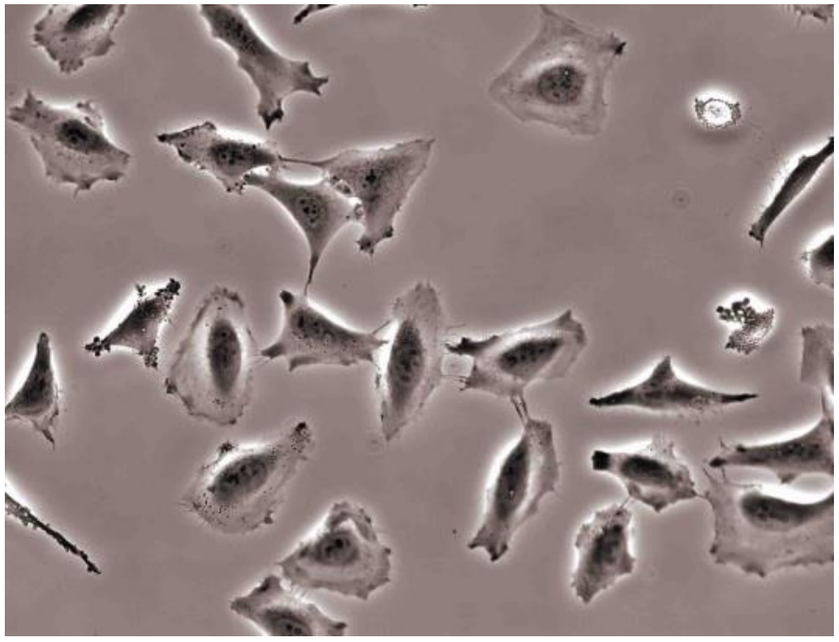
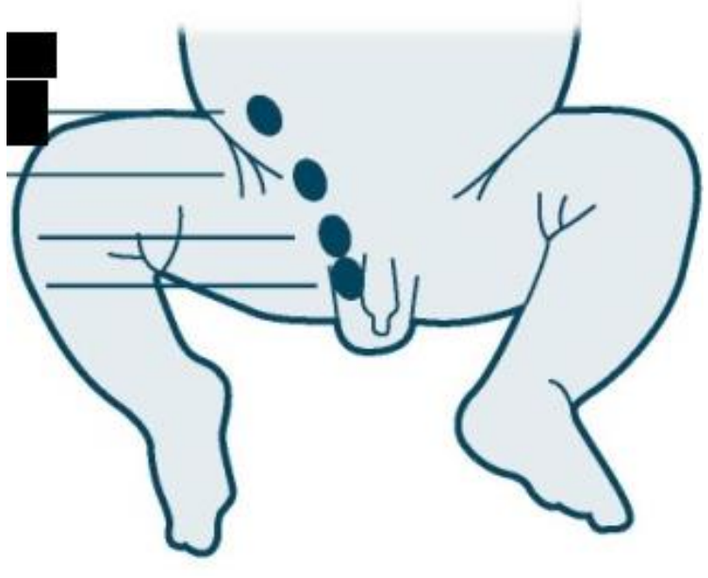
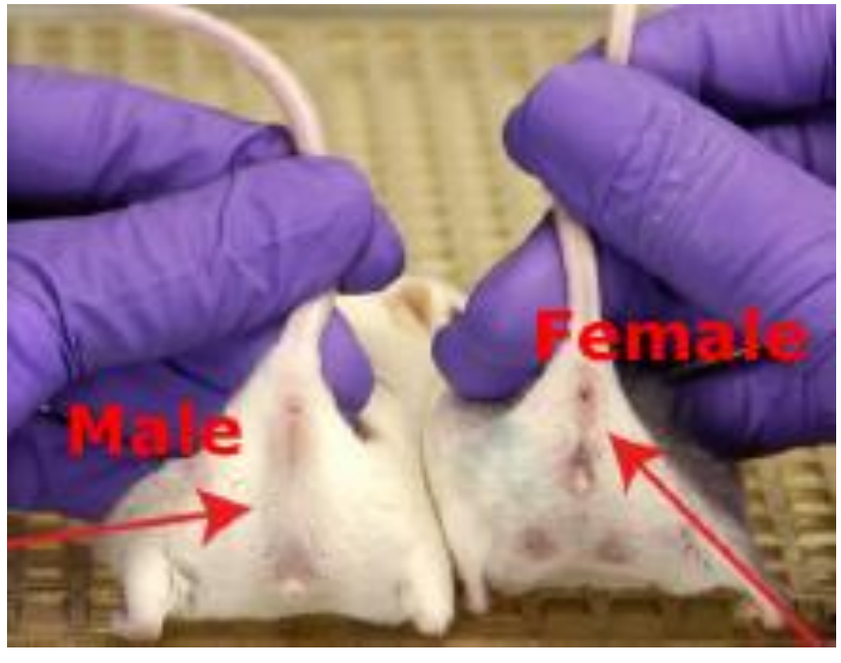
sruptors: From Estrogen-Like Chemicals Over Anti-androgens to C







Sharpe & Skakkebæk *Lancet* 1993

Lancet. 1993 May 29;341(8857):1392-5.

Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract?

Sharpe RM[1], Skakkebaek NE.

⊕ Author information

Abstract

The incidence of disorders of development of the male reproductive tract has more than doubled in the past 30-50 years while sperm counts have declined by about half. Similar abnormalities occur in the sons of women exposed to diethylstilbestrol (DES) during pregnancy and can be induced in animals by brief exposure to exogenous oestrogen/DES during pregnancy. We argue that the increasing incidence of reproductive abnormalities in the human male may be related to increased oestrogen exposure in utero, and identify mechanisms by which this exposure could occur.

Toppari *et al.* *Environ. Health Perspect.* 1996

Environ Health Perspect. 1996 Aug;104 Suppl 4:741-803.

Male reproductive health and environmental xenoestrogens.

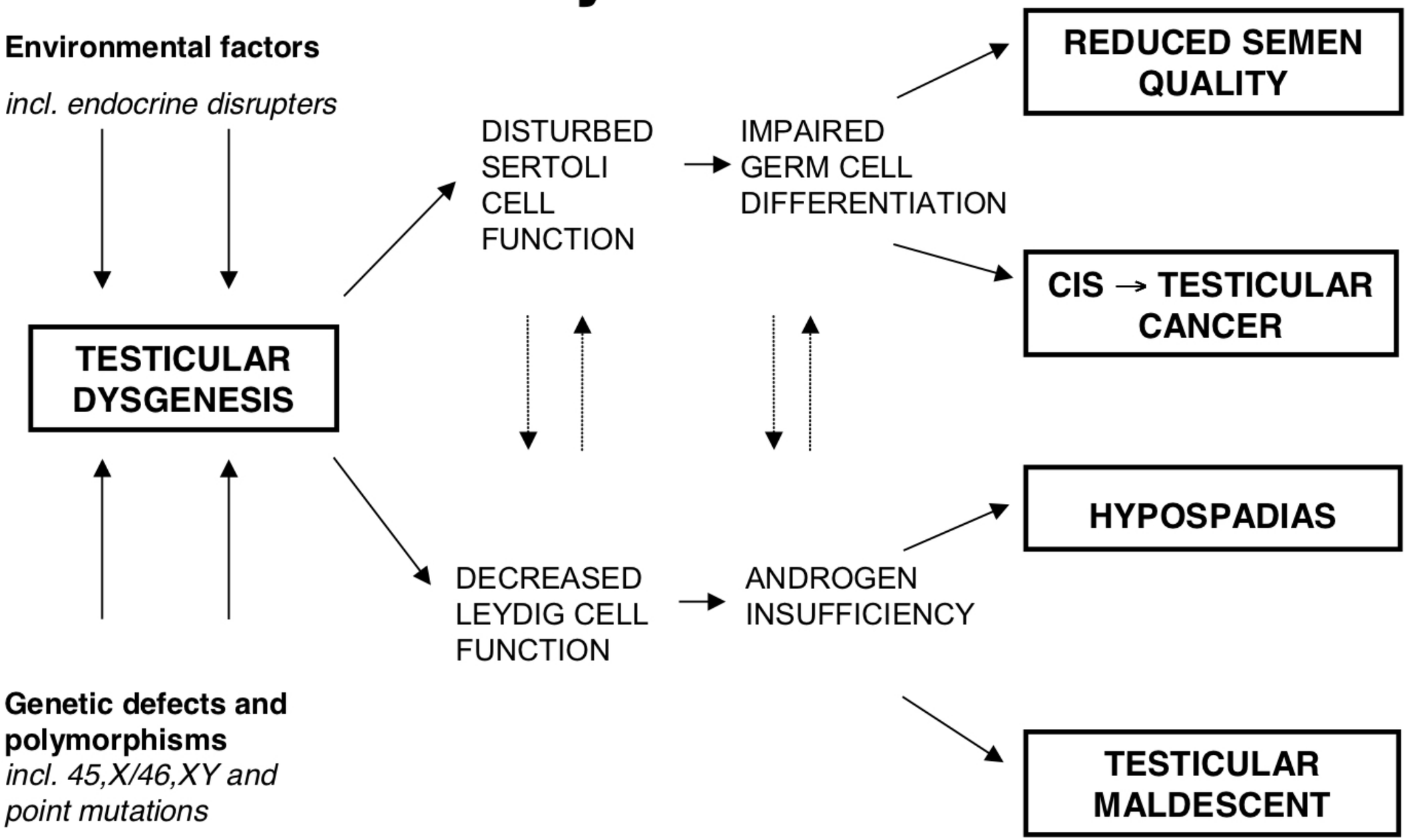
Toppari J[1], Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ Jr, Jégou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Müller J, Rajpert-De Meyts E, Scheike T, Sharpe R, Sumpter J, Skakkebaek NE.

⊕ **Author information**

Abstract

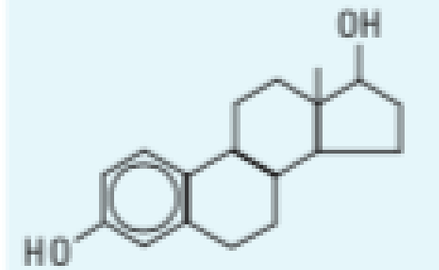
Male reproductive health has deteriorated in many countries during the last few decades. In the 1990s, declining semen quality has been reported from Belgium, Denmark, France, and Great Britain. The incidence of testicular cancer has increased during the same time incidences of hypospadias and cryptorchidism also appear to be increasing. Similar reproductive problems occur in many wildlife species. There are marked geographic differences in the prevalence of male reproductive disorders. While the reasons for these differences are currently unknown, both clinical and laboratory research suggest that the adverse changes may be inter-related and have a common origin in fetal life or childhood. Exposure of the male fetus to supranormal levels of estrogens, such as diethylstilbestrol, can result in the above-mentioned reproductive defects. The growing number of reports demonstrating that common environmental contaminants and natural factors possess estrogenic activity presents the working hypothesis that the adverse trends in male reproductive health may be, at least in part, associated with exposure to estrogenic or other hormonally active (e.g., antiandrogenic) environmental chemicals during fetal and childhood development. An extensive research program is needed to understand the extent of the problem, its underlying etiology, and the development of a strategy for prevention and intervention.

Testicular Dysgenesis Syndrome

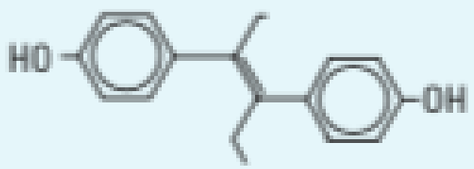


Skakkebæk, N. E., Rajpert-De Meyts, E. & Main, K. M. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Human Reproduction 16, 972–978 (2001).

Jørgensen *et al*. *Environ. Health Perspect.* 2000



17β-Estradiol (E_2)



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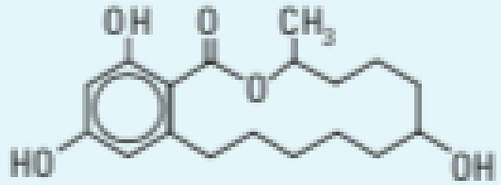

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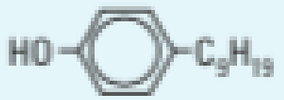

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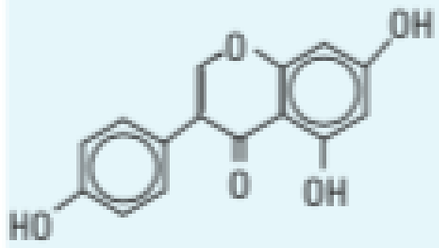

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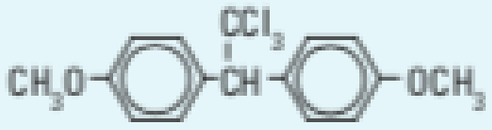
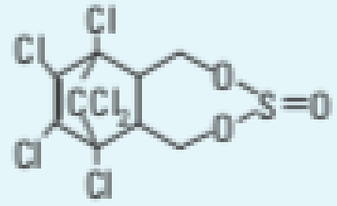


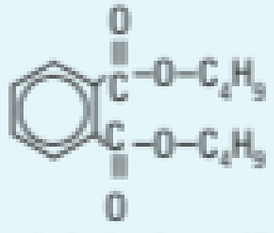
Methoxychlor (MC)



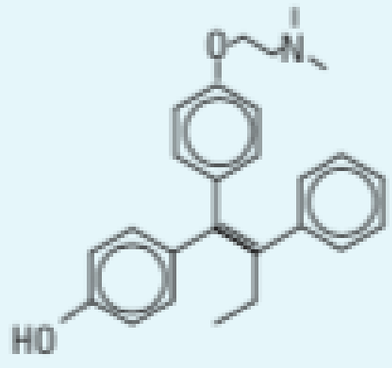
Endosulfan (ES)

***o,p'*-DDE** (DDE)

Bisphenol A (Bis-A)



Dibutylphthalate (DBP)



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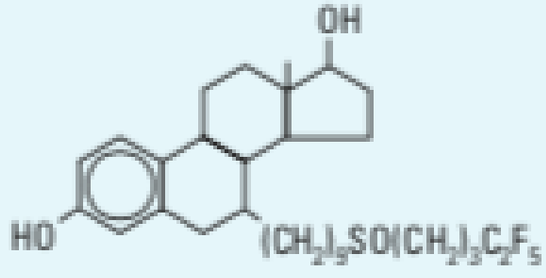
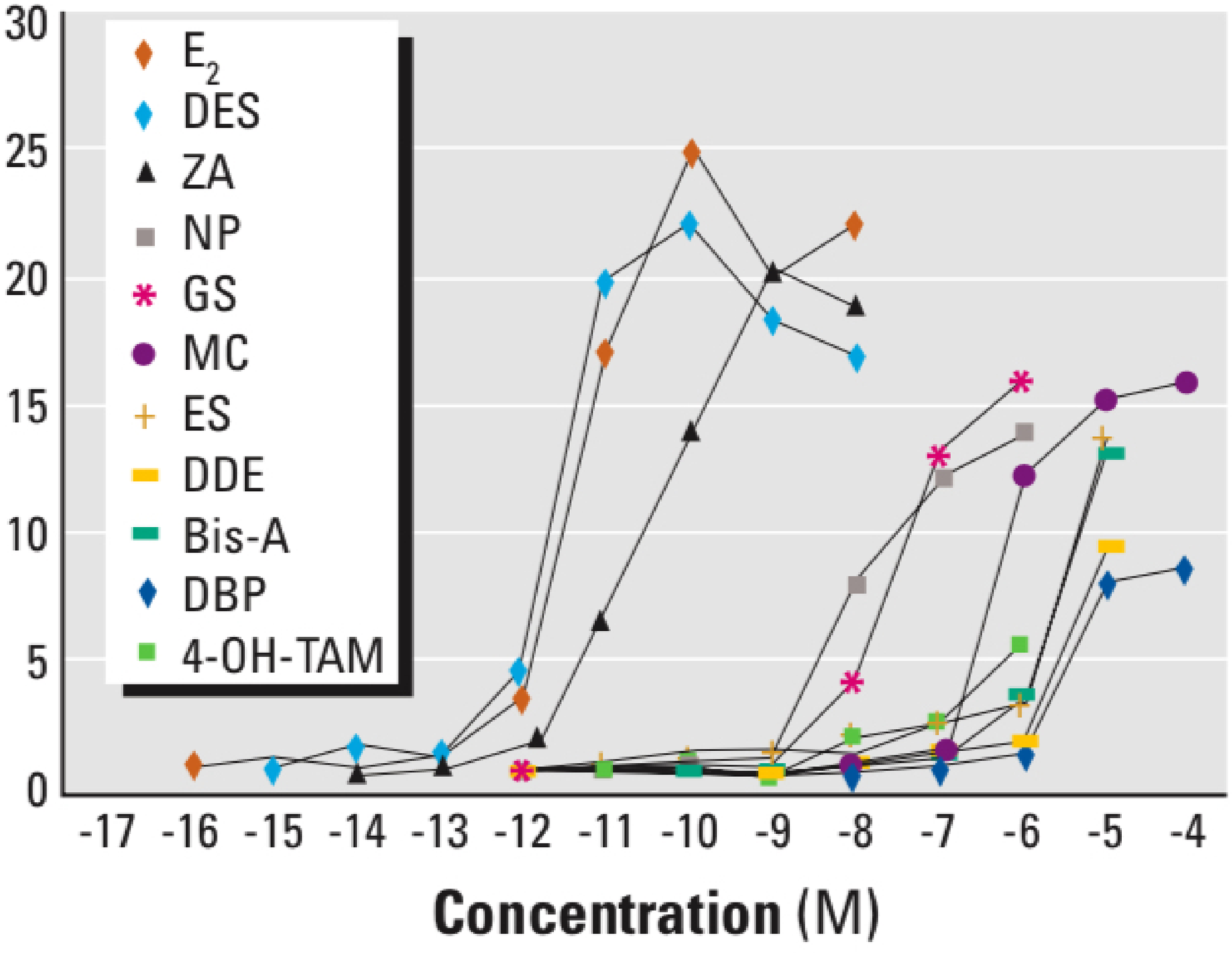


ICI 182.780 (ICI)

Jørgensen *et al*. *Environ. Health Perspect.* 2000



Boisen *et al. Lancet* 2004

Lancet. 2004 Apr 17;363(9417):1264-9.

Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries.

Boisen KA[1], Kaleva M, Main KM, Virtanen HE, Haavisto AM, Schmidt IM, Chellakooty M, Damgaard IN, Mau C, Reunanen M, Skakkebaek NE, Toppari J.

Author information

Abstract

BACKGROUND: Several investigators have shown striking differences in semen quality and testicular cancer rate between Denmark and Finland. Since maldescent of the testis is a shared risk factor for these conditions we undertook a joint prospective study for the prevalence of congenital cryptorchidism.

METHODS: 1068 Danish (1997-2001) and 1494 Finnish boys (1997-99) were consecutively recruited prenatally. We also established prevalence data for all newborns at Turku University Central Hospital, Finland (1997-99, n=5798). Testicular position was assessed by a standardised technique. All subtypes of congenital cryptorchidism were included, but retractile testes were considered normal.

FINDINGS: Prevalence of cryptorchidism at birth was 9.0% (95% CI 7.3-10.8) in Denmark and 2.4% (1.7-3.3) in Finland. At 3 months of age, prevalence rates were 1.9% (1.2-3.0) and 1.0% (0.5-1.7), respectively. Significant geographic differences were still present after adjustment for confounding factors (birthweight, gestational age, being small for gestational age, maternal age, parity, mode of delivery); odds ratio (Denmark vs Finland) was 4.4 (2.9-6.7, $p<0.0001$) at birth and 2.2 (1.0-4.5, $p=0.039$) at three months. The rate in Denmark was significantly higher than that reported 40 years ago.

INTERPRETATION: Our findings of increasing and much higher prevalence of congenital cryptorchidism in Denmark than in Finland contribute evidence to the pattern of high frequency of reproductive problems such as testicular cancer and impaired semen quality in Danish men. Although genetic factors could account for the geographic difference, the increase in reproductive health problems in Denmark is more likely explained by environmental factors, including endocrine disrupters and lifestyle.

Comment in

Differences in the prevalence of cryptorchidism. [Lancet. 2004]

PMID: 15094270 DOI: 10.1016/S0140-6736(04)15998-9

Toppari *et al. Andrology.* 2018

Andrology. 2018 Sep 24. doi: 10.1111/andr.12550. [Epub ahead of print]

An update on semen quality among young Finnish men and comparison with Danish data.

Rodprasert W[1], Virtanen HE[1], Sadov S[1], Perheentupa A[1,2], Skakkebaek NE[3], Jørgensen N[3], Toppari J[1,3,4].

⊕ Author information

Abstract

BACKGROUND: Finnish men used to have higher semen quality than Danish men. However, recent studies showed that semen quality in Finland has declined, but it has been relatively stable in Denmark.

OBJECTIVE: This study aimed to compare new data on semen quality of the young Finnish men to that of Danish men.

MATERIALS AND METHODS: In this cross-sectional study, 18- to 19-year-old men residing in Turku, Finland and Copenhagen, Denmark, were invited to participate in 2008-2011. Each man filled in a questionnaire, provided one semen sample and underwent andrological examination. Semen samples were analyzed according to WHO. Multiway ANOVA was used to adjust semen variables for duration of sexual abstinence and age (and time from ejaculation to the start of semen analysis for sperm motility).

RESULTS: Altogether 287 Finnish men and 873 Danish men participated in the study. The adjusted median sperm concentrations were 49 and 47 million/mL for Finnish and Danish men, respectively ($p = 0.48$). The adjusted median total sperm counts were 148 million in Finland and 146 million in Denmark ($p = 0.87$). The adjusted median percentages of morphologically normal spermatozoa were 6.9% in Finland and 6.5% in Denmark, $p = 0.27$. Finnish men had higher adjusted median percentages of motile spermatozoa (A+B+C) than Danish men (80% vs. 69%, $p < 0.001$). The proportion of men who had low semen quality (sperm concentration, percentage of morphologically normal spermatozoa or percentage of progressively motile spermatozoa below WHO reference limits) was lower in Finland (25.4%) than in Denmark (34.6%), $p = 0.004$.

DISCUSSION: Considerable percentage of men in both countries had low semen quality. The deteriorating semen quality in Finland may result in decreasing fecundity, which is a cause of concern.

CONCLUSION:The formerly high semen quality in Finland has converged to the lower Danish levels. Our findings demonstrate the importance of continuing surveillance of semen quality.

Main *et al. Environ. Health Perspect.* 2004

Environ Health Perspect. 2006 Feb;114(2):270-6.

Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age.

Main KM[1], Mortensen GK, Kaleva MM, Boisen KA, Damgaard IN, Chellakooty M, Schmidt IM, Suomi AM, Virtanen HE, Petersen DV, Andersson AM, Toppari J, Skakkebaek NE.

⊕ Author information

Abstract

Phthalates adversely affect the male reproductive system in animals. We investigated whether phthalate monoester contamination of human breast milk had any influence on the postnatal surge of reproductive hormones in newborn boys as a sign of testicular dysgenesis.

DESIGN: We obtained biologic samples from a prospective Danish-Finnish cohort study on cryptorchidism from 1997 to 2001. We analyzed individual breast milk samples collected as additive aliquots 1-3 months postnatally (n = 130; 62 cryptorchid/68 healthy boys) for phthalate monoesters [mono-methyl phthalate (mMP), mono-ethyl phthalate (mEP), mono-n-butyl phthalate (mBP), mono-benzyl phthalate (mBzP), mono-2-ethylhexyl phthalate (mEHP), mono-isononyl phthalate (miNP)]. We analyzed serum samples (obtained in 74% of all boys) for gonadotropins, sex-hormone binding globulin (SHBG), testosterone, and inhibin B.

RESULTS: All phthalate monoesters were found in breast milk with large variations [medians (minimum-maximum)]: mMP 0.10 (< 0.01-5.53 microg/L), mEP 0.95 (0.07-41.4 microg/L), mBP 9.6 (0.6-10,900 microg/L), mBzP 1.2 (0.2-26 microg/L), mEHP 11 (1.5-1,410 microg/L), miNP 95 (27-469 microg/L). Finnish breast milk had higher concentrations of mBP, mBzP, mEHP, and Danish breast milk had higher values for miNP (p = 0.0001-0.056). No association was found between phthalate monoester levels and cryptorchidism. However, mEP and mBP showed positive correlations with SHBG (r = 0.323, p = 0.002 and r = 0.272, p = 0.01, respectively); mMP, mEP, and mBP with LH:free testosterone ratio (r = 0.21-0.323, p = 0.002-0.044) and miNP with luteinizing hormone (r = 0.243, p = 0.019). mBP was negatively correlated with free testosterone (r = -0.22, p = 0.033). Other phthalate monoesters showed similar but nonsignificant tendencies.

CONCLUSIONS: Our data on reproductive hormone profiles and phthalate exposures in newborn boys are in accordance with rodent data and suggest that human Leydig cell development and function may also be vulnerable to perinatal exposure to some phthalates. Our findings are also in line with other recent human data showing incomplete virilization in infant boys exposed to phthalates prenatally.

PMID: 16451866 PMCID: PMC1367843 DOI: 10.1289/ehp.8075

Phthalates are Not Interferring With the Hormone Receptors

Toxicol Sci. 2009 Oct;111(2):372-82. doi: 10.1093/toxsci/kfp153. Epub 2009 Jul 10.

Phthalates impair germ cell number in the mouse fetal testis by an androgen- and estrogen-independent mechanism.

Lehraiki A[1], Racine C, Krust A, Habert R, Levacher C.

⊕ Author information

Abstract

Data from experiments conducted almost exclusively in the rat have established that some phthalates have deleterious effects on the fetal testis probably due to their antiandrogenic and/or estrogenic effects, but their mechanisms of action remain unknown. A recent study reported that phthalates also have deleterious effects on human fetal testis with germ cell number, but not steroidogenesis altered. Therefore, we used organ culture of fetal testes at different stages of development to analyze the direct effects of phthalates on both steroidogenesis and gonocyte development and to determine if the effects of MEHP on these functions reported in the rat can be extended to other mammalian species. We defined specific periods of sensitivity of the fetal mouse testis to MEHP for these two functions and showed that the effects of phthalates on steroidogenesis vary with the developmental stage. Conversely, the strong deleterious effects of phthalates on germ cells were constantly present during the active phases of gonocyte development and thus share no relationship with the steroidogenic status. Moreover, all the effects of phthalates were unchanged in testes from mice deficient for estrogen (ERalphaKO or ERbetaKO) or androgen (Tfm) receptors. In conclusion, our results demonstrate that phthalates impair mouse fetal germ cell number similarly to other mammalian species, but are neither estrogenic nor antiandrogenic molecules because their effects do not involve, directly or indirectly, ER or AR.

Phthalates are Not Interferring With the Hormone Receptors

Toxicol Sci. 2009 Oct;111(2):372-82. doi: 10.1093/toxsci/kfp153. Epub 2009 Jul 10.

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We demonstrated that the strong deleterious effect of phthalates on the germ cell lineage that is observed in various mammalian species is independent of any antiandrogenic effects and that the phthalates are neither estrogenic nor antiandrogenic because their effects do not involve, directly or indirectly, ER or AR.

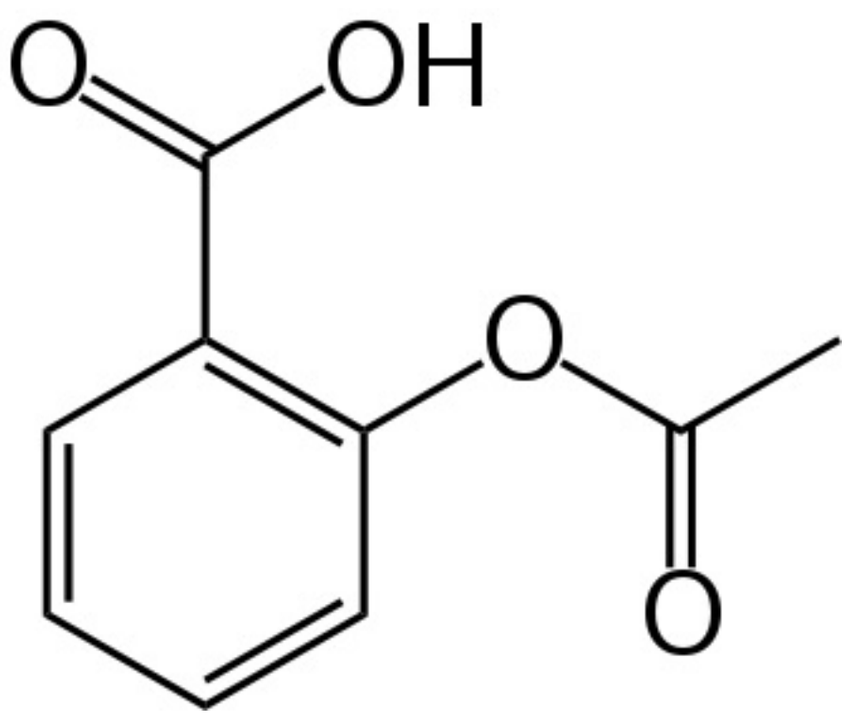
Stones spiller i Parken 5. august

22. mar. 2007, 20:10

af **olst**

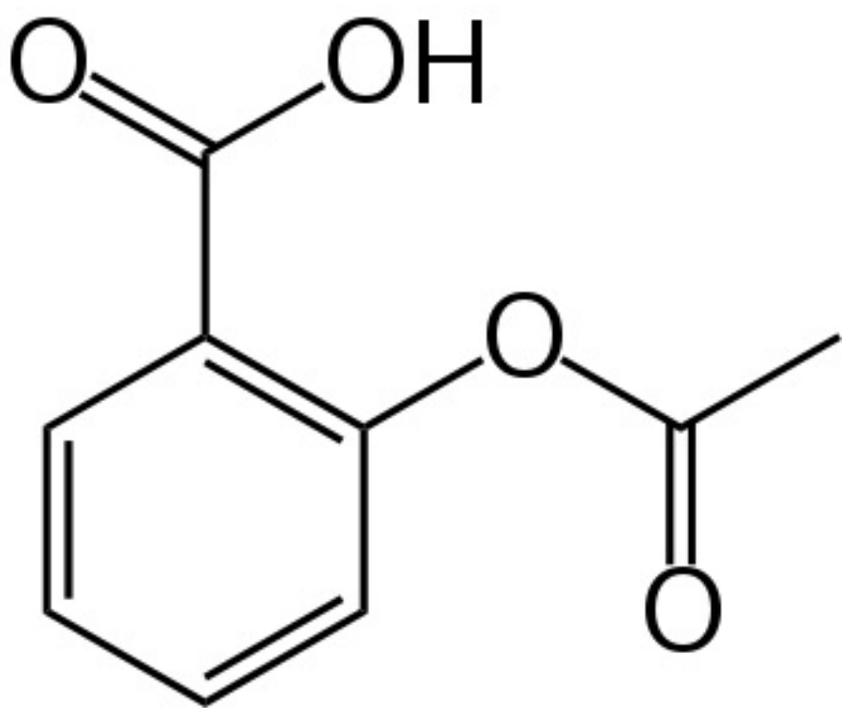
Mick Jagger: Rolling Stones spiller i Parken i København den 5. august

Painkiller or Endocrine Disruptor?

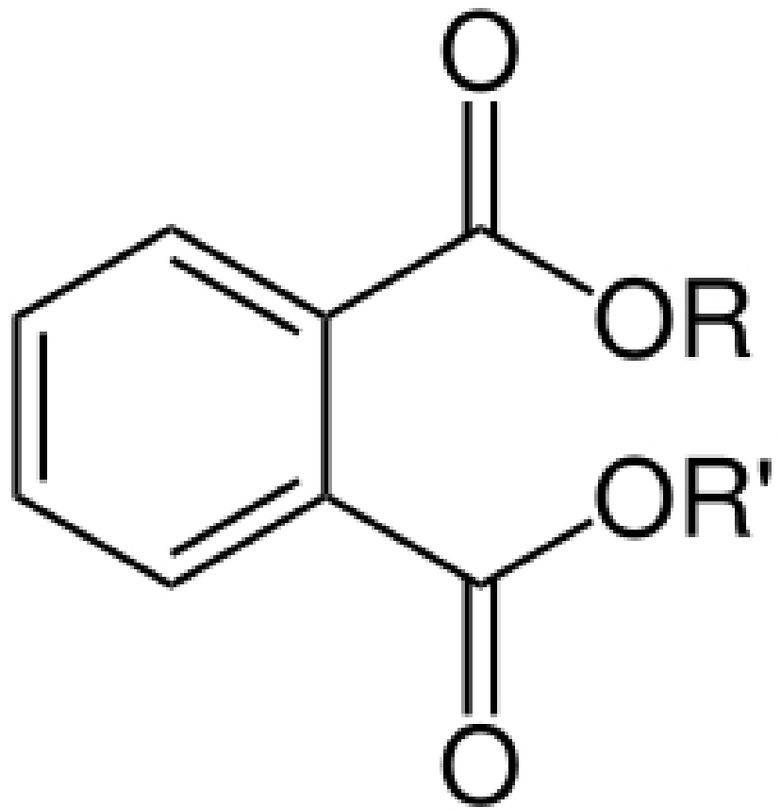


Aspirin

Painkiller or Endocrine Disruptor?

