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

Running title: Pharmaceutical phthalate exposure and risk of gastric cancer

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## **Abstract**

### **Background**

Phthalates are used as excipients in some drug products, and up to a 50-fold increased urinary excretion of phthalate metabolites compared to non-users has been demonstrated in users of such products. *In vitro* studies have demonstrated that phthalates stimulate mechanisms involved in gastric cancer development. We therefore examined the association between cumulative phthalate exposure from drug products and the risk of gastric adenocarcinomas.

### **Methods**

Using the Danish Cancer Registry, we identified all patients with incident gastric adenocarcinoma from 2008-2015 (n=1,525). Cancer cases were matched to ten controls. Linking information retrieved from nationwide Danish registries, we determined individual cumulative phthalate exposure to the *ortho*-phthalates diethyl phthalate (DEP), dibutyl phthalate (DBP) and enteric phthalate polymers from prescription drugs. The association between cumulative phthalate exposure and gastric adenocarcinoma was estimated using conditional logistic regression, adjusting for socioeconomic status and drugs or comorbidities known or suspected to modify the risk of gastric adenocarcinoma.

### **Results**

No association was seen for the risk of gastric adenocarcinomas among individuals with high cumulative exposure to *ortho*-phthalates (exceeding 500 mg) (OR<sub>adj</sub> 1.22, 95%CI:0.84-1.77). Likewise, no associations were observed individually for DEP (OR<sub>adj</sub> 1.06 95% CI: 0.63-1.76) or DBP (OR<sub>adj</sub> 1.32 95% CI: 0.78-2.23). Cumulative exposure to enteric phthalate polymers exceeding 10,000 mg, did not reveal an association with gastric adenocarcinoma (OR<sub>adj</sub> 0.79, 95%CI: 0.54-1.16) and no

association was seen for individual compounds. Additionally, no dose-response pattern was observed across exposure strata ( $p=0.39$ , test for trend).

### **Conclusion**

We did not find an increased risk of gastric adenocarcinoma among Danish users of phthalate containing drug products. Our study is limited by a low number of cases exposed to high cumulative doses of phthalates.

### **Keywords**

Phthalates, diethyl phthalate, dibutyl phthalate, excipients, gastric cancer, Denmark, case-control study

## Introduction

Phthalates are ubiquitous compounds widely used in consumer care goods where they are used as plasticizers (1). Additionally, these compounds maintain color and scent in personal care goods (2). Due to the widespread use of phthalates in such products, most people are exposed. Phthalates are also used as excipients in pharmaceuticals as coating material in the production of sustained or delayed release preparations (3). They are used to prevent disintegration of the pill in the stomach acid (3). However, high exposure among users of phthalate-containing medications have been demonstrated; urine samples have revealed up to a 50-fold increased exposure among users of phthalate-containing medications compared to non-users (4). This potential harmful exposure can be prevented as all phthalate containing drug products are also represented by phthalate free products (5). Furthermore, *In vitro* studies have demonstrated that some phthalates are involved in mechanisms related to carcinogenesis, such as stimulation of the aryl hydrocarbon receptor and epithelial-to-mesenchymal transition (6,7). Mechanisms which are involved in the development of gastric adenocarcinomas (8). However, the carcinogenic properties of phthalates are still uncharacterized and human data are conflicting. Scarce data in the available literature led the U.S. Environmental Protection Agency to classify the ortho-phthalates diethyl phthalate (DEP) and dibutyl phthalate (DBP), as “not classifiable to human carcinogenicity” (9,10). This led us to consider if the potential extensive gastric phthalate exposure from orally administered drugs carries a risk of developing gastric adenocarcinomas. To answer this, we performed a Danish nationwide registry-based case-control study to examine the association between cumulative pharmaceutical phthalate exposure and risk of gastric adenocarcinoma.

## Method

We performed a case-control study investigating the cumulative phthalate exposure from orally administered drug products among individuals diagnosed with gastric adenocarcinoma (cases) and population-based cancer-free persons (controls). The study was reported according to STROBE guidelines for observational studies (11).

