

**FTALATER, LÆGEMIDLER**



**DANSKE SUNDHEDSREGISTRE**

# Ftalateksponering fra lægemidler

## *Eksempler på udnyttelse af danske helbredsregistre*

Per Damkier  
Professor, MD PhD

# Phthalates in drugs

- Delayed release preparations
- Controlled release preparations



## Guidance for Industry Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

December 2012  
CMC

Recommended oral Reference Dose (RfD)

RfD for DBP is 0.1 mg/kg/day

RfD for DEHP is 0.02 mg/kg/day

*DEP, CAP, HPMCP & PVAP not mentioned.*



20 November 2014  
EMA/CHMP/SWP/362974/2012 corr 2<sup>1</sup>  
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the use of phthalates as excipients in human  
medicinal products

Permitted Daily Exposure (PDE)

PDE for DBP of 0.01 mg/kg body weight/day

PDE for DEP of 4 mg/kg/day

*CAP, HPMCP and PVAP no present indication of risk for human  
safety.*

# Den Principielle Idé

- Phthalates are suspected human endocrine disruptors
  - Anti-androgenic effects
  - Sex-hormone homeostasis
  - Adverse effects on reproduction in animal studies
    - Fertility, Hypospadia, Cryptorchidism
  - Fetal growth
  - Carcinogenic effects

# Den Principielle Idé

- Exposure:
  - Kvantitering af eksponering
  - Eksponering fra medicin >> eksponering fra miljø
  - Kan parres med identisk lægemiddel UDEN ftalater

# Danish Registries



**SUNDHEDSDATA-  
STYRELSEN**

- Administrative secondary registries
- Unique person identifier (CPR number)

The Danish online Drug use statistics (MEDSTAT)

The Civil Registration System

The Danish National Prescription Register

The Danish National Patient Register

The Danish Medical Birth Register

The Danish Cancer Registry



**STATISTICS  
DENMARK**

- Income, education, socio economic status etc

O.U.H.  
Odense Universitetshospital  
Svendborg Sygehus

# Other registries

**Danish Breast Cancer  
Group**

**Drug-excipient  
database**

**IVF Registry**

# Population Exposure to Phthalate-containing Drugs

Anne Broe<sup>1,2</sup>, Zandra Nymand Ennis<sup>1,2</sup>, Anton Pottegård<sup>1</sup>, Jesper Hallas<sup>1,2</sup>, Thomas Ahern<sup>3</sup> and Per Damkier<sup>1,4</sup>

<sup>1</sup>Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark, <sup>2</sup>Department of Clinical Chemistry and Pharmacology, Odense University Hospital, Odense, Denmark, <sup>3</sup>Departments of Surgery and Biochemistry, University of Vermont College of Medicine, Burlington, VT, USA and <sup>4</sup>Department of Clinical Research, University of Southern Denmark, Odense, Denmark

(Received 10 January 2017; Accepted 20 March 2017)