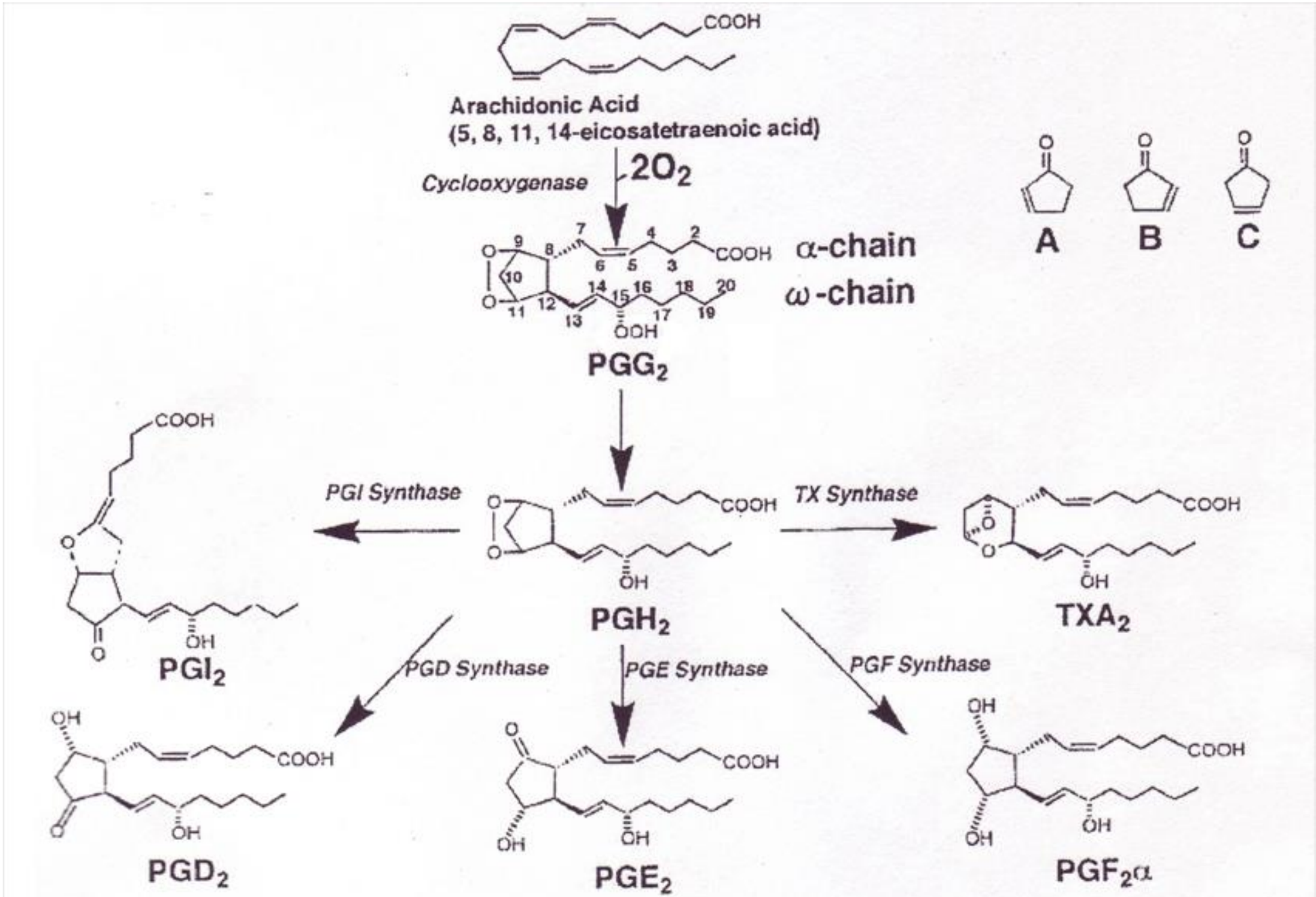


Aspirin

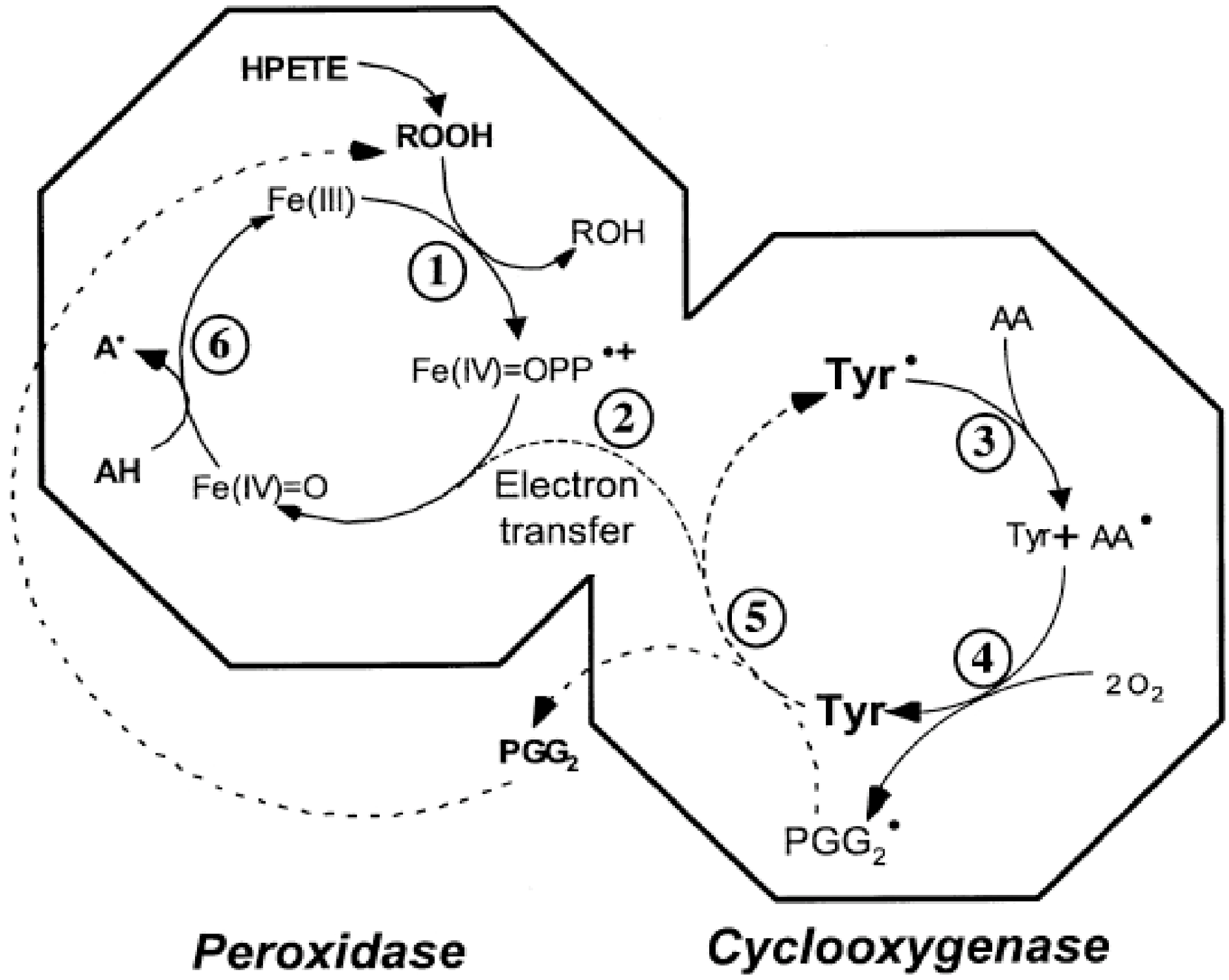


Phthalate

Prostaglandin Synthesis



Cyclooxidase (COX, PGHS) Mode-of-Action

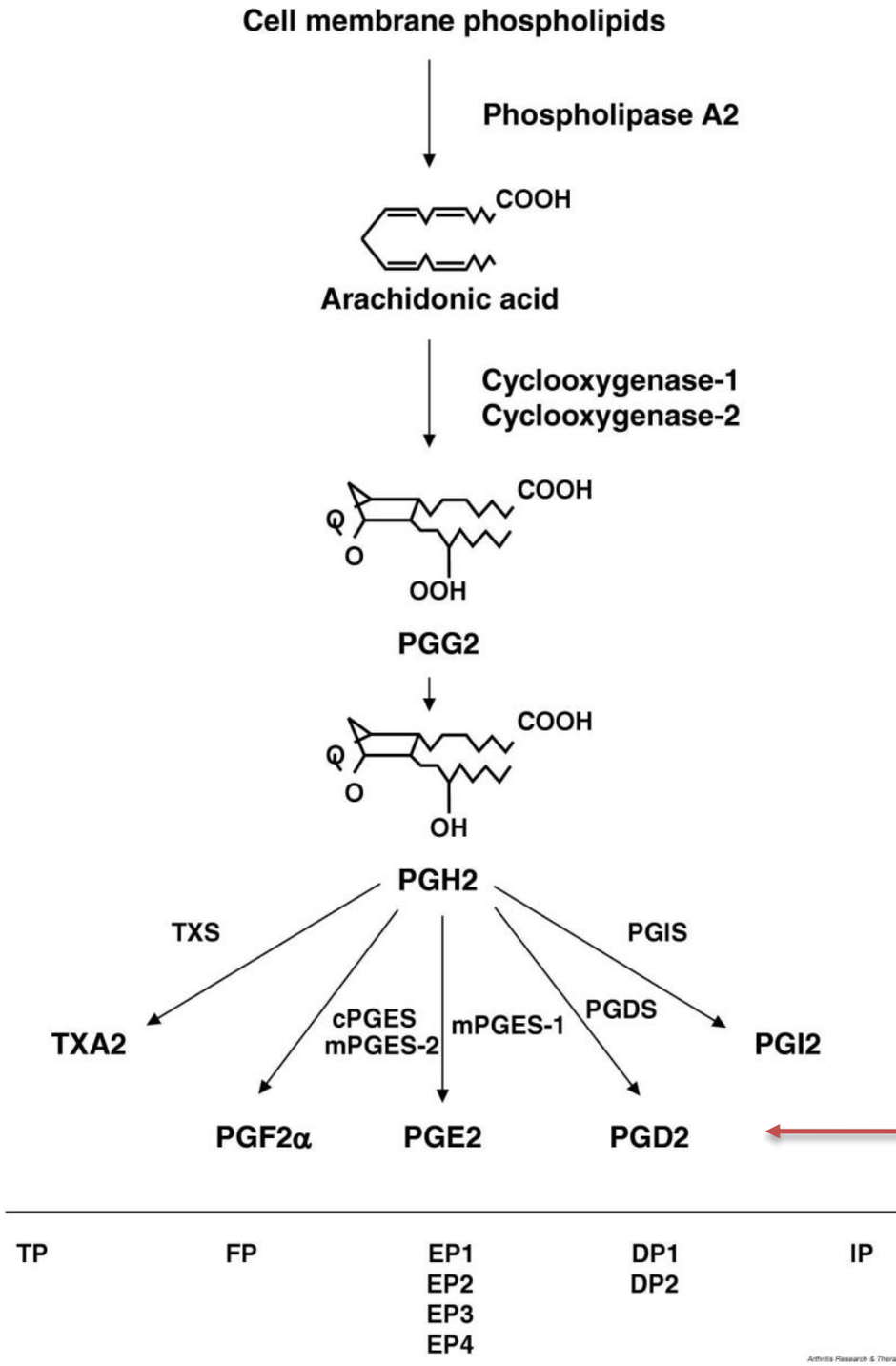


Karthein et al. Eur J Biochem 1988;171:313-20

Aronoff et al. CLINICAL PHARMACOLOGY & THERAPEUTICS, 2006;79(1):9-19

Evidence for Prostaglandin Involvement in Testis Development

The prostaglandin pathway



Development 129, 1155-1164 (2002)
Printed in Great Britain © The Company of Biologists Limited 2002
DEV3592

Sexually dimorphic development of mouse primordial germ cells: switching from oogenesis to spermatogenesis

Ian R. Adams and Anne McLaren*

Wellcome/CRC Institute of Cancer and Developmental Biology, Tennis Court Road, Cambridge CB2 1QR, UK
*Author for correspondence (e-mail: a.mclaren@welc.cam.ac.uk)

Accepted 7 December 2001

SUMMARY

During embryogenesis, primordial germ cells (PGCs) have the potential to enter either spermatogenesis or oogenesis. In a female genital ridge, or in a non-gonadal environment, PGCs develop as meiotic oocytes. However, male gonadal somatic cells inhibit PGCs from entering meiosis and direct them to a spermatogenic fate. We have examined the ability of PGCs from male and female embryos to respond to the masculinising environment of the male genital ridge, defining a temporal window during which PGCs retain a bipotential fate. To help understand how PGCs respond to the male gonadal environment, we have identified molecular differences between male PGCs that are committed to spermatogenesis and bipotential female PGCs. Our results suggest that one way in which PGCs respond to this masculinising environment is to synthesise prostaglandin D_2. We show that this signalling molecule can partially masculinise female embryonic gonads in culture, probably by inducing female supporting cells to differentiate into Sertoli cells. In the developing testis, prostaglandin D_2 may act as a paracrine factor to induce Sertoli cell differentiation. Thus part of the response of PGCs to the male gonadal environment is to generate a masculinising feedback loop to ensure male differentiation of the surrounding gonadal somatic cells.

Key words: Primordial germ cells, Testis development, Sertoli cells, Prostaglandin D synthase, Prostaglandin D_2, Sex reversal, Mouse

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 282, NO. 14, pp. 10553–10560, April 6, 2007

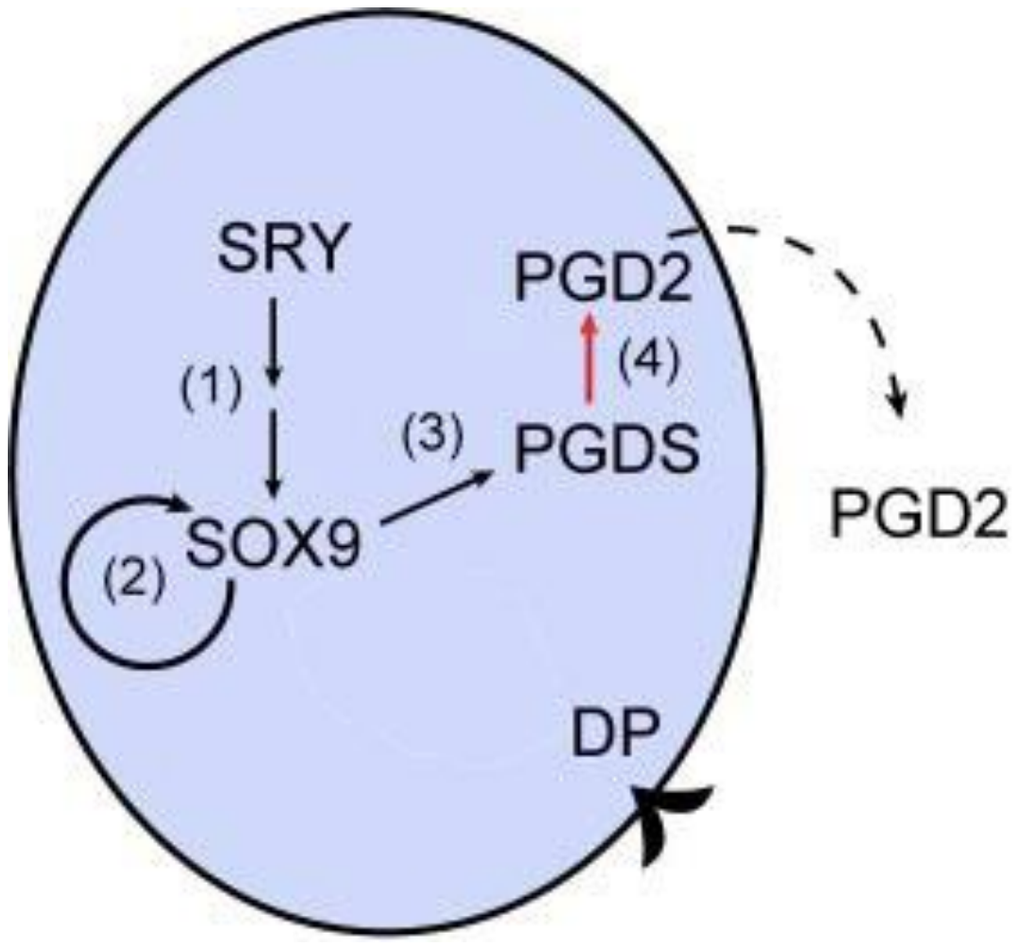
SOX9 Regulates Prostaglandin D Synthase Gene Transcription *in Vivo* to Ensure Testis Development*

Received for publication, October 11, 2006, and in revised form, January 22, 2007 Published, JBC Papers in Press, February 2, 2007, DOI 10.1074/jbc.M609578200

Dagmar Wilhelm[‡1], Ryuji Hiramatsu[§], Hirofumi Mizusaki[‡], Laura Widjaja[‡], Alexander N. Combes[‡], Yoshiakira Kanai[§], and Peter Koopman[‡¶2]

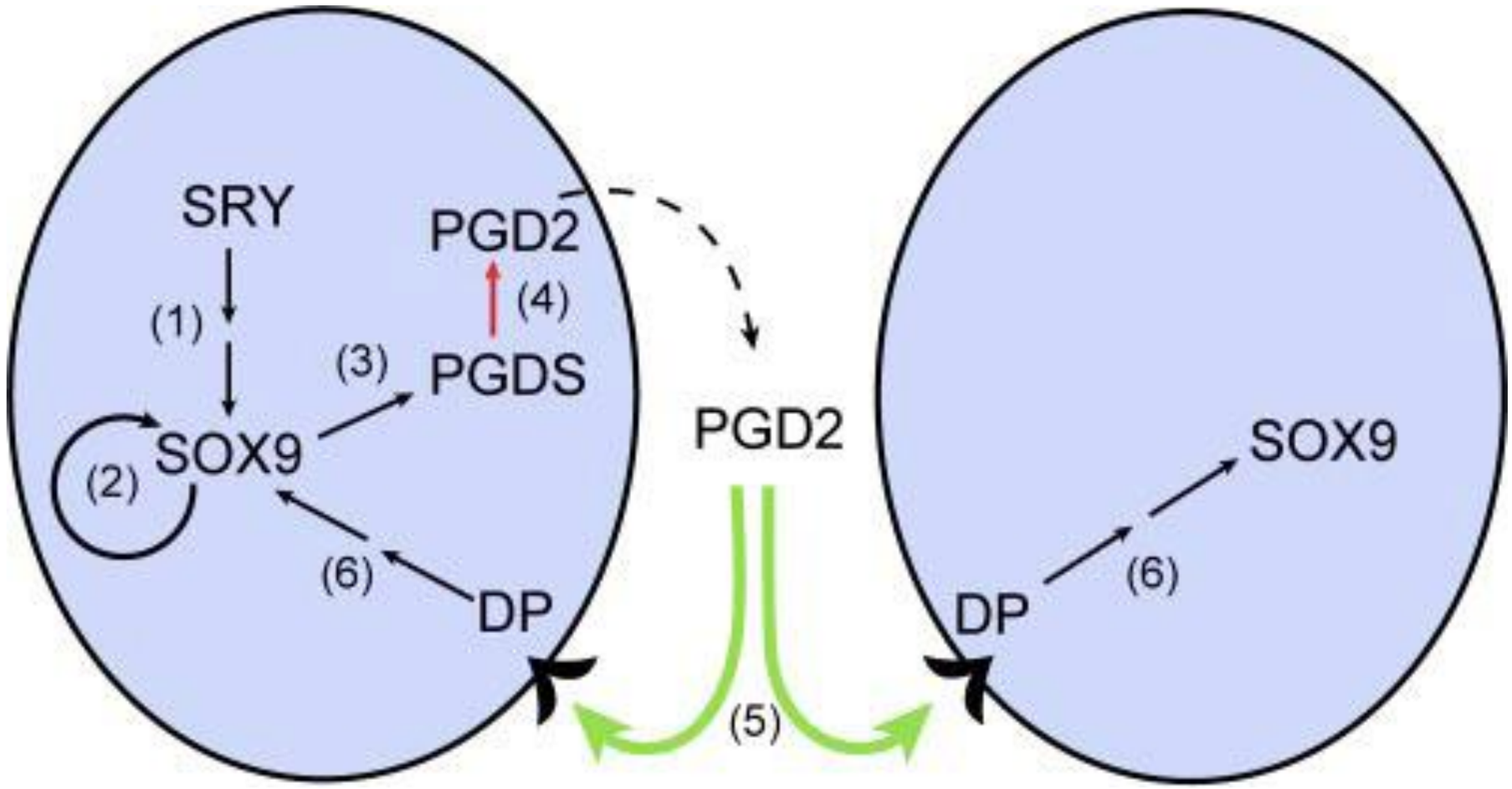
From the [‡]Division of Molecular Genetics and Development, Institute for Molecular Bioscience, The University of Queensland, Brisbane, Qld 4072, Australia, the [§]Department of Veterinary Anatomy, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113-8657, Japan, and the [¶]ARC Centre of Excellence in Biotechnology and Development, Institute for Molecular Bioscience, The University of Queensland, Brisbane, Qld 4072, Australia

