1994) 1993 use	Srour (1994) pred. for 1998
Production vol.	-	530,000 t/a	605,000 t/a
Import	-	30,000 t/a	50,000 t/a
Export	-	3,000 t/a	-
European use	-	555,000 t/a	652,000 t/a
Processing to MDA	71%	410,000 t/a 74%	498,000 t/a 76%
Processing to rubber chem.	15%	88,000 t/a 16%	90,000 t/a 14%
Processing to dyes	5%	38,000 t/a 6.8%	42,000 t/a 6.4%
Processing to pesticides	3%	10,000 t/a 1.8%	10,000 t/a 1.5%
Processing to pharmaceuticals	1.2%	-	-
Processing to fibers	1%	-	-
Processing to others	3.7%	9,000 t/a 1.6%	12,000 t/a 1.8%



"Jan 2013: Workers protecting water ways near Handan, China, after a spill of 39 tons aniline reaching the river Zhuozhang affecting 28 villages and several cities of more >1 million e.g. Handan City of 9 million people."

From: European Union Risk Assessment Report, Aniline, 2004

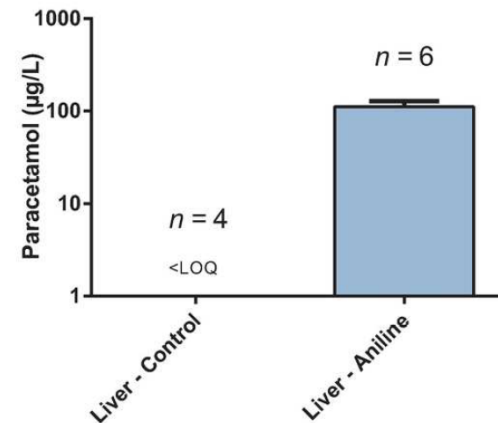
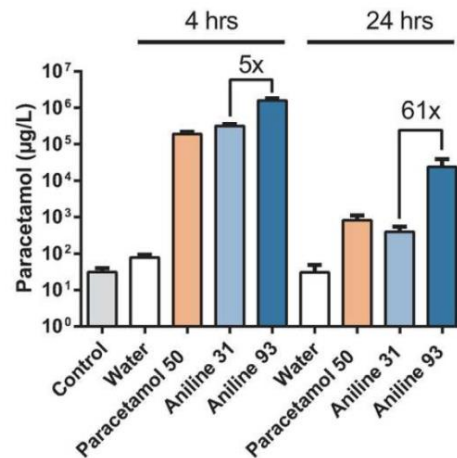
Note: MDA is processed to polyurethane used for insulation foam, wheel, tires synthetic fibers, carpets underlay, hard plastic etc. etc.

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Anilin bliver til paracetamol i vores dyremodel