British Journal of Clinical  
Pharmacology

Br J Clin Pharmacol (2018) 84 1798–1805 1798

## ORIGINAL ARTICLE

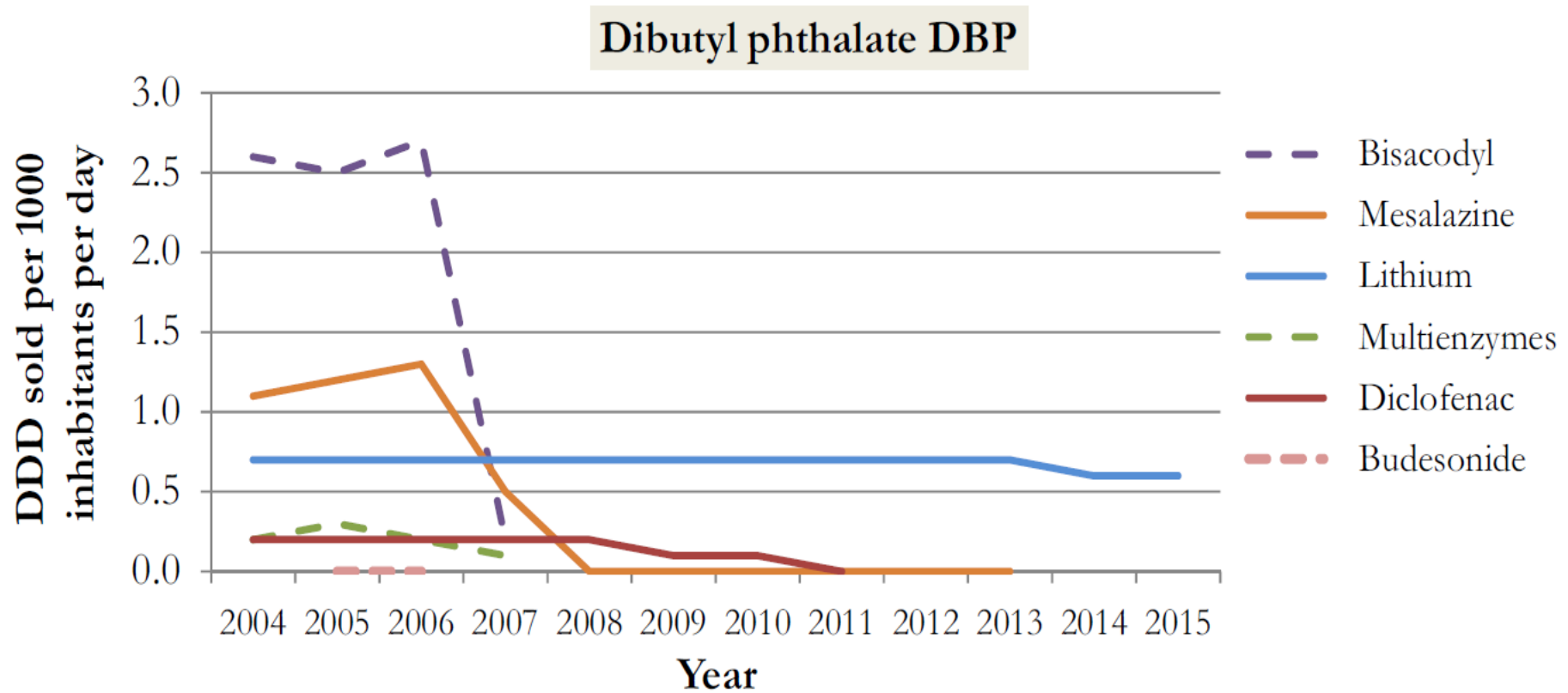
### Cumulative exposure to phthalates from phthalate-containing drug products: a Danish population-wide study

**Correspondence** Zandra Nymand Ennis, Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense. Tel: +45 6550 9183; E-mail: zennis@health.sdu.dk