### Data sources

Five Danish nationwide registries were used to conduct a population-based case-control study: the Danish Cancer Registry (12), the National Prescription Registry (13), the National Patient Register (14), Registers in Statistics Denmark on educational level (15), and the Civil Registration System (16). The majority of medical care in Denmark is funded by the national health authorities, this constellation allows true population-based register studies covering all Danish inhabitants. A personal identification number, a unique identifier, assigned to all Danish residents since 1968 enables linkage of individual data across registers (17).

Detailed information on data sources is presented in **Appendix A**, and codes for cancer diagnoses, drug exposures and covariates are available in **Appendix B**.

The Danish Medicines Agency maintain an internal database on product-specific composition of excipients in drugs with marketing authorization from 2004 onwards. Information on type, amount and changes in composition are recorded and linked with Nordic product codes (VNR numbers) assigned to all unique drug products in the Danish formulary. Active ingredients are classified according to the Anatomic Therapeutic Chemical (ATC) index, developed by the World Health Organization (18). Linking data with the National Prescription Registry, we could quantify cumulative phthalate exposure on an individual level. Only orally administered drugs were included.

### **Sampling of cases and controls**

From the Danish Cancer Registry, we identified all patients (cases) in Denmark with a first-time diagnosis of gastric adenocarcinoma (ICD10: C16) in the period 2008-2015. The case population was individuals with histologically verified adenocarcinoma in the stomach. Their index date was the date of the cancer diagnosis. Exclusion criteria were age outside the range 18-85 years at the index date and any residency outside Denmark within 10 years prior to index date. Cases with a history of other cancers were excluded (except non-melanoma skin cancer) as well as cases with diagnoses associated with an increased risk of gastric cancer: hereditary nonpolyposis colon cancer (19) or familial adenomatous polyposis (19). Use of non-aspirin nonsteroidal anti-inflammatory drugs (na-NSAID's) exert chemoprotective effect against gastric cancers (20) and several of the phthalate containing drug products are na-NSAID's (5). A study by Friis *et al.* demonstrated chemoprotective effect of na-NSAID's among colorectal cancer patients redeeming  $\geq 2$  na-NSAID prescriptions (21). To avoid possible confounding from na-NSAID's, we excluded patients with  $\geq 2$  redeemed na-NSAID prescriptions. This was, however, subject to extensive sensitivity analysis, described below.

For each case, ten cancer-free controls among all Danish residents of the same gender and birth year, was selected, while applying the same exclusion criteria as for the cases. An index date identical to that of the corresponding case, was assigned for each control. Cases were eligible for becoming controls before they became cases. Thereby, the odds ratio (OR) becomes an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study based on the source population (22).

### **Exposure definition**

From the National Prescription Registry, we had information on all prescriptions redeemed by all Danish citizens from 1995 onwards. The database maintained by the Danish Medicines Agency provided detailed information on phthalate content per tablet or pill, in drug-products in Denmark

from 2004 onwards. We defined exposure by the cumulative amount of *ortho*-phthalates or enteric phthalate polymers filled via prescription medicine during the period 2004-2015. This was done by linking information on package size and phthalate amount per tablet or pill for all dispensed prescriptions by all subjects included. *Ortho*-phthalate exposure was characterized by specific phthalates: diethyl phthalate (DEP) and dibutyl phthalate (DBP). Likewise, enteric phthalate polymers were characterized by specific compounds: cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP) and polyvinyl acetate phthalate (PVAP). Exposure was divided in strata according to expected number of cases and controls within each stratum. *Ortho*-phthalate exposure was divided in three strata; <250 mg of cumulative phthalate exposure, 250-499 mg of cumulative exposure and >500 mg of cumulative exposure over the study period. For enteric phthalate polymers, the corresponding strata were <4,999 mg, 5,000-9,999 mg, and >10,000 mg of cumulative exposure. Furthermore never-exposed categories were defined for *ortho*-phthalates and enteric phthalate polymers respectively.

We disregarded exposure during the period - one year prior to the index date. This was done to reduce the possibility of reverse causation, while also judging that such recent exposure is unlikely to affect gastric cancer development (23).