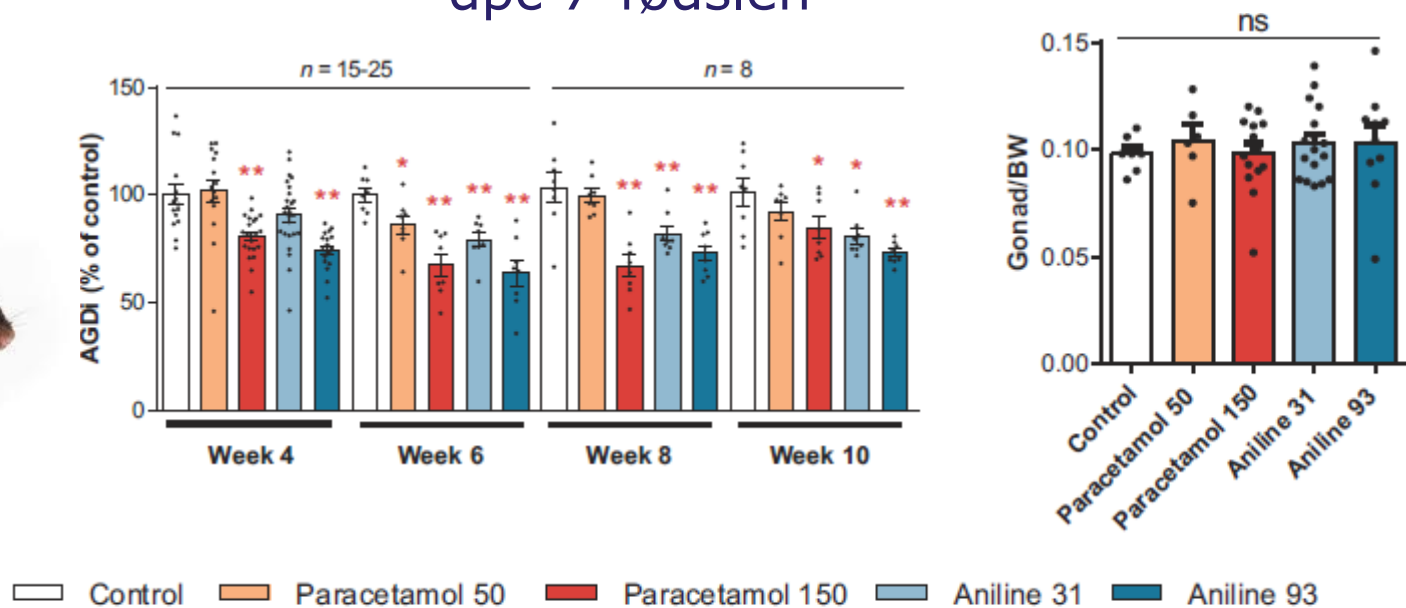
The C57BL/6

Holm *et al.* 2015 Tox.Sci.

Intrauterine eksponering med anilin og paracetamol dpc 7-fødslen



The C57BL/6



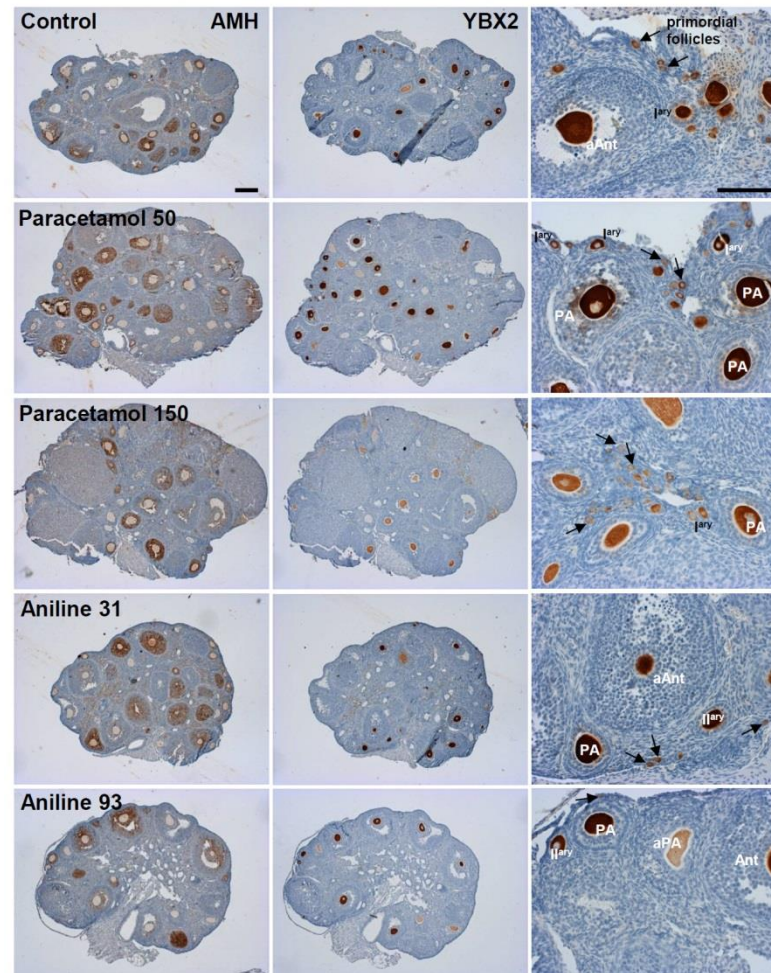
Intrauterine exposure dpc 7-birth using C57BL/6

Holm & Mazaud-Guittot
et al. 2016, Tox Sci.