PGD2 Masculinise Sertoli Cells



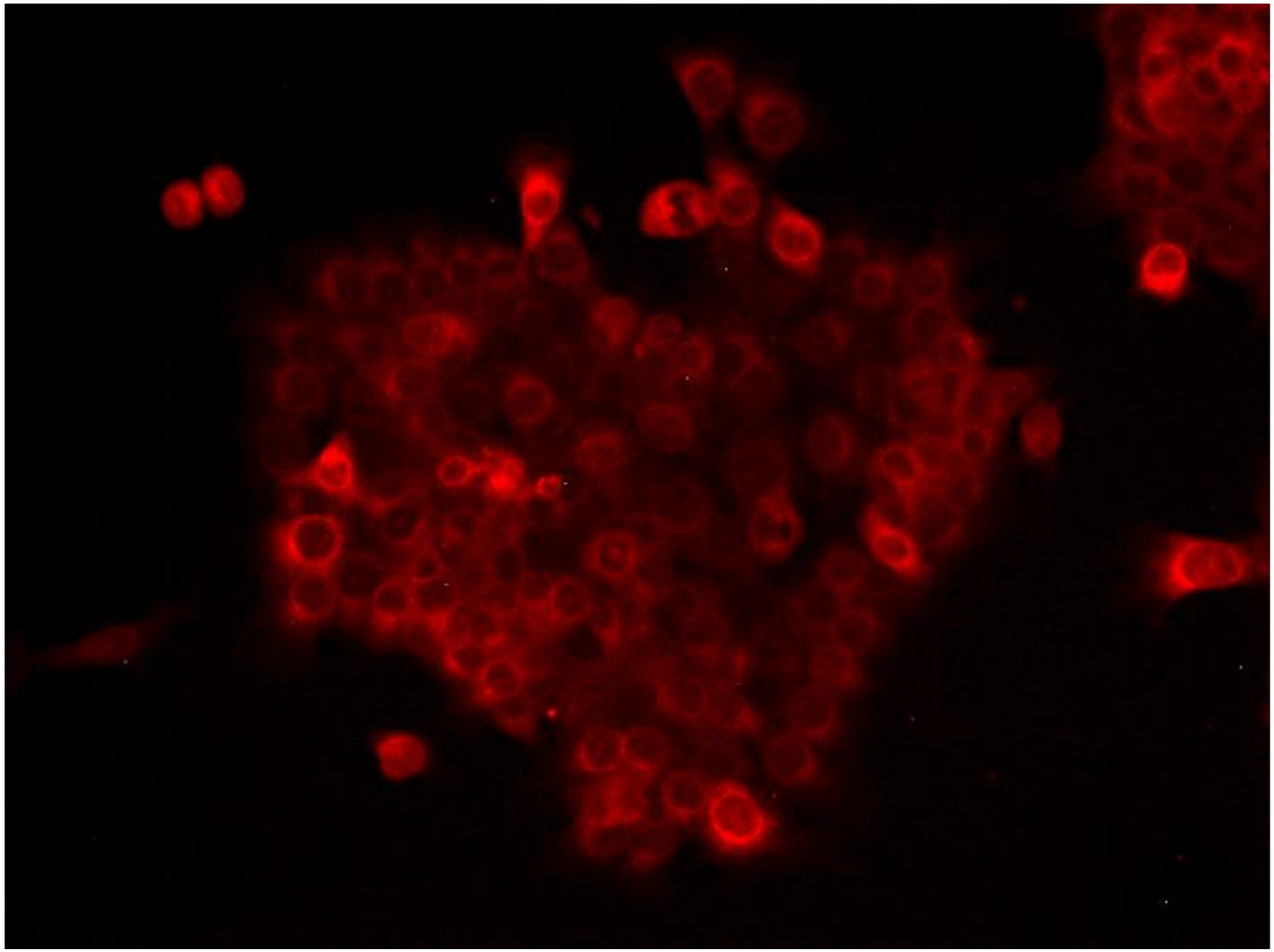
Wilhelm, Palmer, & Koopman. Physiol Rev, 87, 1-28, 2007

PGD2 Masculinise Sertoli Cells



Wilhelm, Palmer, & Koopman. Physiol Rev, 87, 1-28, 2007

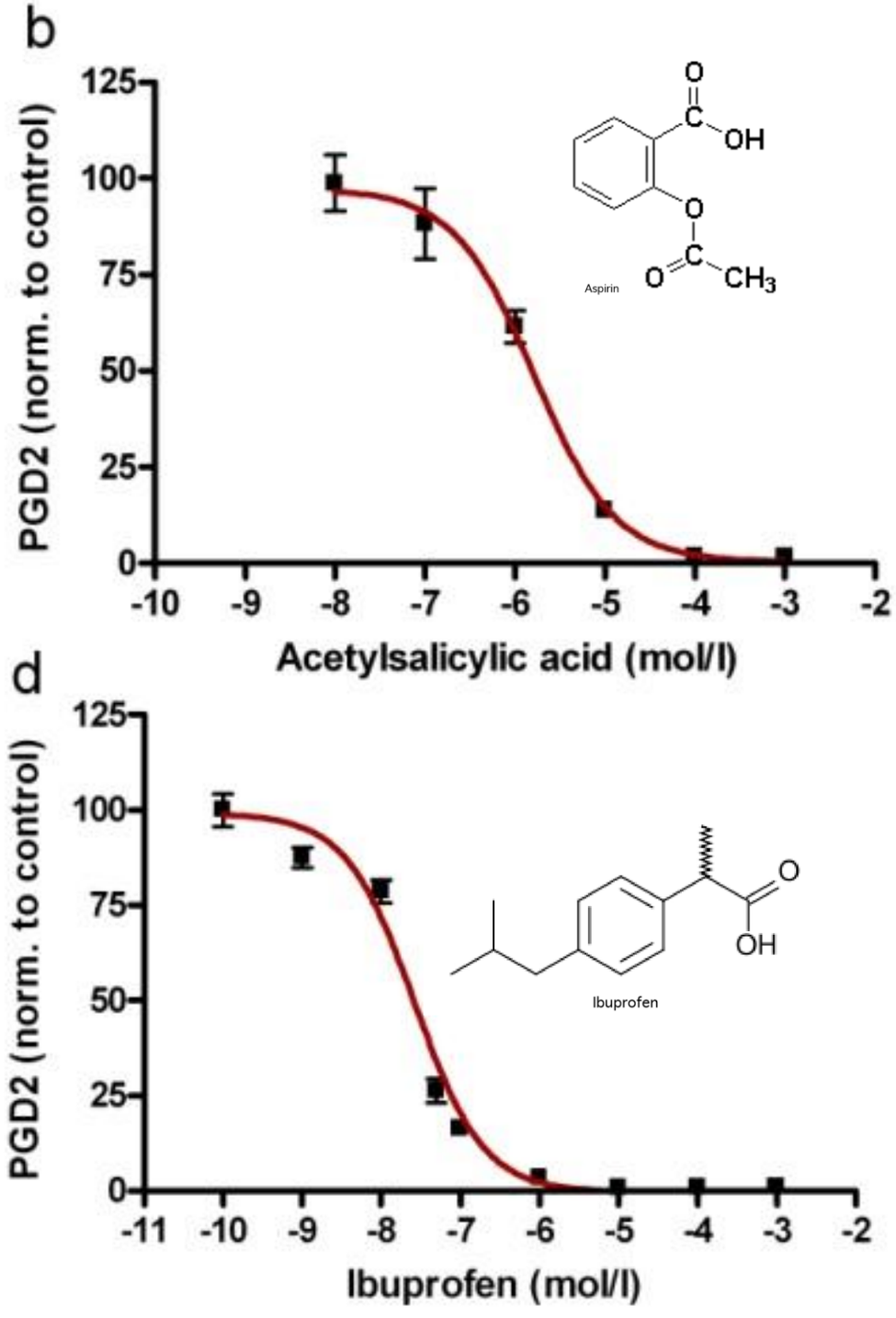
A Cell-Based Assay for Inhibition of PG Synthesis

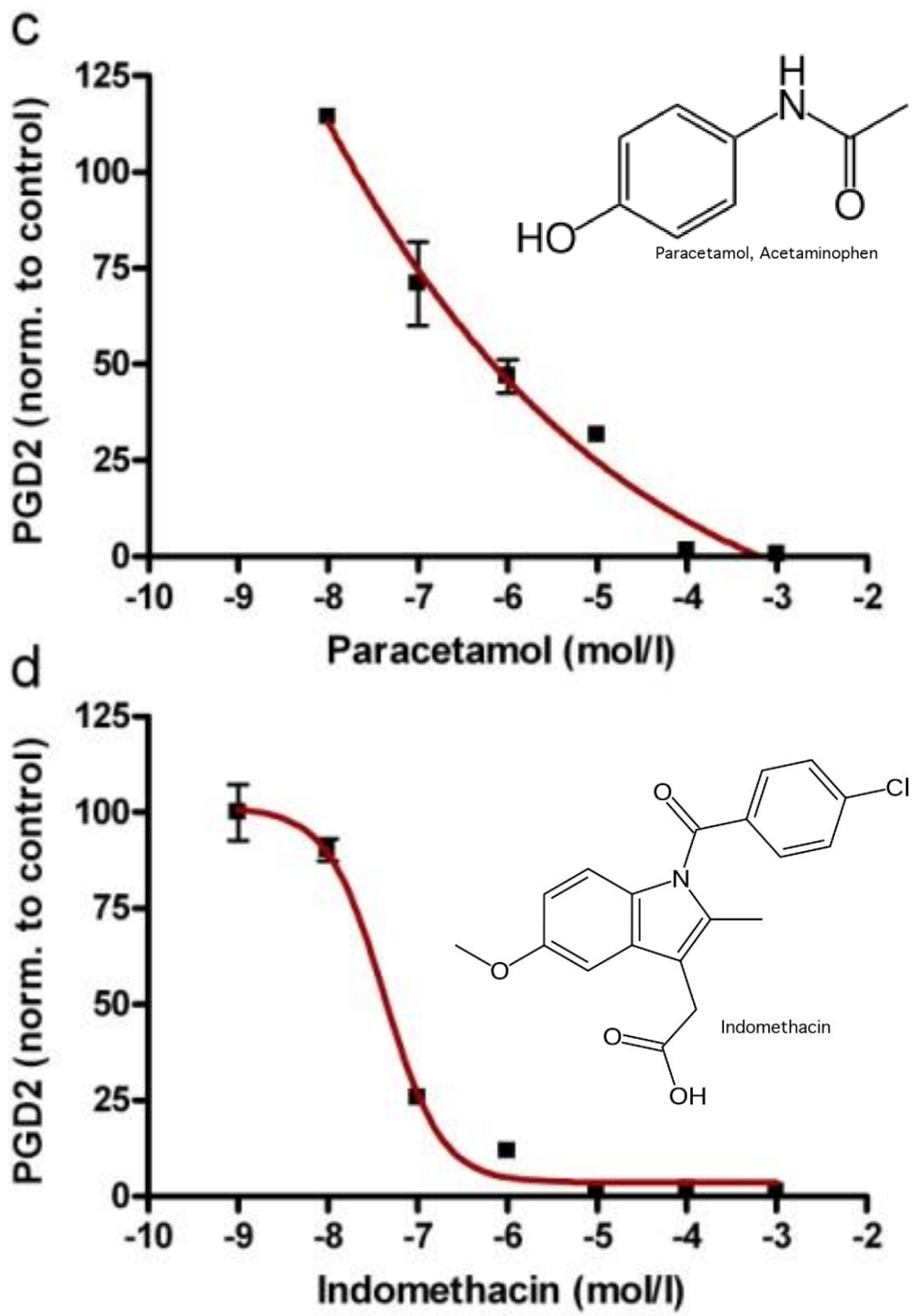


Mouse SC5 Sertoli cells stained for Cox2

David Møbjerg Kristensen et al. RH

Mild Analgesics Inhibit PGD2 Synthesis in SC5 cells



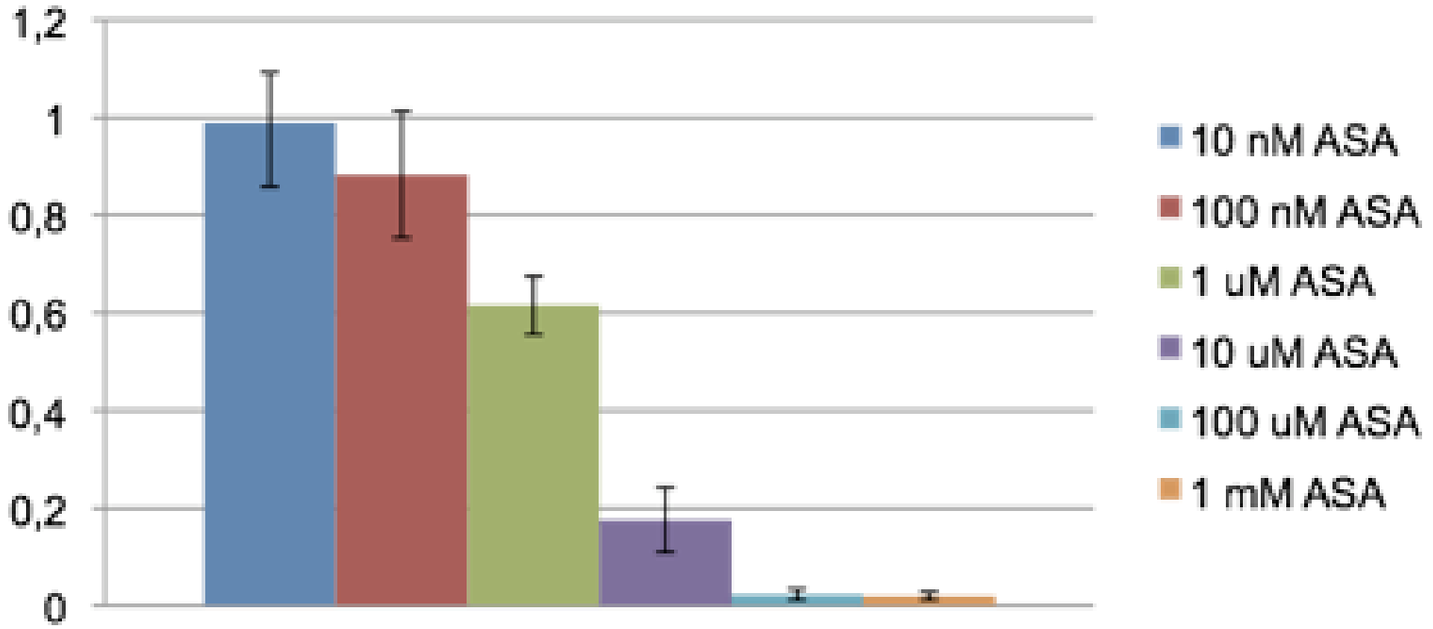


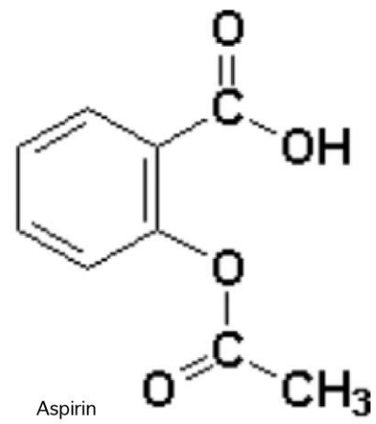
David Møbjerg Kristensen et al. RH

Do EDS Inhibit PGD2 Synthesis in SC5 Cells?