### **Confounding variables**

The following potential confounders and risk factors were identified and incorporated in the adjusted analyses a) Use of drugs known or suspected to modify the risk of gastric adenocarcinoma including use of menopausal hormonal therapy (MHT), antidiabetics, drugs used to treat alcohol-related conditions, the combination metronidazole, clarithromycin and PPIs used to *H. pylori* eradication, NSAIDs, and Aspirin. Use of low-dose aspirin (ASA) was incorporated as a categorical variable in the adjusted analyses based on number of redeemed prescriptions: 0, 1-15 or >15 redeemed prescriptions. b) comorbidities known or suspected to modify the risk of gastric adenocarcinoma: *H. pylori* infection, chronic atrophic gastritis, duodenal ulcers, pernicious anemia,



diabetes, alcohol-related diseases, chronic obstructive pulmonary disease (COPD). c)

Socioeconomic status: Educational level was incorporated as a crude measure of socio-economic status as a categorical variable with four categories (unknown, 10 years, 11-13 year or >13 years). As in the assessment of drug exposure, we disregarded the period one year prior to the index date in the identification of confounder status (ICD-10 codes and ATC-codes are listed in Appendix B). This was done to reduce the possibility of reverse causation, while also judging that such recent exposure is unlikely to affect cancer development (23).

### **Main analysis**

The analysis followed a conventional matched case-control approach. We tabulated the frequency and proportion of cases and controls within categories of the exposures and covariates. We used conditional logistic regression to estimate ORs for gastric adenocarcinoma associated with high exposure to any *ortho*-phthalate, DEP, DBP or to any enteric phthalate polymer, adjusting for potential confounders. We performed dose-response analyses using above mentioned pre-defined exposure groups. In all analyses exposure to any phthalate was compared with never-exposure (reference category).

### **Pre-planned sensitivity and sub-analyses**

We examined heterogeneity of associations between phthalate exposure and gastric adenocarcinoma within strata of sex, age groups (<50, 50-69 or ≥70 years), stage of disease, history of diabetes, history of alcohol abuse or history of H. pylori infection. Further we performed an analysis excluding lithium-treated patients because DBP exposure is mainly driven by lithium products (24). Test for trend was performed among ever-exposed to either *ortho*-phthalates or enteric phthalate polymers from drug products. We estimated incremental changes in OR for every 10,000 mg of *ortho*-phthalate or enteric phthalate polymer using logistic regression, adjusting for age, sex and confounders, risk factors and

previous diagnoses listed in Appendix B. Further, we examined whether including- or excluding all patients redeeming na-NSAID prescriptions changed our results.

## Other

The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board (25).

## Results

We included 1,525 cases with gastric adenocarcinoma (**Figure 1**). Using risk-set sampling, cases were matched by age and gender to 15,250 cancer-free population controls. The majority of included cases and controls were men (72.1%) above 50 years of age (92.1%). *Ortho*-phthalate exposure was similar in cases and controls; 15.3% and 14.1% had been exposed to phthalate containing drug products. Drug use and comorbidities were balanced between cases and controls, but a larger proportion of cases (40,7%) had been diagnosed with- or eradicated for *H. pylori* infection compared with controls (31.4%). The controls had higher educational level with 62,2% having at least 11 years of education, compared with 54,7% of the cases. The baseline characteristics of cases and controls are shown in **Table 1**.

Among cases, 234 (15.3%) had been exposed to *ortho*-phthalate containing orally administered drugs during the study period compared with 2,149 (14.1%) of controls. Among these 35 cases (2.2%) and 253 controls (1.7%) were classified as having high exposure to *ortho*-phthalates, which yielded an adjusted OR of 1.22 (95%CI: 0.84-1.77) for the association between high *ortho*-phthalate exposure and the risk of gastric adenocarcinoma (**Table 2**).

We did not find evidence of a dose-response effect among those exposed to *ortho*-phthalates ( $p=0.39$ , test for trend). There were no association between exposure to *ortho*-phthalates and the risk of gastric adenocarcinoma when specifying on DEP or DBP respectively. Likewise, there were no

associations for the enteric phthalate polymers, CAP or HPMCP respectively. The few individuals exposed to PVAP did not allow for estimating the associations between exposure and risk of gastric adenocarcinoma.

Stratifying on age, sex, stage of disease as well as excluding patients diagnosed with diabetes, patients treated with lithium, patients treated for alcohol abuse, or excluding patients treated or diagnosed with H.pylori infection did not alter our findings (**Table 3**).