Ovarier fra voksne mus efter eksponering fra dpc 7 til fødslen

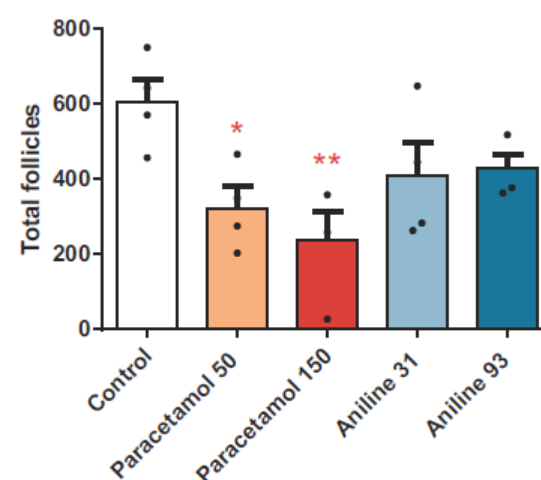
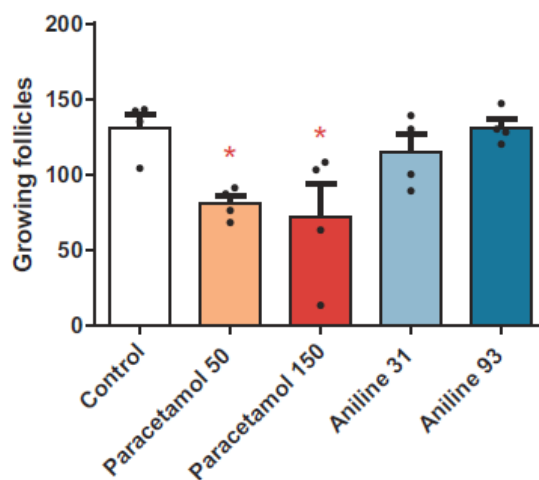
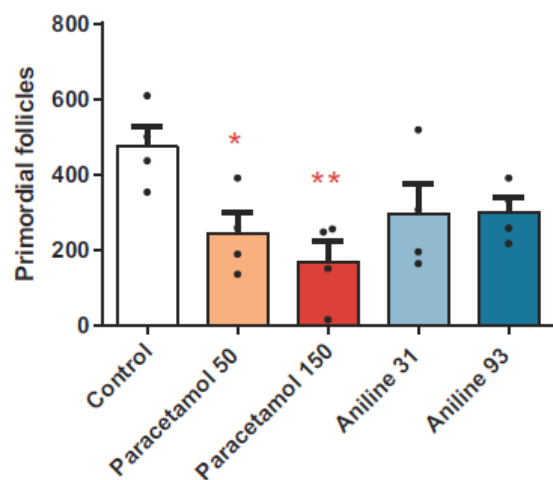


