

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

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phthal•ate

\ 'tha-,lát \

noun

Definition: chemical plasticizers that have been widely used since the 1950s to soften plastics that would otherwise be brittle and crack when bent. Because phthalates are not chemically bound to the plastics they're added to, they're continuously released into the air, food or liquid. The chemicals from these products can be absorbed through the skin and into the bloodstream.



Effekter

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- Associeret med cancer-udvikling

Danske regler

- Siden 1999: Dansk forbud mod salg og produktion af legetøj og småbørnsartikler 0-3 år, hvis produkterne indeholder mere end 0,05 vægtprocent ftalater.
- Krav skærpet i 2006 med EU-forordning

Baggrunds-eksponering

Ftalater og medicin

Ftalater og medicin

- Anvendelse: coating, blødgørere, binder og print
- Syrestabil funktion udnyttes depot-formuleringer
- Typer af ftalater i p.o. formuleringer
 - a) Lavmolekylære: Diethyl phthalate (DEP), Dibutyl phthalate (DBP)
 - b) Enteriske polymerer: Celluloseacetat phthalate (CAP), Hypromellose phthalate (HPMCP) og Polyvinylacetat phthalate (PVAP)

Op til 50 gange øget konc. af ftalat-metabolitter i urinen hos brugere af ftalat-holdig medicin vs. ikke-brugere

Medications as a Potential Source of Exposure to Phthalates in the U.S. Population

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FDA

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

EMA



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/SWP/362974/2012 corr 2¹
Committee for Medicinal Products for Human Use (CHMP)

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

Draft agreed by Safety Working Party	February 2013
Adopted by CHMP for release for consultation	25 April 2013
Start of public consultation	08 May 2013
End of consultation (deadline for comments)	31 October 2013
Agreed by Safety Working Party	October 2014
Adopted by CHMP	20 November 2014
Date for coming into effect	01 June 2015

Keywords	Excipients, Phthalates, Endocrine disruptors, DBP, DEP, CAP, HPMCP, PVAP
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Rekommanderede grænser

- Diethyl phthalate: 4 mg/kg kropsvægt/dag
- Dibutyl phthalate: 0.01 mg/kg kropsvægt/dag

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Omregnet for en person på 70 kg

- Diethyl phthalate: 102.200 mg/år
- Dibutyl phthalate : 255.5 mg/år

Problemet

Vi kender ikke omfanget af ftalat-eksponering blandt brugere af ftalat-holdig medicin

Få alternativer til ftalater

Målet med vores studie:

At kvantificere den årlige kumulerede ftalat-eksponering fra peroralt administrerede lægemidler blandt brugere af ftalat-holdig medicin i Danmark i perioden 2004-2016

- Database hos lægemiddelstyrelsen:

Komplet fortegnelse over alle hjælpestoffer i lægemidler med Dansk markedsføringstilladelse fra 2004 og fremefter