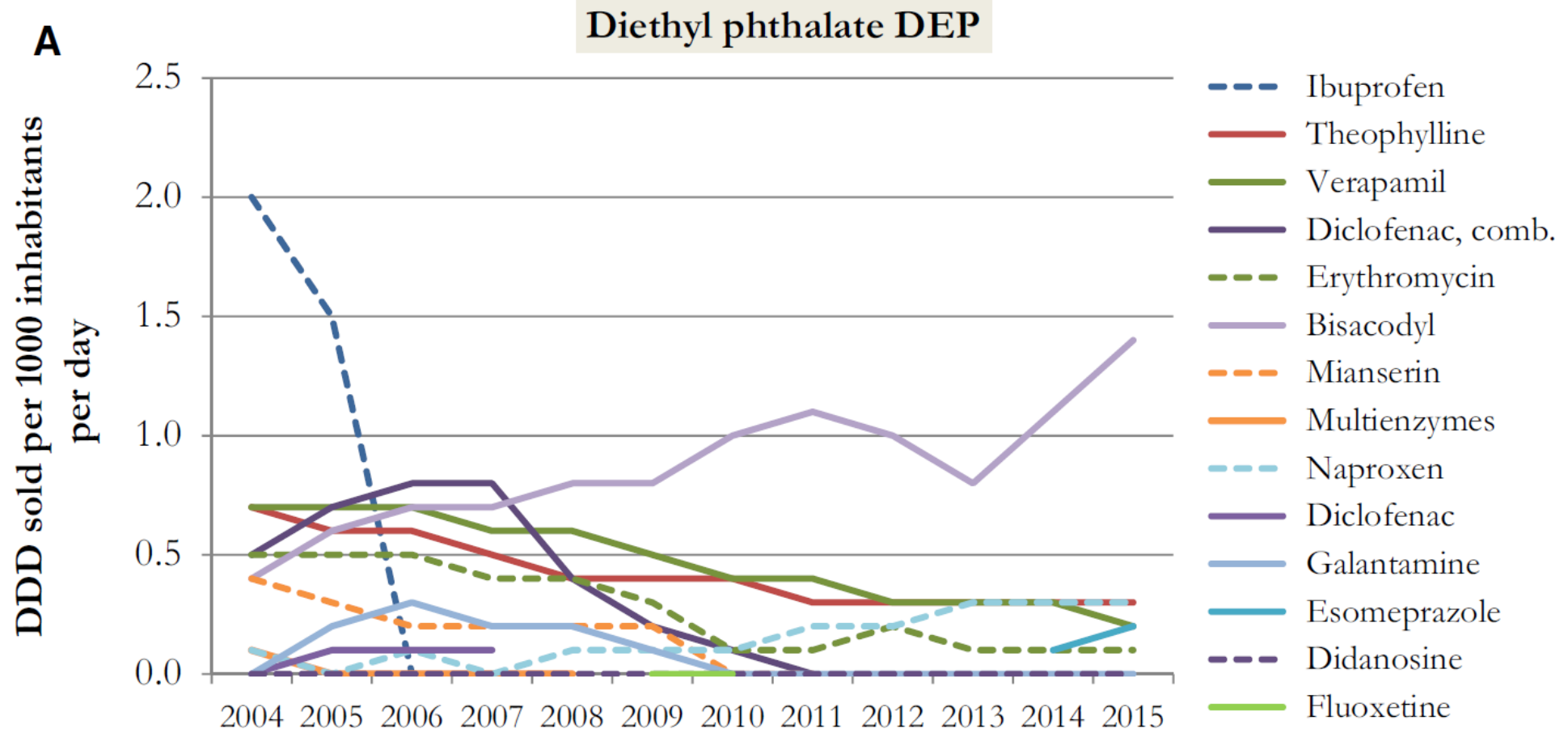
**Received** 18 September 2017; **Revised** 4 April 2018; **Accepted** 15 April 2018

Zandra Nymand Ennis<sup>1</sup> , Anne Broe<sup>2</sup>, Anton Pottegård<sup>2</sup> , Thomas P. Ahern<sup>3</sup>, Jesper Hallas<sup>1,2</sup> and Per Damkier<sup>1,4</sup> 

# DBP containing drugs in DK




# DEP containing drugs in DK





Volume 33, Issue 3  
March 2018

## Association between use of phthalate-containing medication and semen quality among men in couples referred for assisted reproduction FREE

A Broe , A Pottegård, J Hallas, T P Ahern, J Fedder, P Damkier

*Human Reproduction*, Volume 33, Issue 3, March 2018, Pages 503–511,  
<https://doi.org/10.1093/humrep/dey009>