Acetylsalicylic acid (ASA)

PGD2 levels relative to control

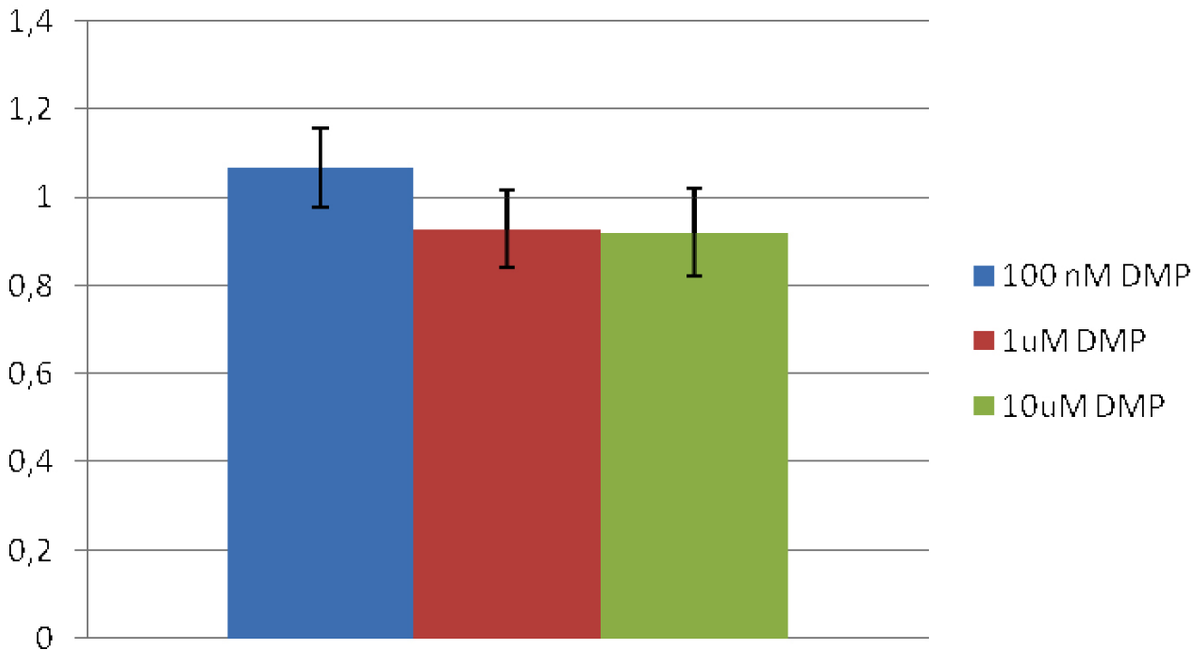


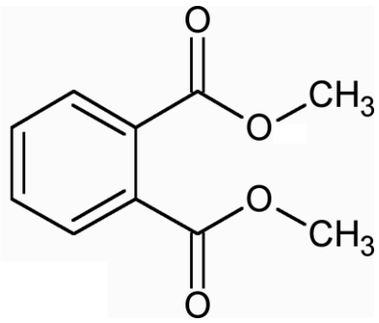


Aspirin

Dimetyl phthalate (DMP)

PGD2 levels relative to control



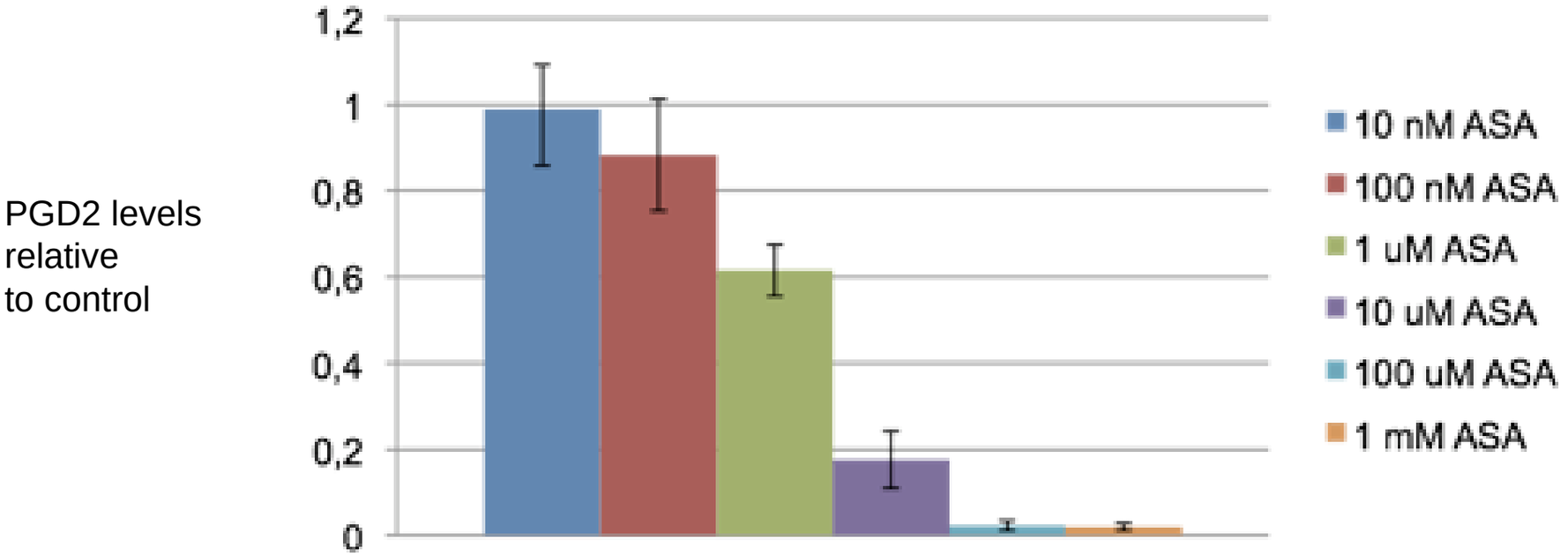


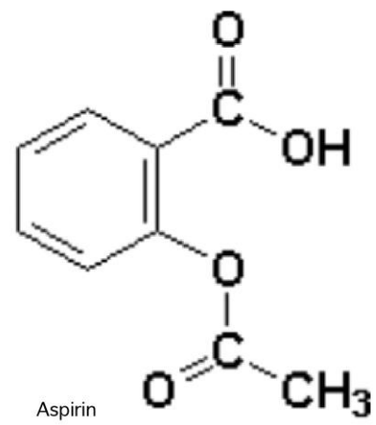
DMP

David Møbjerg Kristensen et al. RH

Do EDS Inhibit PGD2 Synthesis in SC5 Cells?

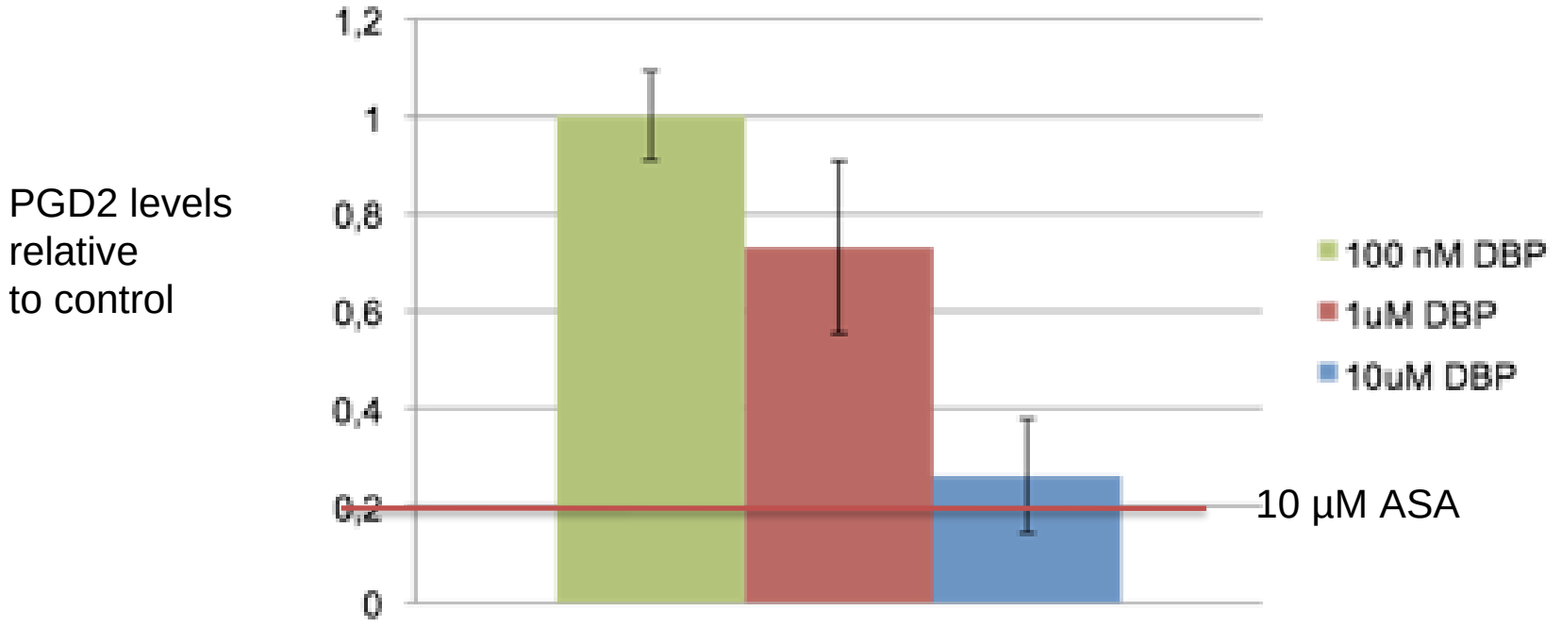
Acetylsalicylic acid (ASA)

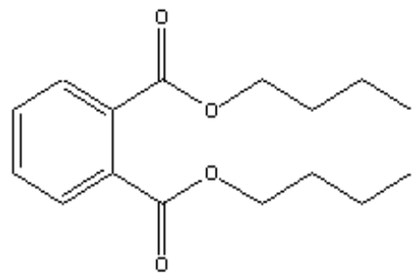




Aspirin

Dibutyl phthalate (DBP)



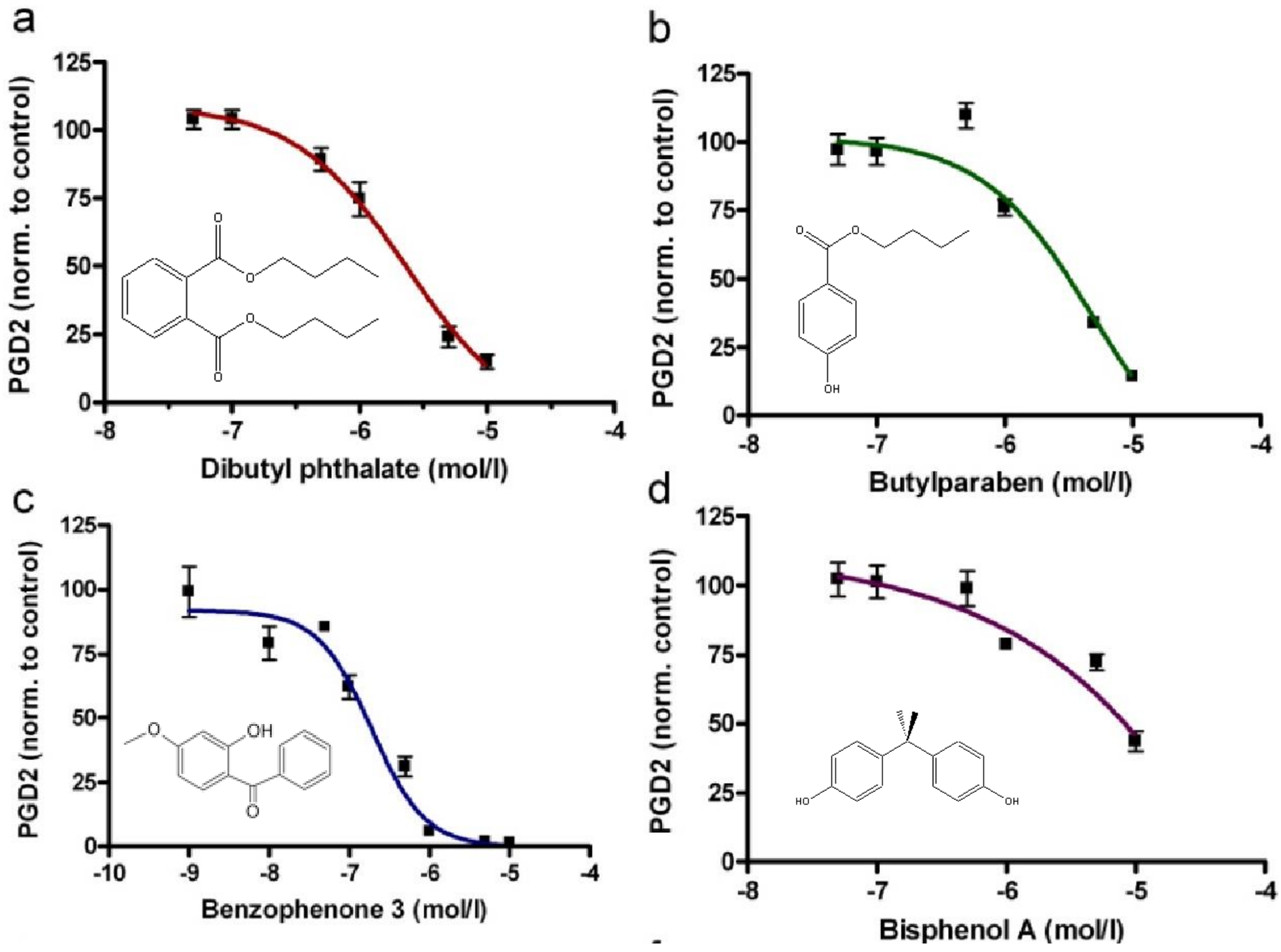


DBP

10 µM DBP is almost as potent as 10 µM aspirin!

David Møbjerg Kristensen et al. RH

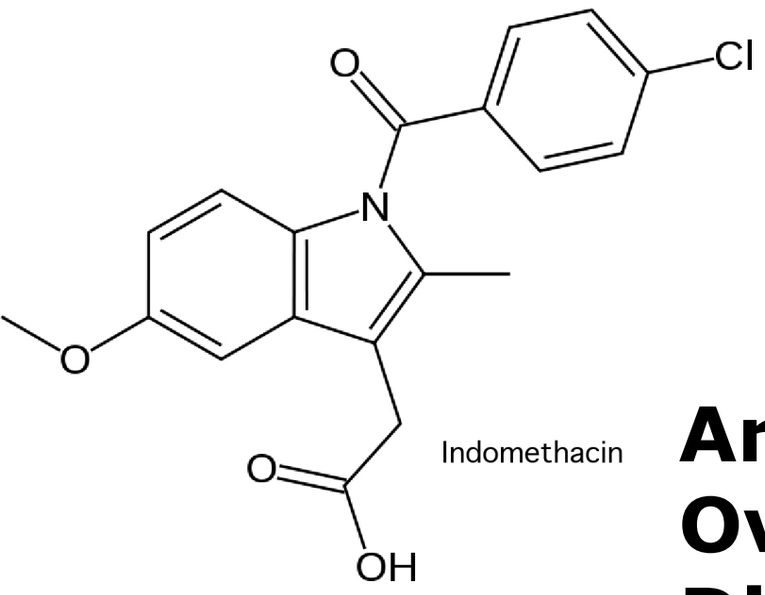
Many EDS Inhibit PGD2 Synthesis in SC5 cells



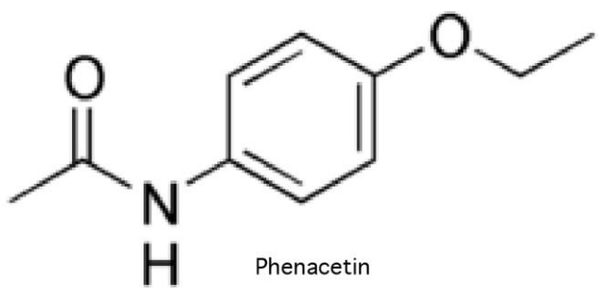
David Møbjerg Kristensen et al. RH

A Very Important Question:

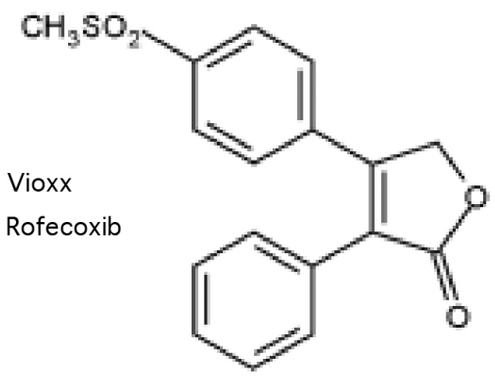
Are Pharmaceutical Painkillers Over-the-Counter Endocrine Disruptors?