We investigated whether including or excluding all patients redeeming na-NSAID prescriptions altered our results. Excluding all patients redeeming  $\geq 1$  na-NSAID prescription, left us with 712 cases and 7,120 controls. Among these, 11 cases and 119 controls were exposed to  $>500$  mg *ortho*-phthalate from drug products, yielding an adjusted OR of 0.81 (95%CI: 0.43-1.54). If we included all patients redeeming na-NSAID prescriptions we had 3,050 cases and 30,500 controls. Among these, 123 cases and 1,052 controls were exposed to  $>500$  mg *ortho*-phthalate from drug products, yielding an adjusted OR of 1.06 (95%CI: 0.86-1.30).

## **Discussion**

In this population-based case-control study, we did not demonstrate an increased risk of gastric adenocarcinoma among individuals with high exposure to *ortho*-phthalates from drug products. Further, we did not find any associations between use of phthalate-containing drug products and the risk of gastric adenocarcinoma when stratifying on exposure to individual compounds or stratifying by age, gender, or cancer stage. Subgroup analyses did not alter our findings and neither did including or excluding patients redeeming na-NSAID prescriptions.

The main strength of this study is the use of nationwide registries with high completeness covering all Danish inhabitants. We were able to eliminate primary non-adherence, because our data are based on dispensed prescriptions rather than issued prescriptions (**26**). Furthermore, a decreased impact of secondary non-adherence can be expected as exposure to phthalates was quantified in

cumulative amount. The coverage of a prescription is often stretched by patients missing doses of regular medications and in this way, these patients are exposed to the entire amount of phthalates from the package (27). However, patients stopping their medications without finishing the dispensed package, are sources of misclassification.

The registries we used do not hold information on some factors known to increase the risk of gastric cancers such as smoking, alcohol ingestion, ethnicity, diet and body weight. However, the essentially random allocation of phthalate exposure from products with a common drug substance does not lead to the suspicion that these factors were imbalanced between our exposure groups.

Compared with other studies investigating the association between phthalate exposure and risk of cancer in humans, the use of registry data allowed large sample size and identification of up to 11 years of individual exposure history. Other epidemiological studies are based on questionnaire- or biomonitoring data (28–30). Data on the carcinogenic potential of ortho-phthalates are scarce and there are no other studies on gastric cancers. Phthalates are not classified as carcinogenic substances by the U.S. environmental protection agency and the U.S. Consumer Product Safety Commission due to lack of data (9,10,31,32). . An In vitro study demonstrated that combined presence of phthalates and  $17\beta$  estradiol exerted additive proliferative effect on MCF-7 human breast cancer cells through a downstream PI3K/Akt signaling pathway. Additionally, the combination of phthalates and  $17\beta$  estradiol prevented apoptosis (33). Epidemiological studies have investigated the association between phthalate exposure and hormone driven cancers. One study did not find an association between breast cancer in women and high urinary concentrations of monoethyl- or monobutyl phthalate, the major metabolites of DEP and DBP (28). On the contrary, another study found elevated risk of breast cancer among women with high urinary concentrations of monoethyl phthalate when compared to individuals with low concentrations (29). Occupational exposure to diethyl hexyl phthalate (DEHP) containing polyvinyl chloride has been suggested to increase the risk of testicular cancer in men (30). Several potentially harmful exposures were investigated in this

study and the phthalate of interest was DEHP, which is not used in orally administered drug products. Gastric adenocarcinoma incidence is lower in women than in men, suggesting a protective effect of estrogens. Even though DEP and DBP exert weak estrogenic activity (34), the mechanistic effect of ortho-phthalates in gastric adenocarcinoma development has not been investigated. However, upregulation and activation of the PI3K/Akt signaling pathway in gastric cancers have been linked to increased cell growth, proliferation, metabolism and angiogenesis in gastric cancers (35)

We did not find any association between gastric adenocarcinoma and phthalate exposure from drug products. Our findings may be explained by either of two scenarios: The lack of demonstrating an association in this study, could be explained by the lack of a *true* association between exposure to phthalates from drug products and gastric adenocarcinoma. Alternatively, if a true association exist, we might have missed it.