Registreret type- og mængde af ftalat, samt ændringer over tid

- Lægemiddelstatistikregisteret

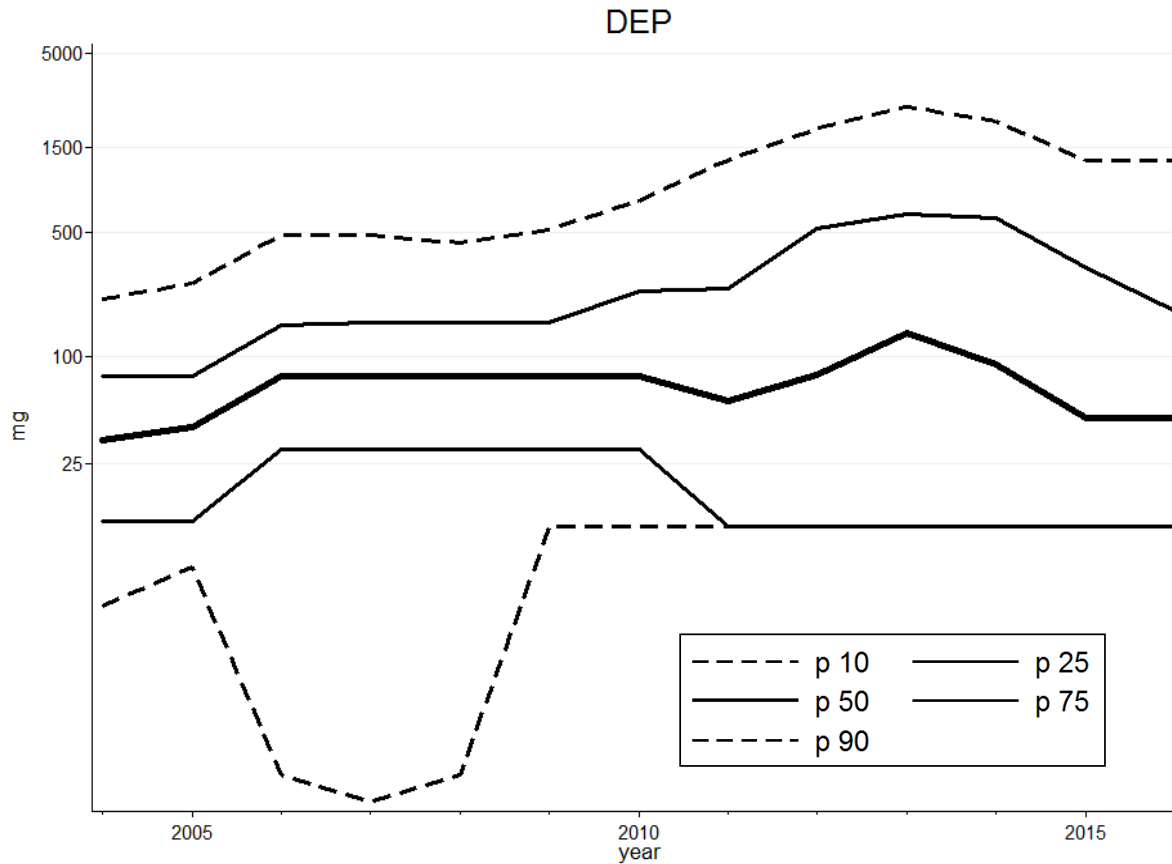
Specifikt varenummer (VNR) der identificerer de enkelte produkter og muliggør kobling af data

Diethyl phthalate

DEP	Year	N exposed
	2004	157.841
	2005	153.674
	2006	87.723
	2007	78.517
	2008	64.957
	2009	55.668
	2010	31.359
	2011	17.244
	2012	14.754
	2013	12.653
	2014	17.967
	2015	23.154
	2016	21.647