Indomethacin

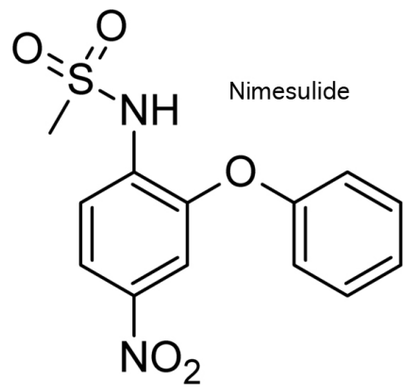


Phenacetin

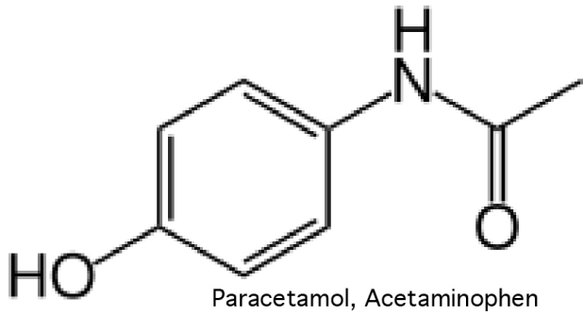


Vioxx

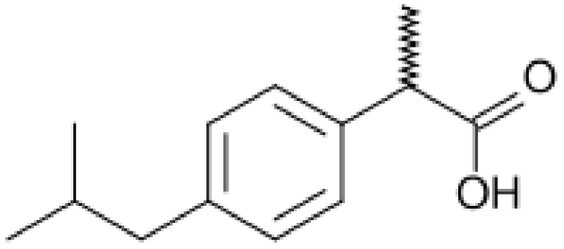
Rofecoxib



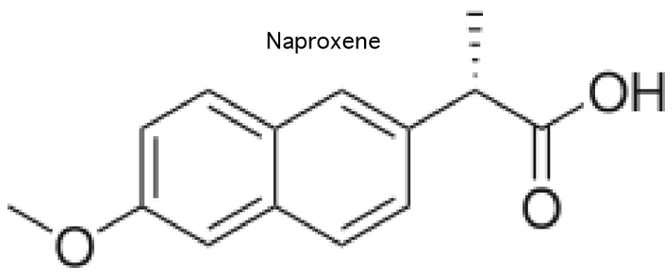
Nimesulide



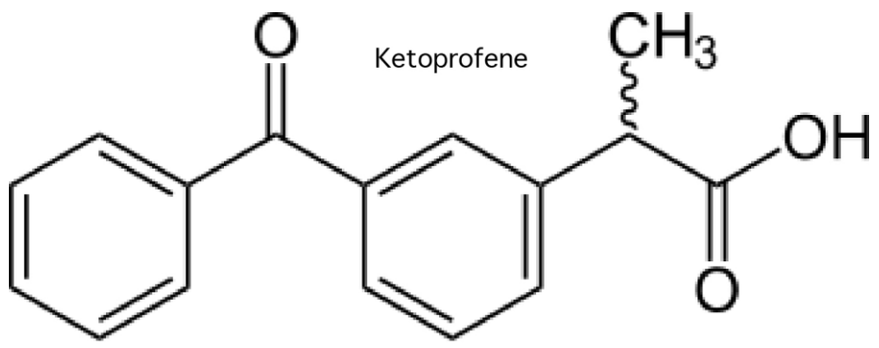
Paracetamol, Acetaminophen



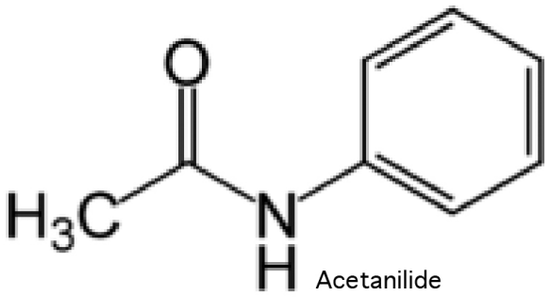
Ibuprofen



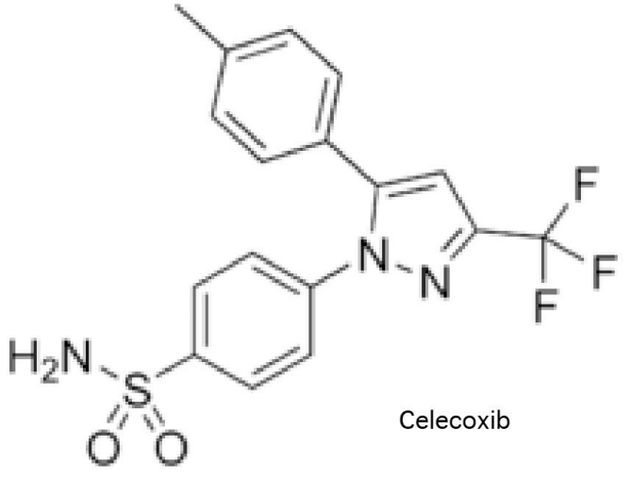
Naproxene



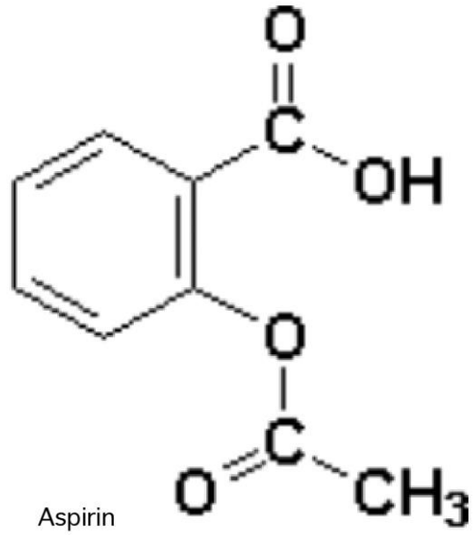
Ketoprofene



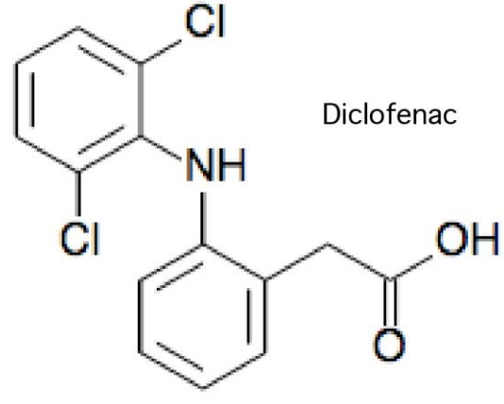
Acetanilide



Celecoxib

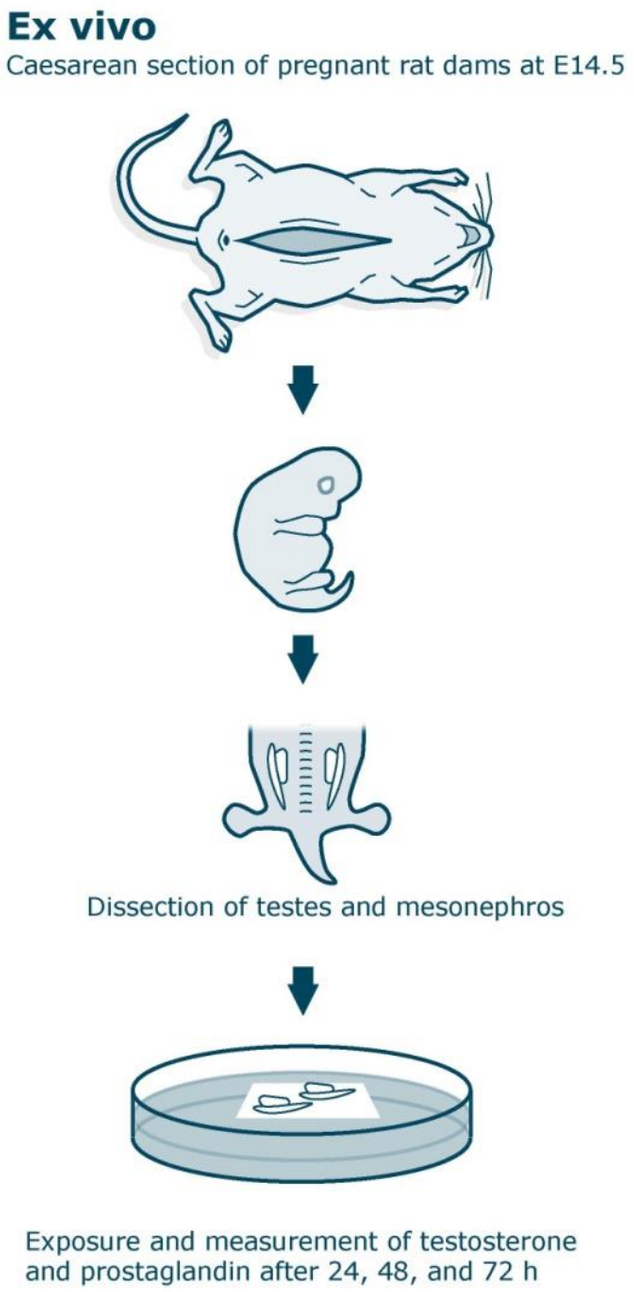


Aspirin



Diclofenac

Organo-Culture of Fetal Rat Testis



Testes are collected from 14.5 day old rat male foetal testes.

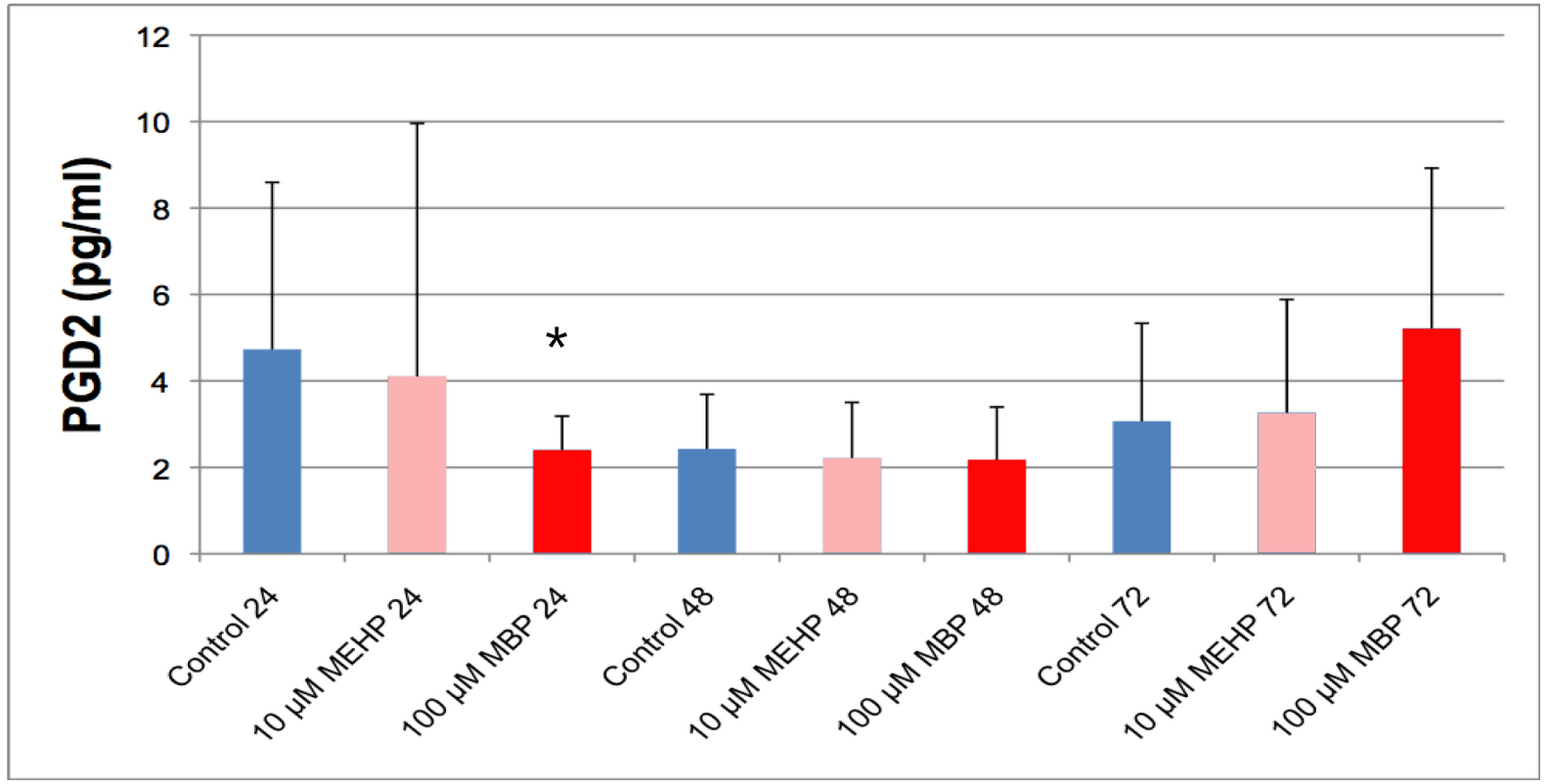
The testes are placed in culture.

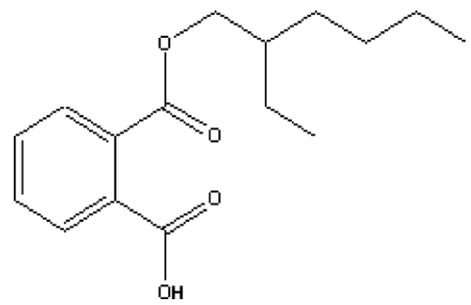
Testis are kept “alive” for up to 3 days, equivalent to the “phthalate window”.

Many of the *in vivo* observations can be reproduced in the assay.

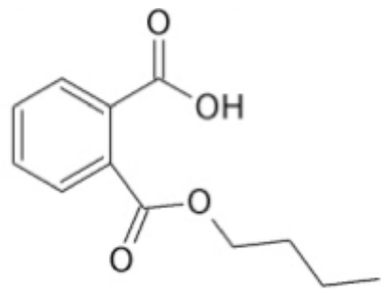
Bernard Jégou et al, INSERM.