**Published:** 07 February 2018 **Article history** ▼





European Journal of Obstetrics & Gynecology  
and Reproductive Biology

Volume 240, September 2019, Pages 293–299



Full length article

## Phthalate exposure from drugs during pregnancy and possible risk of preterm birth and small for gestational age

Anne Broe <sup>a, b</sup>  , Anton Pottegård <sup>b</sup>, Jesper Hallas <sup>a, b</sup>, Thomas Patrick Ahern <sup>c</sup>, Ronald Francis Lamont <sup>d, e</sup>, Per Damkier <sup>a, f</sup>

**ORIGINAL REPORT**

WILEY

## Exposure to phthalate-containing prescription drugs and the risk of colorectal adenocarcinoma: A Danish nationwide case-control study

Zandra Nymand Ennis<sup>1</sup>  | Anton Pottegård<sup>2</sup>  | Thomas Patrick Ahern<sup>3</sup>  | Jesper Hallas<sup>1,2</sup>  | Per Damkier<sup>1,4</sup> 


**Journal of Clinical Oncology**  
An American Society of Clinical Oncology Journal

Enter words / phrases / DOI / ISBN / authors / keywords / etc.

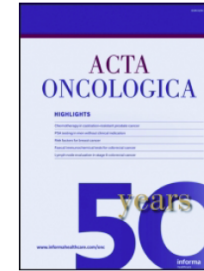
Newest Articles | Issues | Browse By Topic | Special Content | Authors | Subscribers

ORIGINAL REPORTS | Breast Cancer

### Phthalate Exposure and Breast Cancer Incidence: A Danish Nationwide Cohort Study

[Thomas P. Ahern](#), PhD, MPH<sup>1</sup> ; [Anne Broe](#), MD, PhD<sup>2,3</sup>; [Timothy L. Lash](#), DSc<sup>4,5</sup>; [Deirdre P. Cronin-Fenton](#), PhD<sup>5</sup>; [Sinna Pilgaard Ulrichsen](#), MSc<sup>5</sup>; [Peer M. Christiansen](#), MD, DMSci<sup>5</sup>; [Bernard F. Cole](#), PhD<sup>1</sup>; [Rulla M. Tamimi](#), ScD<sup>6,7</sup>; [Henrik Toft Sørensen](#), MD<sup>5</sup>; and [Per Damkier](#), MD, PhD<sup>2,3</sup>

Odense Universitetshospital  
Svendborg Sygehus



Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: <https://www.tandfonline.com/loi/ionc20>



## Use of phthalate-containing prescription drugs and the risk of gastric cancer: a Danish nationwide case-control study

Zandra Nymand Ennis, Sidsel Arnspang Pedersen, Morten Rix Hansen, Anton Pottegård, Thomas Patrick Ahern, Jesper Hallas & Per Damkier

# Journal of Clinical Oncology<sup>®</sup>

An American Society of Clinical Oncology Journal

Enter words / phrases / DOI / ISBN / authors / keywords / etc.

Newest Articles

Issues

Browse By Topic


Special Content

Authors

Subscribers

ORIGINAL REPORTS | Breast Cancer

## Phthalate Exposure and Breast Cancer Incidence: A Danish Nationwide Cohort Study

[Thomas P. Ahern](#), PhD, MPH<sup>1</sup> ; [Anne Broe](#), MD, PhD<sup>2,3</sup>; [Timothy L. Lash](#), DSc<sup>4,5</sup>; [Deirdre P. Cronin-Fenton](#), PhD<sup>5</sup>; [Sinna Pilgaard Ulrichsen](#), MSc<sup>5</sup>; [Peer M. Christiansen](#), MD, DMSci<sup>5</sup>; [Bernard F. Cole](#), PhD<sup>1</sup>; [Rulla M. Tamimi](#), ScD<sup>6,7</sup>; [Henrik Toft Sørensen](#), MD<sup>5</sup>; and [Per Damkier](#), MD, PhD<sup>2,3</sup>