Antallet af DEP-eksponerede individer i perioden 2004-2016

Diethyl phthalate



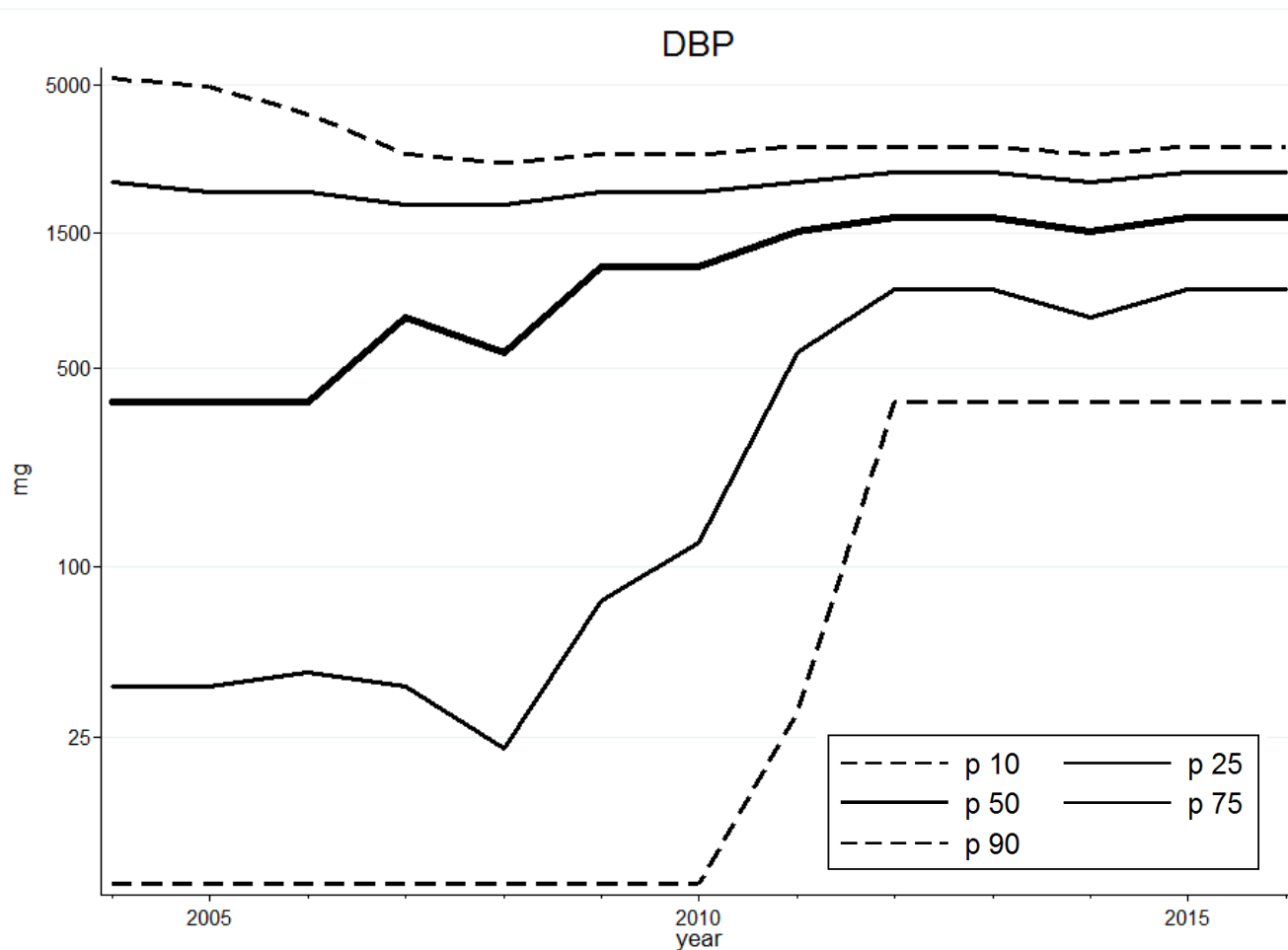
Distribution af årlig kumuleret DEP-eksponering , angivet i percentiler over perioden 2004-2016

Dibutyl phthalate

DBP	Year	N exposed
	2004	21.499
	2005	20.415
	2006	18.556
	2007	14.113
	2008	10.550
	2009	8.935
	2010	8.486
	2011	7.038
	2012	5.972
	2013	5.959
	2014	5.726
	2015	5.435
	2016	5.400