The C57BL/6

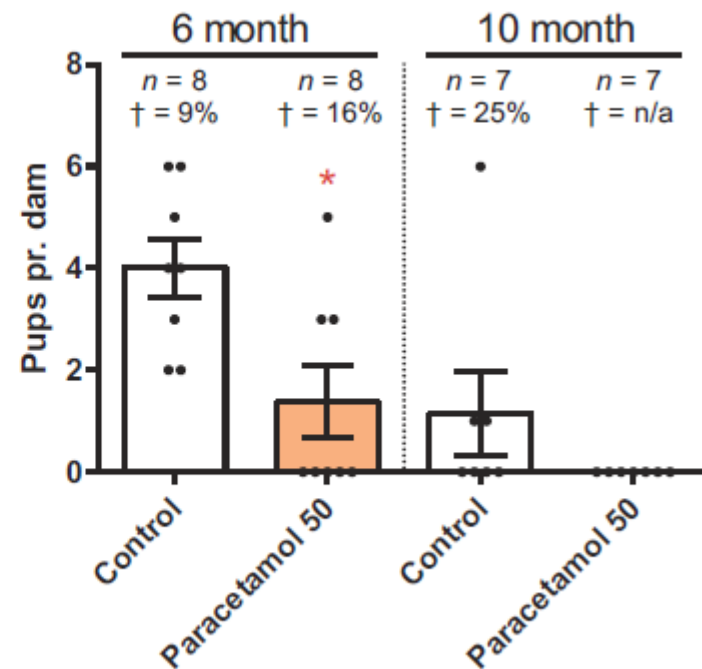
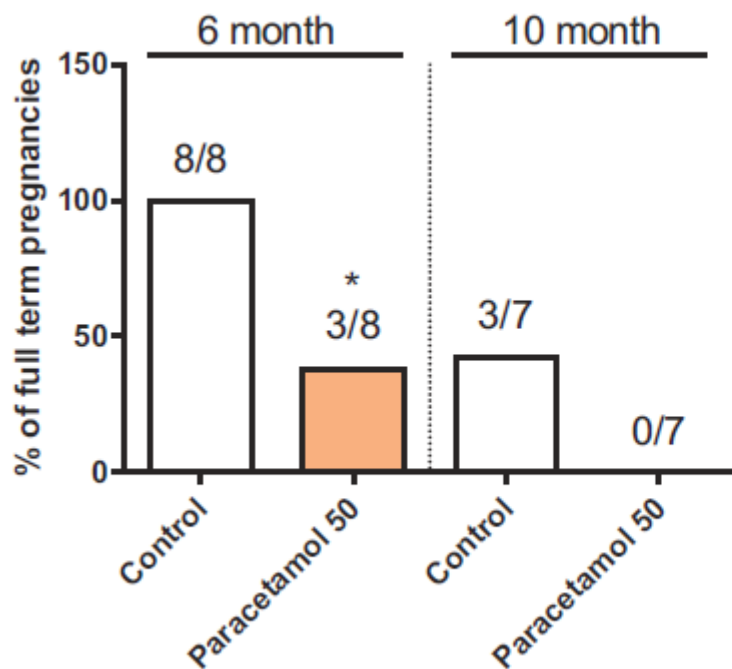


Holm & Mazaud-Guittot
et al. 2016, Tox Sci.

Reducering af follikler efter føtal eksponering



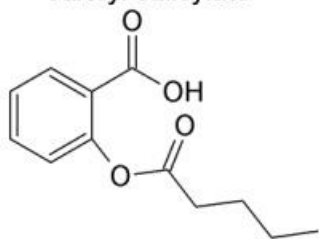
Reducering af fertilitet efter føtal eksponering



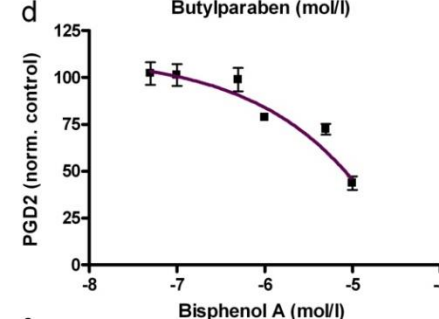
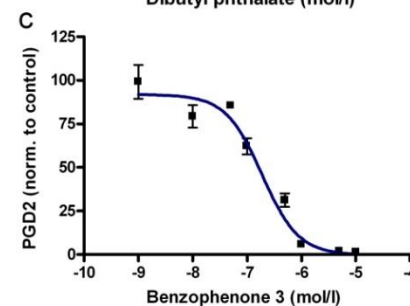
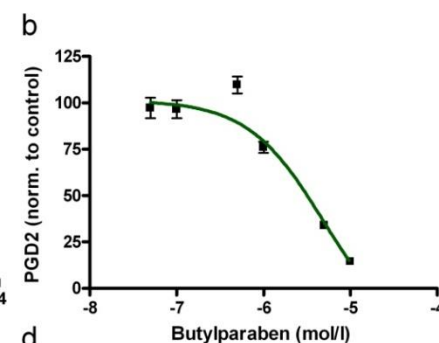
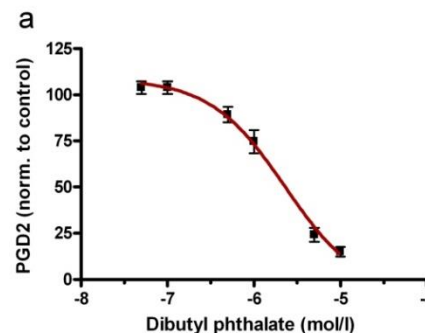
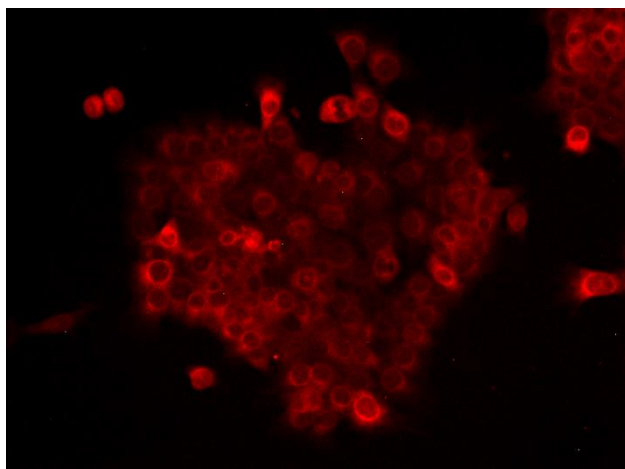
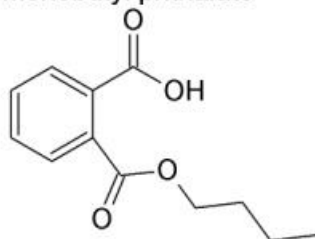
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Vores resultater viser, at en lang række kendte hormonforstyrrende også inhiberer prostaglandinsyntesen