MonoPhthalates Inhibit PG Synthesis in Fetal Rat Testis

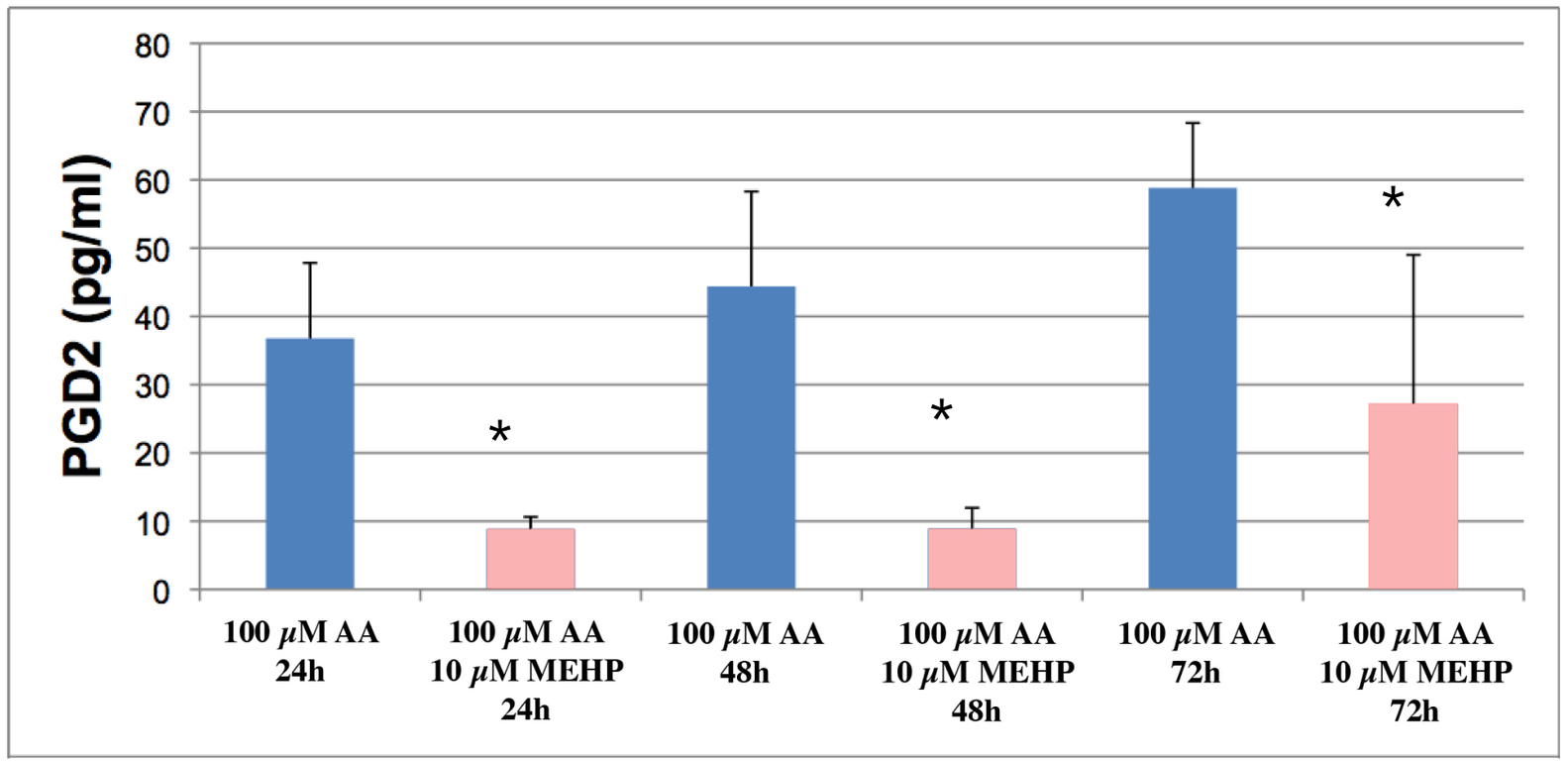




MEHP



MBP

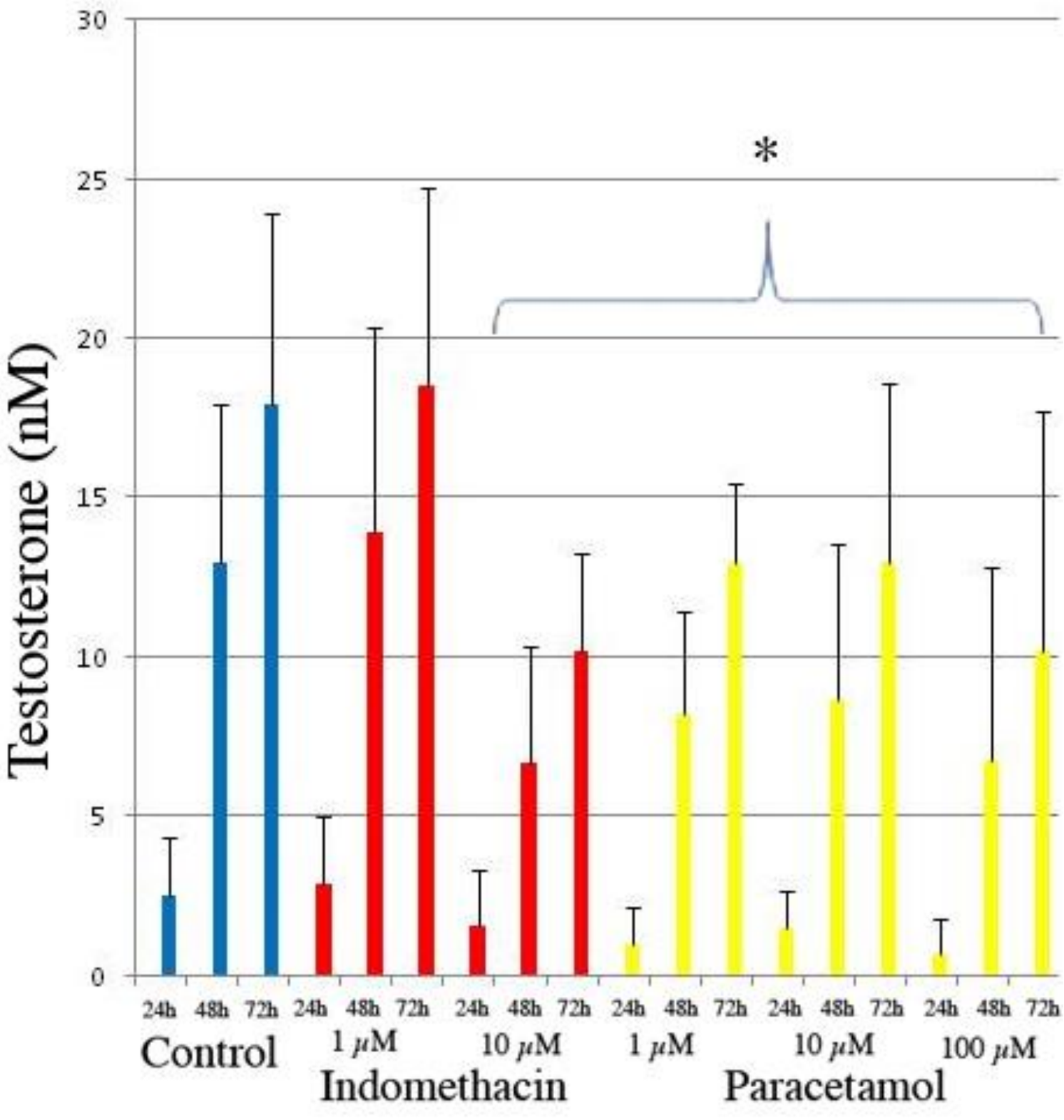


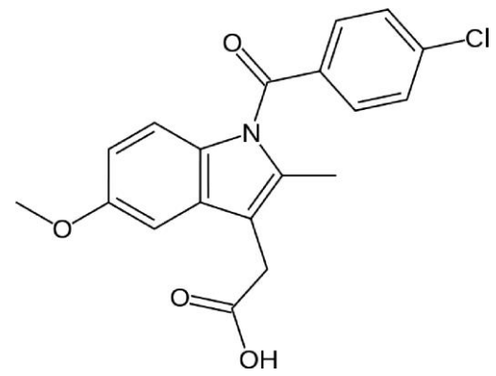
* $p < 0.05$

AA = arachidonic acid

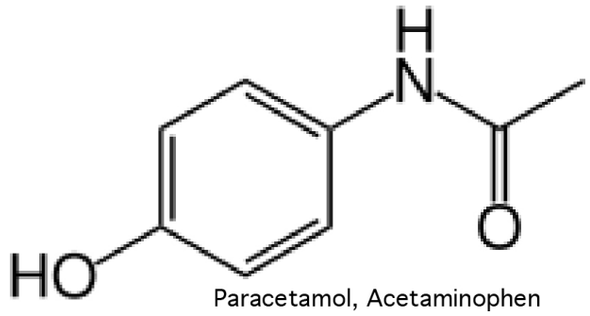
Laurianne Lesne, Christele Desdoits-Lethimonier, David Møbjerg Kristensen (RH), Bernard Jégou, INSERM, Rennes

Mild Analgesics Inhibit Testosterone Production in Fetal Rat Testis





Indomethacin



Paracetamol, Acetaminophen

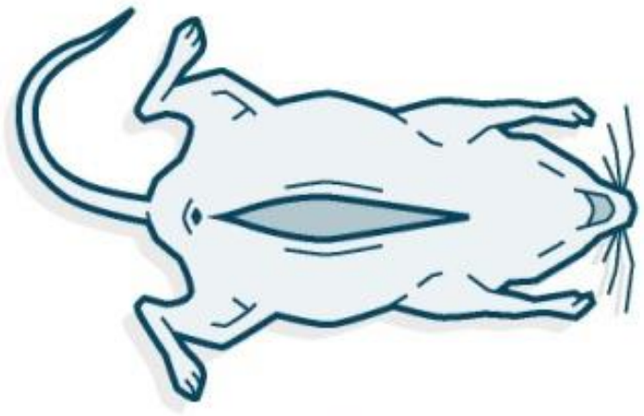
* $p < 0.05$

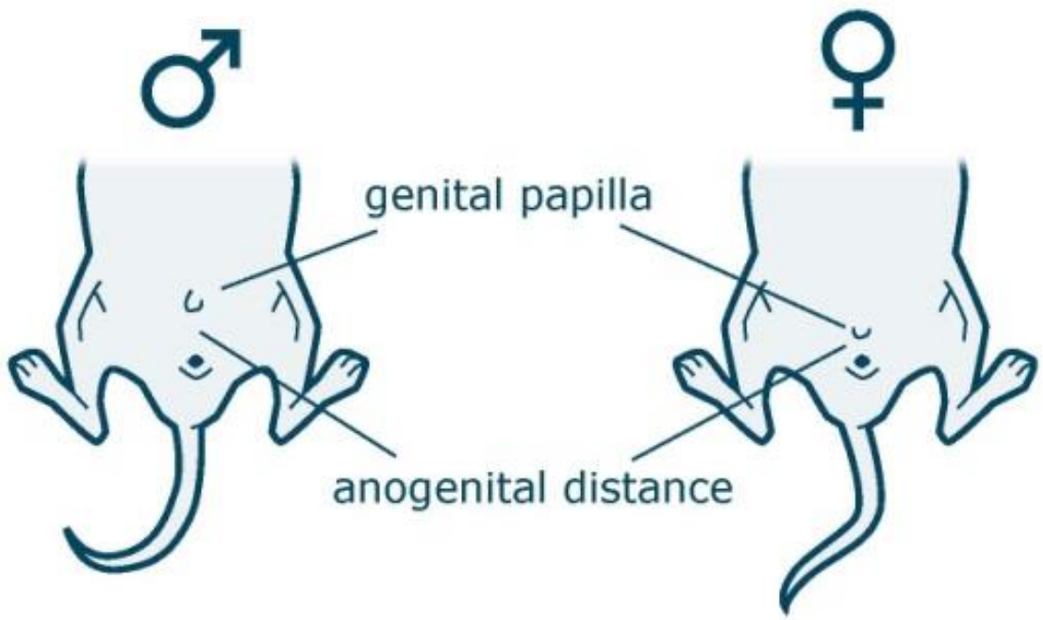
Laurianne Lesne, Christele Desdoits-Lethimonier, David Møbjerg Kristensen (RH), Bernard Jégou, INSERM, Rennes

In Vivo Studies

In utero

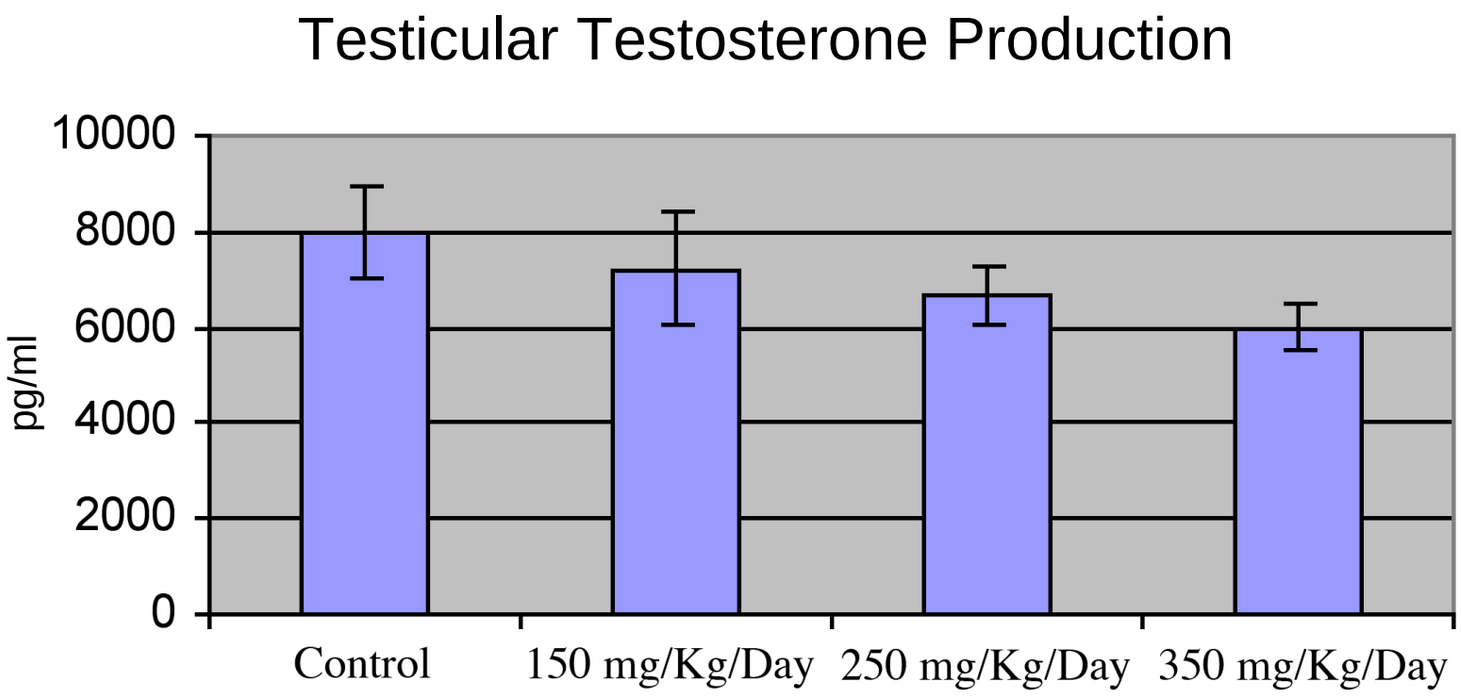
Caesarean section of pregnant rat dams at E21 after gavage with compounds from E13-E21

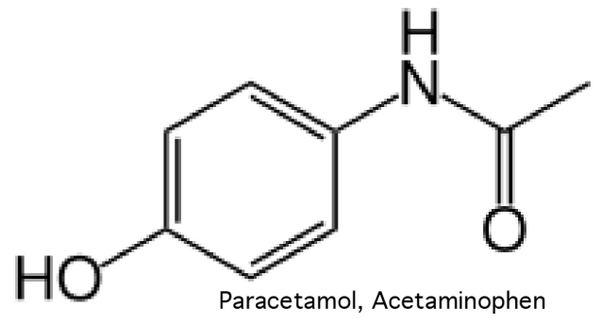




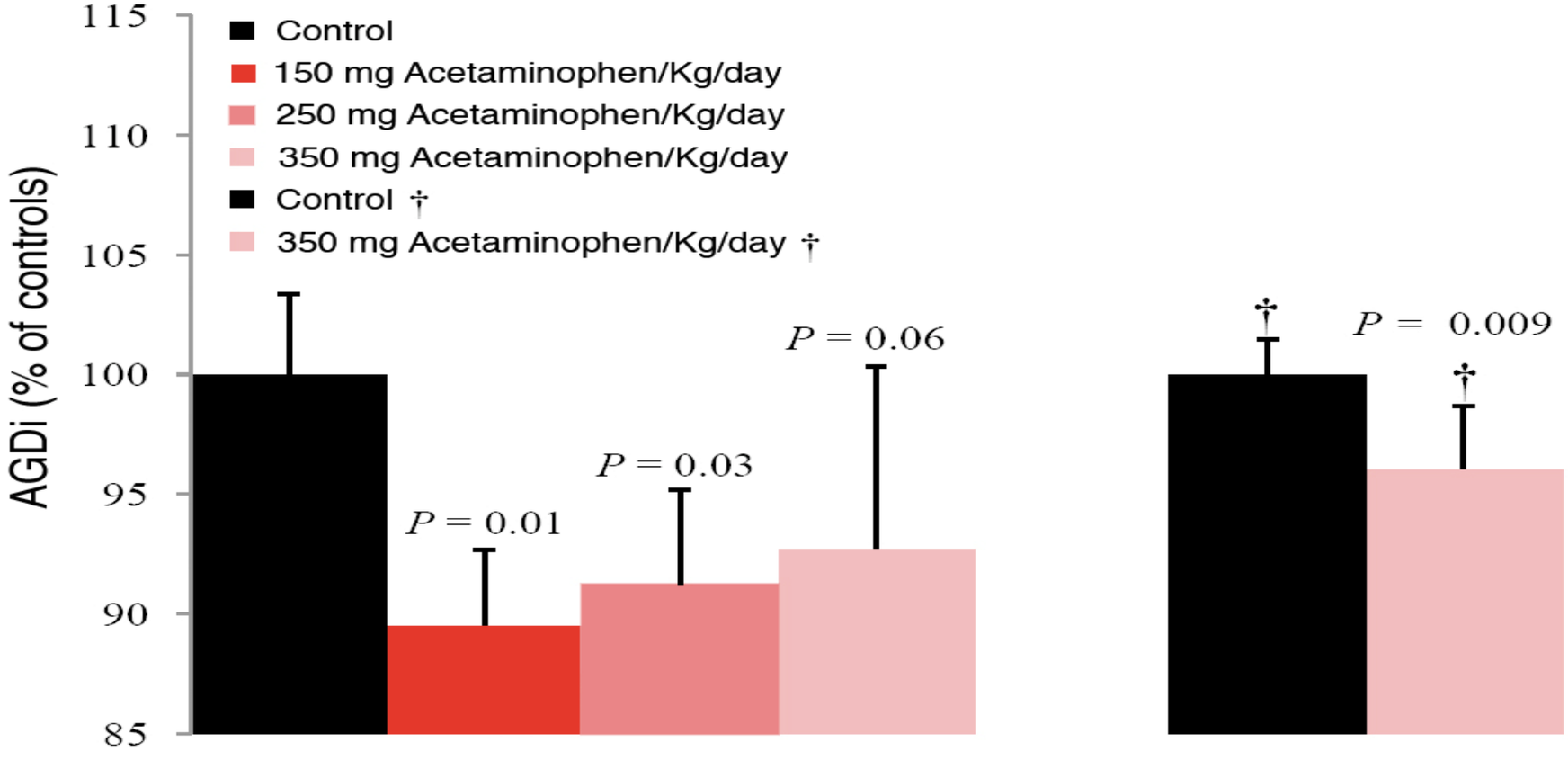
Measurement of anogenital distance and dissection of testes

In Utero Exposure to Paracetamol





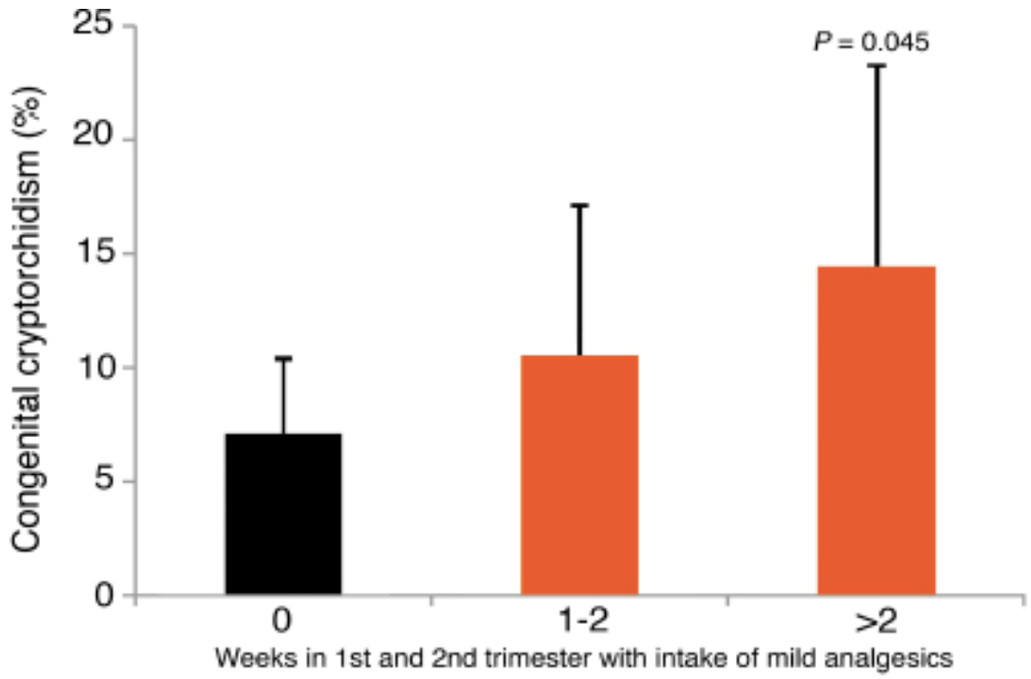
Paracetamol, Acetaminophen

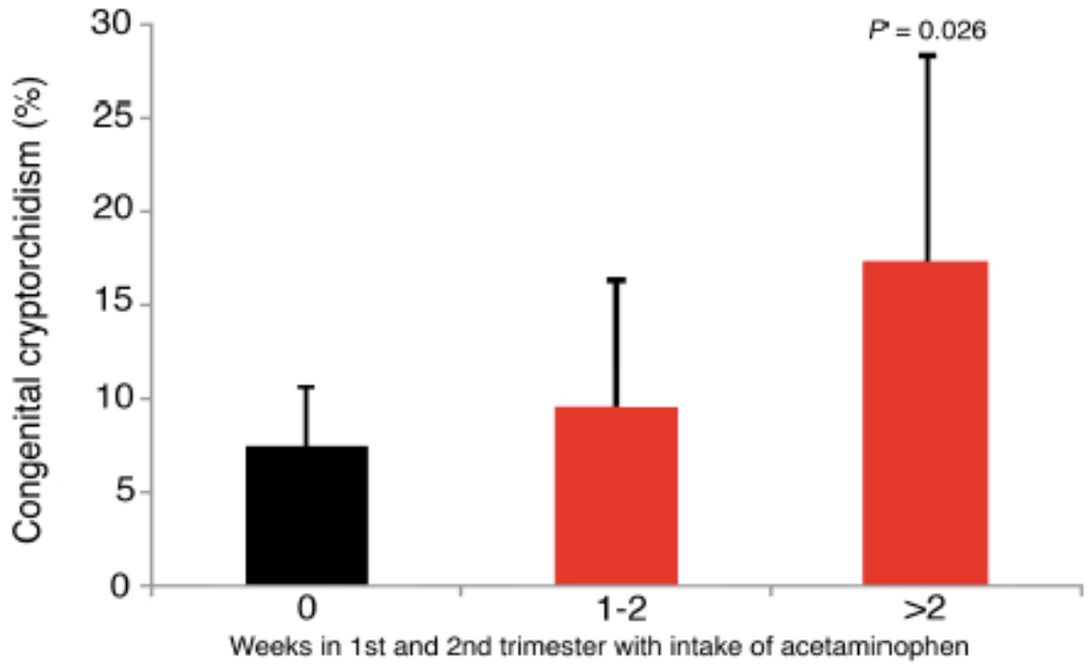


Julie Boberg, Christine Nellemann, Ulla Hass, The Food Institute, DTU

Do Mild Analgesics Affect Human Testis Development?