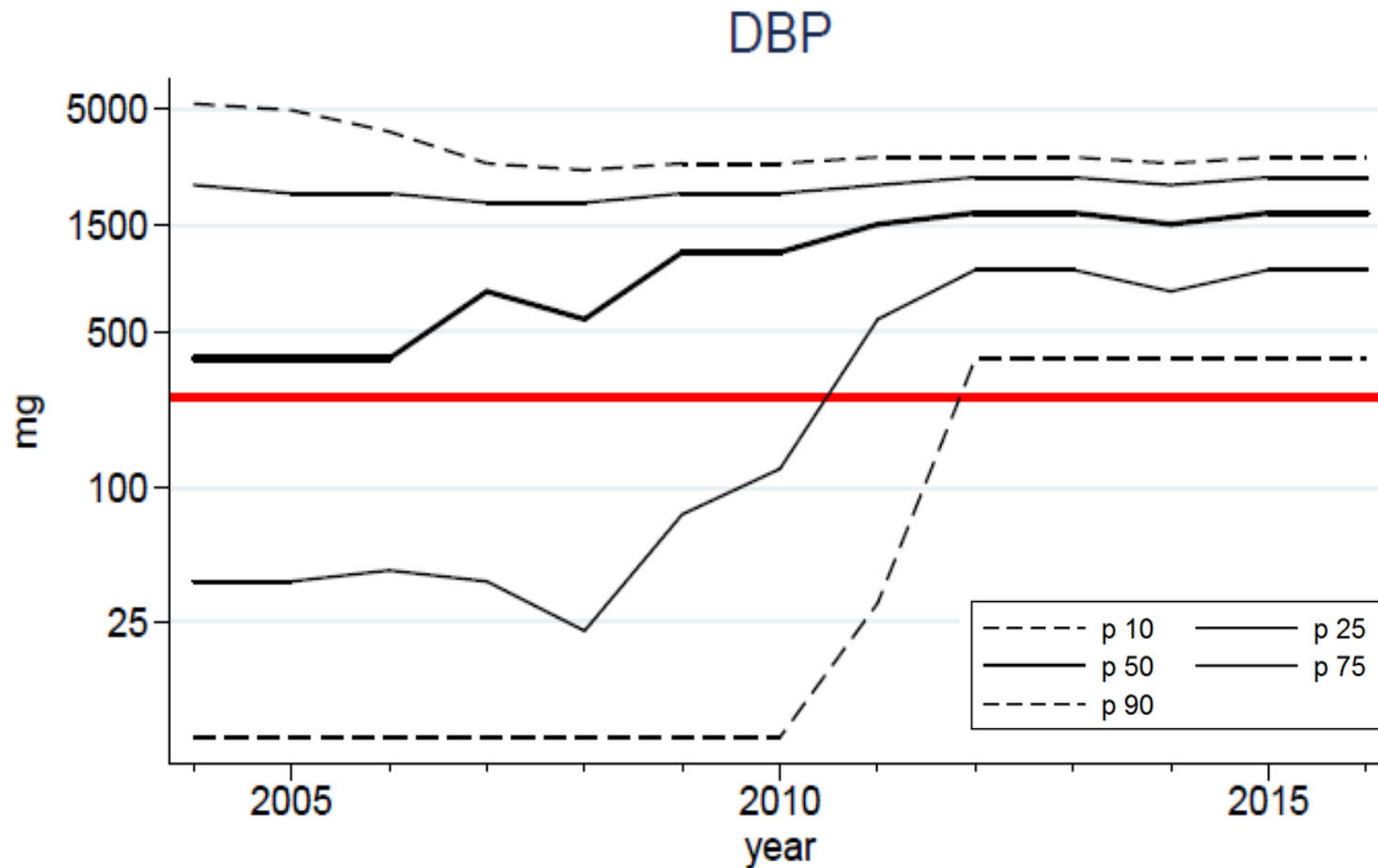
Antallet af DBP-eksponerede individer i perioden 2004-2016

Dibutyl phthalate



Distribution af årlig kumuleret DBP-eksponering, angivet i percentiler over perioden 2004-2016