Valeryl salicylate

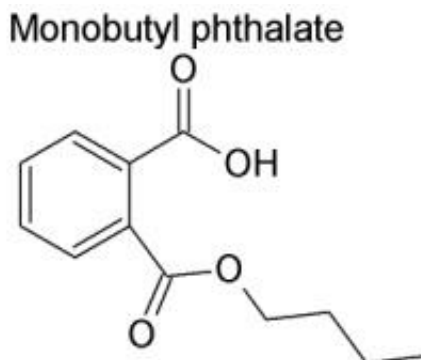
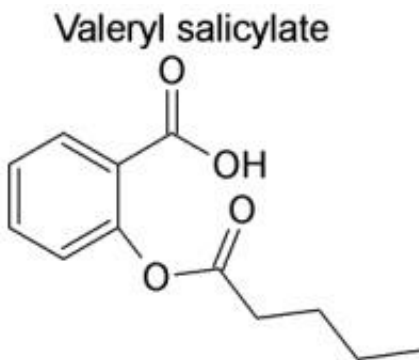


Monobutyl phthalate

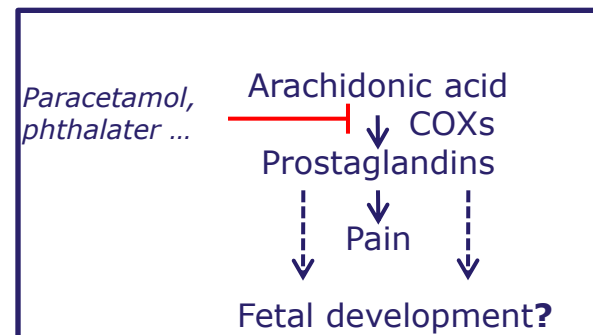


Kristensen *et al.* 2011 EHP.

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Kristensen *et al.* 2011 EHP.



“The similarity between known endocrine disrupting compounds and mild analgesics led us to hypothesise that inhibition of **prostaglandins** and use of **mild analgesics** during **pregnancy** could impair foetal **masculinisation** and therefore play a role in the decrease in male reproductive health!”



Konklusioner:

- Hovedpinemedicinen paracetamol kan påvirke den reproduktive udvikling.
- Eksponering til anilin eller derivater heraf kan være grunden til den allestedsværende paracetamol.
- Mange kendte hormonforstyrrende stoffer er potente hæmmere af prostaglandinsignalering ligesom paracetamol ... dette giver mulighed for additive effekter.



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