Epidemiology: Association to Cryptorchidism





Compound	Weeks of usage	N*	Cryptorchidism (%)**	OR crude (95% CI)	OR adjusted (95% CI)***
Mild analgesics	0	238	7.1	1	1
	1-2	85	10.6	1.49 (0.64-3.47)	1.5 (0.63-3.55)
	>2	62	14.5	2.19 (0.92-5.18)	2.47 (1.02-5.96)
Acetaminophen	0	279	7.5	1	1
	1-2	73	9.6	1.28 (0.52-3.13)	1.26 (0.5-3.14)
	>2	46	17.4	2.58 (1.07-6.23)	2.78 (1.13-6.84)
Acetylsalicylic acid	0	454	7.9	1	1
	1-2	11	18.2	2.58 (0.54-12.4)	2.75 (0.56-13.5)
	>2	13	23.1	3.35 (0.92-13.2)	4.07 (1.05-15.8)
Ibuprofen	0	470	8.2	1	1
	1-2	11	27	4.14 (1.06-16.3)	3.85 (0.93-15.9)
	>2	5	0	-	-
Use of >1 compound	0	479	7.9	1	1
	1-2	6	33.3	4.63 (0.87-24.7)	4.63 (0.83-52.8)
	>2	3	66.7	23.16 (2.05-261)	21.69 (1.83-258)

* The numbers differ between the different mild analgesics since not all women provided information about duration of use.
** Testis defined as cryptorchid if it was high scrotal, supra-scrotal, inguinal, and non-palpable.
*** Adjusted for gestational age, reported disease, and use of medicine during pregnancy.

Grete Lottrup, Katharina Main et al., RH

You All have Paracetamol in Your Urine!

Reproduction. 2014 Mar 4;147(4):R105-17. doi: 10.1530/REP-13-0527. Print 2014.

Ubiquitous presence of paracetamol in human urine: sources and implications.

Modick H[1], Weiss T, Dierkes G, Brüning T, Koch HM.

⊕ Author information

Abstract

N-acetyl-4-aminophenol (acetaminophen/paracetamol, NA4AP) is one of the most commonly used over-the-counter analgesic and antipyretic drugs. Recent studies have reported anti-androgenic effects of NA4AP in vitro and possible associations between intrauterine exposure to NA4AP and the development of male reproductive disorders in humans. NA4AP is also a major metabolite of aniline (phenylamine), representing 75-86% of the aniline dose excreted in urine. Aniline is an important large-volume intermediate in several industrial processes. Besides individuals in various occupational settings with aniline exposure, the general population is also known to be ubiquitously exposed to aniline. In this article, we provide an overview of the recent literature concerning the intake of NA4AP during pregnancy and the possible anti-androgenic effects of NA4AP as well as literature concerning its known metabolic precursor aniline. We also present new research data, including the first human biomonitoring data on NA4AP excretion in urine, showing ubiquitous NA4AP body burdens in the general population at a wide range of concentrations. We found a small but significant impact of smoking on urinary NA4AP concentrations. We further present preliminary data on NA4AP excretion after therapeutic acetaminophen use, after aniline exposure in an occupational setting, and during a controlled fasting study (excluding oral exposure to both aniline and acetaminophen). Our findings indicate exposure to aniline (or aniline-releasing substances) as well as nutrition (next to the direct use of acetaminophen as medication) as possible sources of internal body burdens of NA4AP.

PMID: 24451225 DOI: 10.1530/REP-13-0527

You All have Paracetamol in Your Urine!

Toxicol Sci. 2015 Nov;148(1):288-98. doi: 10.1093/toxsci/kfv179. Epub 2015 Aug 10.

Aniline Is Rapidly Converted Into Paracetamol Impairing Male Reproductive Development.

Holm JB[1], Chalmey C[2], Modick H[3], Jensen LS[4], Dierkes G[3], Weiss T[3], Jensen BA[1], Nørregård MM[1], Borkowski K[1], Styrishave B[4], Martin Koch H[3], Mazaud-Guittot S[2], Jegou B[5], Kristiansen K[1], Kristensen DM[6].

⊕ Author information

Abstract

Industrial use of aniline is increasing worldwide with production estimated to surpass 5.6 million metric tons in 2016. Exposure to aniline occurs via air, diet, and water augmenting the risk of exposing a large number of individuals. Early observations suggest that aniline is metabolized to paracetamol/acetaminophen, likely explaining the omnipresence of low concentrations of paracetamol in European populations. This is of concern as recent studies implicate paracetamol as a disrupter of reproduction. Here, we show through steroidogenic profiling that exposure to aniline led to increased levels of the Δ4 steroids, suggesting that the activity of CYP21 was decreased. By contrast, paracetamol decreased levels of androgens likely through inhibition of CYP17A1 activity. We confirm that aniline in vivo is rapidly converted to paracetamol by the liver. Intrauterine exposure to aniline and paracetamol in environmental and pharmaceutical relevant doses resulted in shortening of the anogenital distance in mice, a sensitive marker of fetal androgen levels that in humans is associated with reproductive malformations and later life reproductive disorders. In conclusion, our results provide evidence for a scenario where aniline, through its conversion into antiandrogenic paracetamol, impairs male reproductive development.

KEYWORDS: acetaminophen; aniline; endocrine disruptors; paracetamol; reproduction; testosterone

PMID: 26259604 DOI: 10.1093/toxsci/kfv179

Citation From Holm *et al.*, 2015:

We tested if adult male C57BL/6JBomTac mice in our animal facility ha

Female Reproductive Development is Also Affected by Paracetamol

Toxicol Sci. 2016 Mar;150(1):178-89. doi: 10.1093/toxsci/kfv332. Epub 2016 Jan 5.

Intrauterine Exposure to Paracetamol and Aniline Impairs Female Reproductive Development by Reducing Follicle Reserves and Fertility.

Holm JB[1], Mazaud-Guittot S[2], Danneskiold-Samsøe NB[3], Chalmey C[2], Jensen B[3], Nørregård MM[3], Hansen CH[4], Styrishave B[4], Svingen T[5], Vinggaard AM[5], Koch HM[6], Bowles J[7], Koopman P[7], Jégou B[8], Kristiansen K[3], Kristensen DM[9].

⊕ Author information

Abstract

Studies report that fetal exposure to paracetamol/acetaminophen by maternal consumption can interfere with male reproductive development. Moreover, recent biomonitoring data report widespread presence of paracetamol in German and Danish populations, suggesting exposure via secondary (nonpharmaceutical) sources, such as metabolic conversion from the ubiquitous industrial compound aniline. In this study, we investigated the extent to which paracetamol and aniline can interfere with female reproductive development. Intrauterine exposure to paracetamol by gavage of pregnant dams resulted in shortening of the anogenital distance in adult offspring, suggesting that fetal hormone signaling had been disturbed. Female offspring of paracetamol-exposed mothers had ovaries with diminished follicle reserve and reduced fertility. Fetal gonads of exposed animals had also reduced gonocyte numbers, suggesting that the reduced follicle count in adults could be due to early disruption of germ cell development. However, ex vivo cultures of ovaries from 12.5 days post coitum fetuses showed no decrease in proliferation or expression following exposure to paracetamol. This suggests that the effect of paracetamol occurs prior to this developmental stage. Accordingly, using embryonic stem cells as a proxy for primordial germ cells we show that paracetamol is an inhibitor of cellular proliferation, but without cytotoxic effects. Collectively, our data show that intrauterine exposure to paracetamol at levels commonly observed in pregnant women, as well as its precursor aniline, may block primordial germ cell proliferation, ultimately leading to reduced follicle reserves and compromised reproductive capacity later in life.

KEYWORDS: aniline; development; follicle reserves; intrauterine exposure; paracetamol/acetaminophen; reproduction

PMID: 26732887 DOI: 10.1093/toxsci/kfv332

Development of the Brain is Dependent on Prostaglandins

Genes Brain Behav. 2018 Jul 20:e12506. doi: 10.1111/gbb.12506. [Epub ahead of print]

Autism-related behaviors in the cyclooxygenase-2-deficient mouse model.

Wong CT[1,2], Bestard-Lorigados I[1,2], Crawford DA[1,2,3].

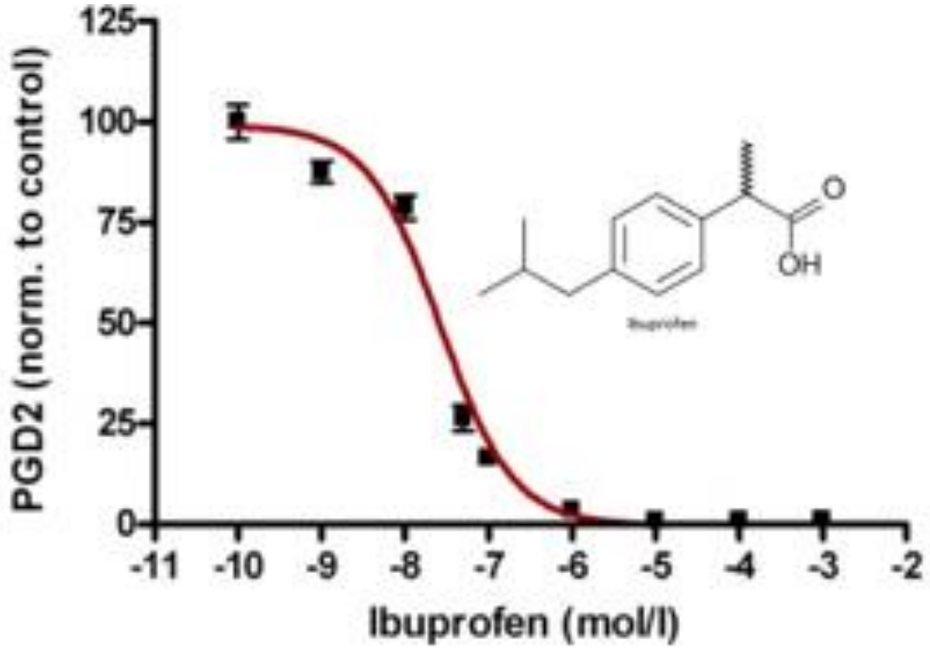
⊕ Author information

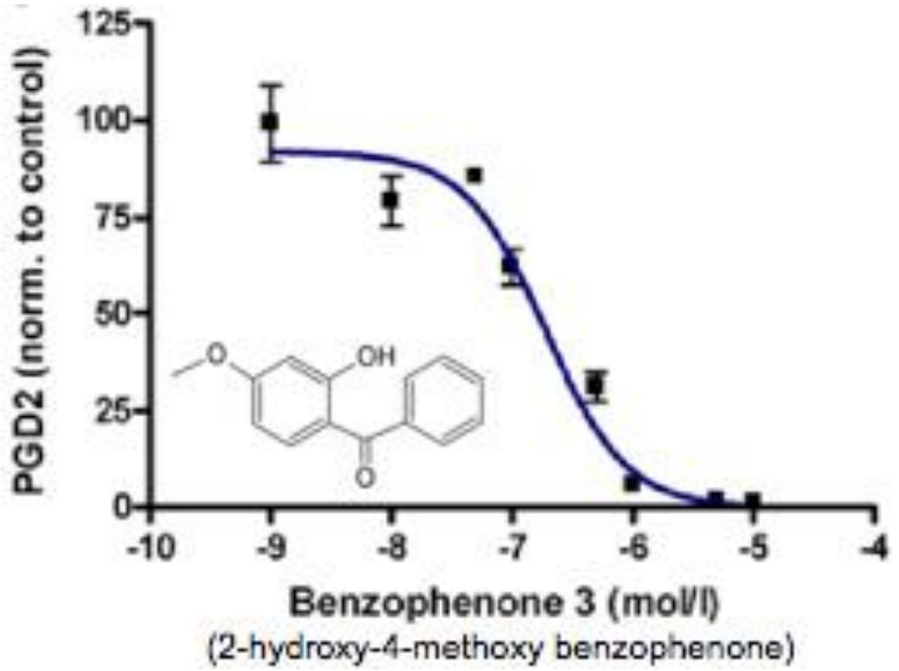
Abstract

Prostaglandin E2 (PGE2) is an endogenous lipid molecule involved in normal brain development. Cyclooxygenase-2 (COX2) is the main regulator of PGE2 synthesis. Emerging clinical and molecular research provides compelling evidence that abnormal COX2/PGE2 signaling is associated with autism spectrum disorder (ASD). We previously found that COX2 knockout mice had dysregulated expression of many ASD genes belonging to important biological pathways for neurodevelopment. The present study is the first to show the connection between irregular COX2/PGE2 signaling and autism-related behaviors in male and female COX2-deficient knockin, (COX)-2^{-} , mice at young (4-6 weeks) or adult (8-11 weeks) ages. Autism-related behaviors were prominent in male (COX)-2^{-} mice for most behavioral tests. In the open field test, (COX)-2^{-} mice traveled more than controls and adult male (COX)-2^{-} mice spent less time in the center indicating elevated hyperactive and anxiety-linked behaviors. (COX)-2^{-} mice also buried more marbles, with males burying more than females, suggesting increased anxiety and repetitive behaviors. Young male (COX)-2^{-} mice fell more frequently in the inverted screen test revealing motor deficits. The three-chamber sociability test found that adult female (COX)-2^{-} mice spent less time in the novel mouse chamber indicative of social abnormalities. In addition, male (COX)-2^{-} mice showed altered expression of several autism-linked genes: Wnt2, Glo1, Grm5 and Mmp9. Overall, our findings offer new insight into the involvement of disrupted COX2/PGE2 signaling in ASD pathology with age-related differences and greater impact on males. We propose that (COX)-2^{-} mice might serve as a novel model system to study specific types of autism.

KEYWORDS: COX2; age differences; autism; behavior; gene expression; inverted screen test; knockin model; lipid signaling; marble burying test; neurodevelopmental disorders; open field test; prostaglandin; sex differences; three-chamber sociability test

PMID: 30027581 DOI: 10.1111/gbb.12506


PGD2 (norm. to control)
125
100
75
50
25
0
-11
-10
-9
-8
-7
-6
-5
-4
-3
-2
Ibuprofen (mol/l)
O
OH


PGD2 (norm. to control)
125
100
75
50
25
0
-10
-9
-8
-7
-6
-5
-4
Benzophenone 3 (mol/l)
(2-hydroxy-4-methoxy benzophenone)
O
OH
O

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Systemic absorption of the sunscreens benzophenone-3, octyl-methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans.

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Author information

Abstract

Recent in vitro and animal studies have reported estrogen-like activity of chemicals used in sunscreen preparations. We investigated whether the three sunscreens benzophenone-3 (BP-3), octyl-methoxycinnamate (OMC), and 3-(4-methylbenzylidene) camphor (4-MBC) were absorbed and influenced endogenous reproductive hormone levels in humans after topical application. In this 2-wk single-blinded study 32 healthy volunteers, 15 young males and 17 postmenopausal females, were assigned to daily whole-body topical application of 2 mg per cm(2) of basic cream formulation without (week 1) and with (week 2) the three sunscreens at 10% (wt/wt) of each. Maximum plasma concentrations were 200 ng per mL BP-3, 20 ng per mL 4-MBC, and 10 ng per mL OMC for females and 300 ng per mL BP-3, 20 ng per mL 4-MBC, and 20 ng per mL OMC for men. All three sunscreens were detectable in urine. The reproductive hormones FSH, LH were unchanged but minor differences in testosterone levels were observed between the 2 wk. A minor difference in serum estradiol and inhibin B levels were observed in men only. These differences in hormone levels were not related to sunscreen exposure.

Comment in

If it's not the hamburgers, it's the sunscreens. [J Invest Dermatol. 2004]

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