Gastric cancers are slowly developed (36) and by using a registry with information on exposure from 2004 onwards, we might not have sufficient look-back time to capture the exposure required to demonstrate a possible effect. Even though our sample size is large compared to other studies, the finding of an OR of 1.22 (95%CI:0.84-1.77) does not rule out a small protective or harmful effect. Judged by the upper bound of the confidence interval, the worst-case scenario would be an 77% increased risk of gastric adenocarcinoma among users of phthalate containing drug products receiving more than 500 mg across the study period compared with population controls.

The lack of an association in this study could also be explained by factors introducing bias towards also the null. We could not account for exposure from environmental- or occupational sources in this study, but we have no reason to believe that such exposure is unequally distributed between cases and controls.

The phthalate exposure came from different drugs (List of phthalate containing drugs used by study population in supplementary material, Table A1 and A2). However, confounding by indication is of minor concern, because DBP exposure mainly came from mesalazine (63,7%), lithium (26,6%) and

multienzymes (9,4%) and neither inflammatory bowel disease, bipolar disease or exocrine pancreatic insufficiency, are diseases associated with lowered risk of gastric cancers (37). Most of the DEP exposure came from theophylline (82,9%), erythromycin (7,3%) and verapamil (4,1%) and neither chronic obstructive lung disease (COPD), infections/acne or atrial fibrillation, are diseases associated with lowered risk of gastric cancers (37). On the contrary some of the diseases such as COPD, bipolar disease and exocrine pancreatic insufficiency caused by excessive use of alcohol, are diseases associated with factors known to increase the risk of gastric cancers such as smoking or low socioeconomic status (38,39). Lastly, confounding introduced by drugs lowering the risk of gastric adenocarcinoma, could explain lack of an association in this study. Use of the anti-inflammatory agent mesalazine constituted the majority of DBP exposure. Chemoprotective effect of mesalazine, similar to that of NSAIDs, has not been demonstrated for gastric adenocarcinoma (40) and sensitivity analyses demonstrated that use of NSAIDs did not have impact on our results.

## **Conclusion**

We did not find an increased risk of gastric adenocarcinoma among Danish users of phthalate containing drug products. However, our study is limited by a low number of cases exposed to high cumulative doses of phthalates.

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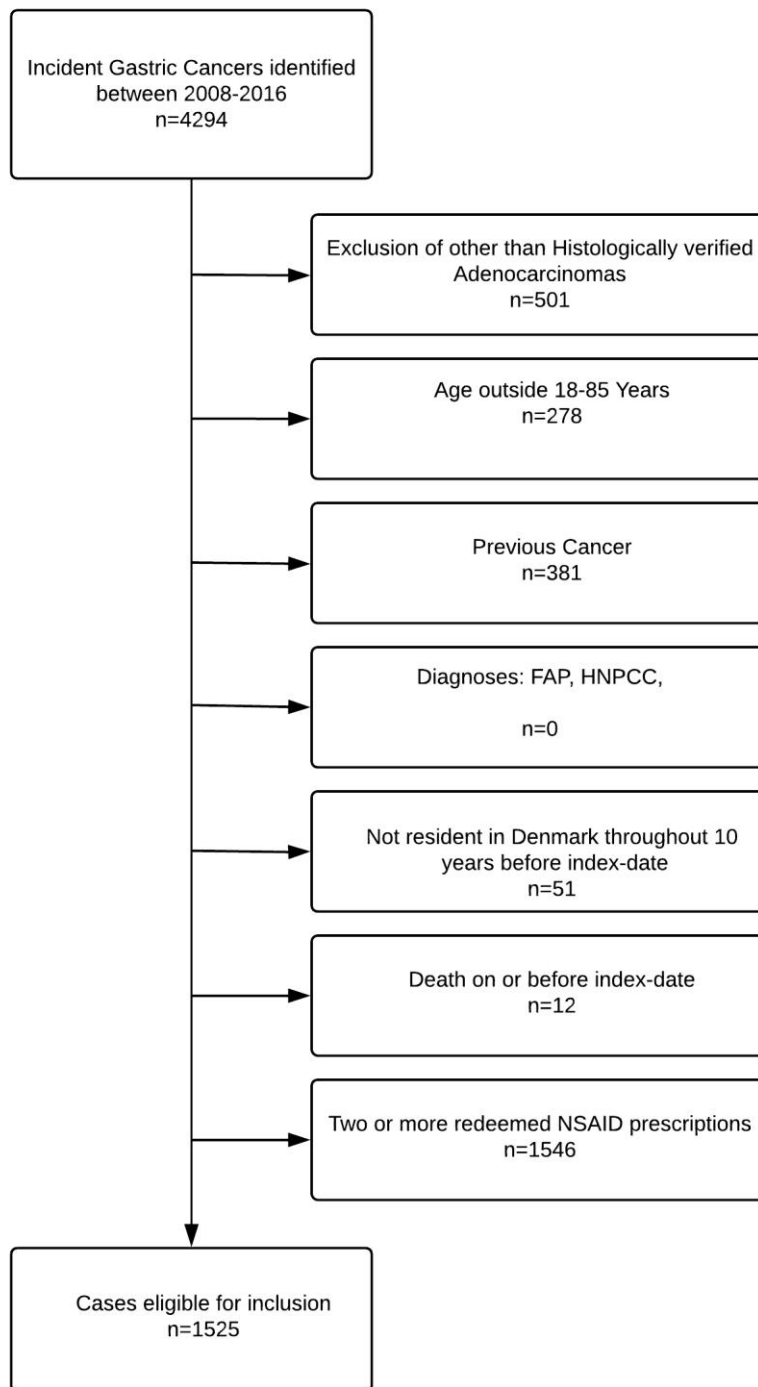
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## **Additional information**