# Exposure estimation & modeling

Cumulative milligrams of **CAP, DEP, DBP, HPMCP, & PVAP** exposure based on prescription fills—pre-specified categories

Cox regression of breast cancer incidence on **time-varying phthalate exposure** and potential confounders

Exposure updated annually; 1 year lag

# Results

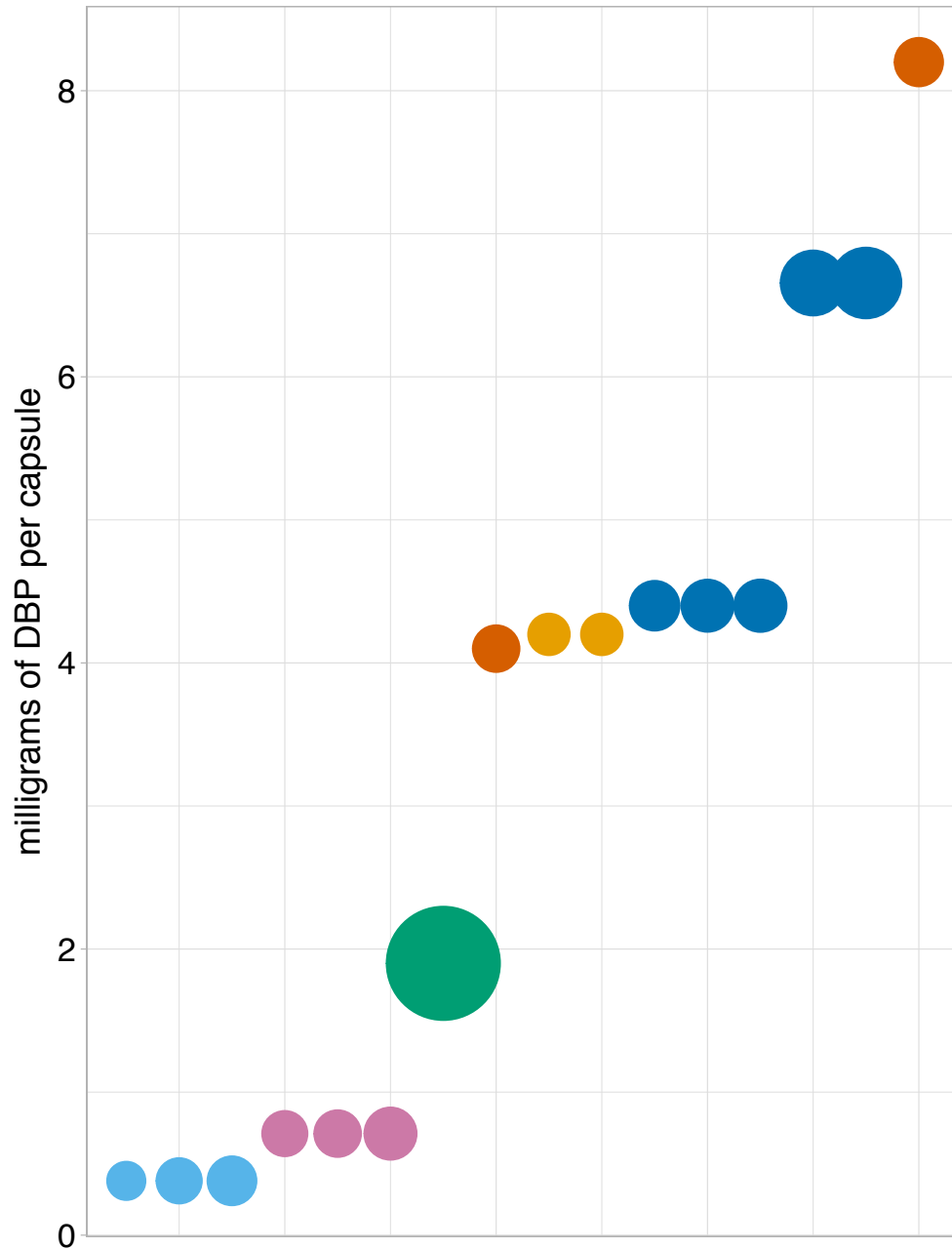
1,122,042 women in the cohort

161,737 (14%) exposed to  $\geq 1$  phthalate

10 million woman-years of follow-up

27,111 invasive breast cancer cases (84% ER-positive)