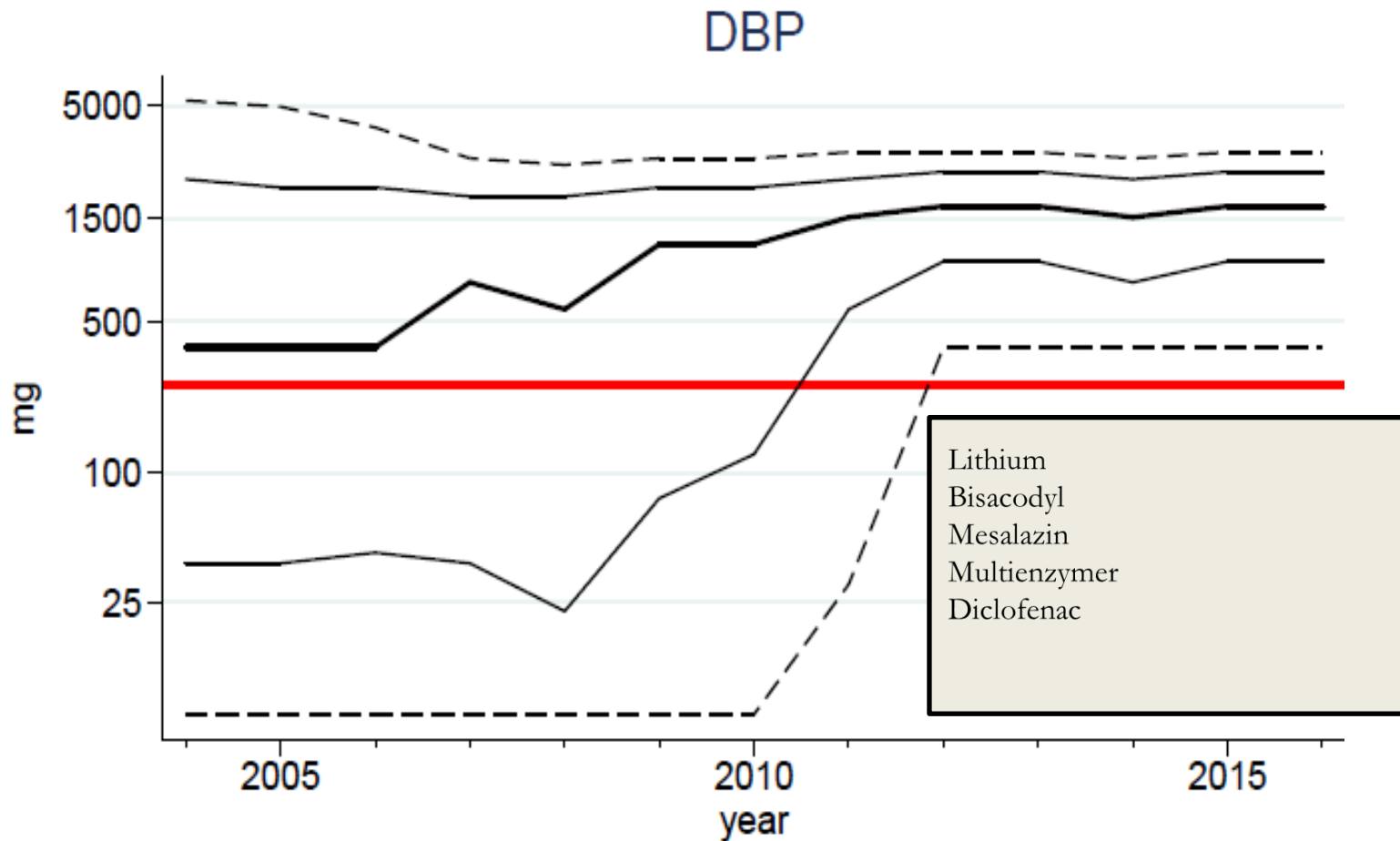
Dibutyl phthalate



Rød linje angiver regulatorisk grænse for DBP-eksponering: 0.01mg/kg/dag

Her omregnet for person på 70kg = 255.5 mg/år

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Konklusion

Antallet af eksponerede individer er faldet over studieperioden

DEP-eksponering er ikke et problem i forhold til regulatoriske grænser

En stigende proportion af DBP-eksponerede overskrider regulatoriske grænser

Tak for jeres tid

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