Medication name	ATC code	Number of unique drug products prescribed to the cohort					
		CAP	DBP	DEP	HPMCP	PVAP	Phthalate-free
bisacodyl	A06AB02		3	5	5		9
budesonide	A07EA06		2				27
clarithromycin	J01FA09				9		48
diclofenac	M01AB05	2	3	2			144
diclofenac, combination	M01AB55	2		2			16
dipyridamole	B01AC07				3		17
duloxetine	N06AX21				9		39
erythromycin	J01FA01			15	15		26
esomeprazole	A02BC05			5			172
fluoxetine	N06AB03			2			48
galantamine	N06DA04			3			50
ibuprofen	M01AE01			13			120
lithium	N05AN01		1				1
mesalamine	A07EC02		5				63
mianserin	N06AX03			14			24
multienzyme	A09AA02	2	2	2	13		47
mycophenolic acid	L04AA06				1		14
naproxen	M01AE02	8		8			24
platelet inhibitors, combination	B01AC30				2		9
pentoxyverine	R05DB05	1					2
propantheline	A03AB05	2					2
rabeprazole	A02BC04				7		8
sulfasalazine	A07EC01	3					15
theophylline	R03DA04	6		2			6
valproic acid	N03AG01	3				9	40
verapamil	C08DA01			13			56
Total number of products		29	16	86	64	9	1,057
Milligrams of phthalate per capsule (min—max) [median]		(0.35—60) [24]	(0.38—8.2) [1.9]	(0.003—10) [0.45]	(4.5--150) [4.7]	(18—69) [47]	N/A



Medication	Function	Indication(s)
bisacodyl	laxative	constipation
budesonide	steroid	IBD
diclofenac	NSAID	arthritis/migraines
lithium	antipsychotic	bipolar disorder
mesalazine	aminosalicylate	IBD
multienzymes	digestive aid	indigestion

# No associations with DEP, CAP, HPMCP, PVAP

Diethyl phthalate, mg					
Unexposed	1.0	Ref	1.0	Ref	
1-9	1.1	0.93 to 1.2	1.2	0.88 to 1.5	
10-99	0.98	0.92 to 1.1	1.2	1.0 to 1.4	
≥ 100	0.93	0.84 to 1.0	1.0	0.80 to 1.3	
Cellulose acetate phthalate, mg					
Unexposed	1.0	Ref	1.0	Ref	
1-249	0.86	0.70 to 1.1	1.3	0.86 to 2.0	
250-999	0.88	0.68 to 1.1	1.3	0.80 to 2.2	
1,000-9,999	0.96	0.79 to 1.2	1.1	0.67 to 1.7	
≥ 10,000	0.92	0.69 to 1.2	0.84	0.40 to 1.8	
Hypromellose phthalate, mg					
Unexposed	1.0	Ref	1.0	Ref	
1-249	1.0	0.82 to 1.2	0.59	0.29 to 1.2	
250-999	0.96	0.87 to 1.1	1.2	0.95 to 1.5	
1,000-9,999	0.87	0.78 to 0.98	1.0	0.78 to 1.3	
≥ 10,000	0.83	0.65 to 1.0	0.46	0.21 to 1.0	
Polyvinyl acetate phthalate					
Unexposed	1.0	Ref	1.0	Ref	
Any exposure	0.91†	0.55 to 1.5	0.36†	0.05 to 2.6	

# No associations with DEP, CAP, HPMCP, PVAP

Diethyl phthalate, mg	1.0	Ref		
Unexposed	1.1	0.93 to 1.2	1.0	Ref
1-9	0.98	0.92 to 1.1	1.2	0.88 to 1.5
10-99	0.93	0.84 to 1.0	1.2	1.0 to 1.4
≥ 100			1.0	0.80 to 1.3
Cellulose acetate phthalate, mg	1.0	Ref		
Unexposed	0.86	0.70 to 1.1	1.0	Ref
1-249	0.88	0.68 to 1.1	1.3	0.86 to 2.0
250-999	0.96	0.79 to 1.2	1.3	0.80 to 2.2
1,000-9,999	0.92	0.69 to 1.2	1.1	0.67 to 1.7
≥ 10,000			0.84	0.40 to 1.8
Hypromellose phthalate, mg	1.0	Ref		
Unexposed	1.0	0.82 to 1.2	1.0	Ref
1-249	0.96	0.87 to 1.1	0.59	0.29 to 1.2
250-999	0.87	0.78 to 0.98	1.2	0.95 to 1.5
1,000-9,999	0.83	0.65 to 1.0	1.0	0.78 to 1.3
≥ 10,000			0.46	0.21 to 1.0
Polyvinyl acetate phthalate				
Unexposed	1.0	Ref	1.0	Ref
Any exposure	0.91†	0.55 to 1.5	0.36†	0.05 to 2.6

# Breast cancer and cumulative DBP exposure

**TABLE 4.** Associations Between Cumulative Phthalate Exposure and Incidence of ER-Positive and ER-Negative Invasive Breast Cancer, Denmark 2005 to 2015

Exposure	ER-Positive Breast Cancer		ER-Negative Breast Cancer	
	Adjusted HR*	95% CI	Adjusted HR*	95% CI
Dibutyl phthalate, mg				
Unexposed	1.0	Ref	1.0	Ref
1-249	0.92	0.73 to 1.2	1.1	0.66 to 1.8
250-999	0.65	0.35 to 1.2	1.5	0.55 to 3.9
1,000-9,999	0.71	0.43 to 1.2	0.26	0.04 to 1.8
≥ 10,000	1.9	1.1 to 3.5	0.99	0.14 to 7.0

Adjusted for age, menopausal status, other phthalate exposures, use of potentially confounding co-medications (cardiac glycosides, hormone therapy, aspirin, and statins), therapeutic drug classes, and Charlson comorbidity index.

# Breast cancer and cumulative DBP exposure

**TABLE 4.** Associations Between Cumulative Phthalate Exposure and Incidence of ER-Positive and ER-Negative Invasive Breast Cancer, Denmark 2005 to 2015

Exposure	ER-Positive Breast Cancer		ER-Negative Breast Cancer	
	Adjusted HR*	95% CI	Adjusted HR*	95% CI
Dibutyl phthalate, mg				
Unexposed	1.0	Ref	1.0	Ref
1-249	0.92	0.73 to 1.2	1.1	0.66 to 1.8
250-999	0.65	0.35 to 1.2	1.5	0.55 to 3.9
1,000-9,999	0.71	0.43 to 1.2	0.26	0.04 to 1.8
<b>≥ 10,000</b>	<b>1.9</b>	<b>1.1 to 3.5</b>	<b>0.99</b>	<b>0.14 to 7.0</b>

Adjusted for age, menopausal status, other phthalate exposures, use of potentially confounding co-medications (cardiac glycosides, hormone therapy, aspirin, and statins), therapeutic drug classes, and Charlson comorbidity index.

# Konklusion

- Unik mulighed for kvantitering af eksponering
- Praktisk begrænsning:
  - <2005 : Ikke pålidelig nok
  - N (eksponeret): afhængig af population
  - >2014: Ingen lægemidler med orthoftalater bortset fra Lithium



“Yes ... I believe there's a question there in the back.”