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2865 words



**Figure 1** Flowchart displaying case selection

	Cases	Controls
<b>All</b>	(n=1,525)	(n=15,250)
Male gender	1,099 (72.1%)	10,990 (72.1%)
<b>Age</b>		
Median (IQR, years)	68 (60-76)	68 (60-76)
<50 years	121 (7.9%)	1,210 (7.9%)
50-69 years	700 (45.9%)	7,000 (45.9%)
70+ years	704 (46.2%)	7,040 (46.2%)
<b>Cancer localization</b>		
Cardia	762 (50.0%)	-
Corpus	481 (31.5%)	-
Unknown	282 (18.5%)	-
<b>Ortho-phthalate exposure</b>		
Never	1,291 (84.7%)	13,101 (85.9%)
0-249 mg	186 (12.2%)	1,763 (11.6%)
250-499 mg	13 (0.9%)	133 (0.9%)
≥500 mg	35 (2.3%)	253 (1.7%)
<b>Drug use</b>		
Low-dose aspirin	424 (27.8%)	3,848 (25.2%)
Non-aspirin NSAID's	813 (53.3%)	7,624 (50.0%)
MHT	155 (10.2%)	1,708 (11.2%)
<b>Comorbidities</b>		
Diabetes	110 (7.2%)	997 (6.5%)
COPD	81 (5.3%)	637 (4.2%)
Alcohol-related diseases	98 (6.4%)	619 (4.1%)
H.pylori infection	620 (40.7%)	4,793 (31.4%)
Chronic atrophic gastritis	26 (1.7%)	149 (1.0%)
Duodenal ulcers	23 (1.5%)	206 (1.4%)
Pernicious anemia	-	-
<b>Education</b>		
Short (7-10 years)	619 (40.6%)	4,977 (32.6%)
Medium (11-13 years)	579 (38.0%)	5,960 (39.1%)
Long (>13 years)	254 (16.7%)	3,595 (23.6%)
Unknown	73 (4.8%)	718 (4.7%)

**Table 1:** Characteristics of cases of gastric adenocarcinoma and matched population based controls.

IQR: Inter Quartile Range, NSAID's: Non-Steroid Anti-inflammatory Drugs.

MHT: Menopausal Hormonal Therapy, COPD: Chronic Obstructive Pulmonary Disease

	Cases	Controls	Crude OR <sup>1</sup>	Adjusted OR <sup>2</sup>
Never exposed	1,220	12,482	1.0 (ref.)	1.0 (ref.)
<b>Ortho-phthalates</b>				
Ever exposed	234	2,149	1.12 (0.96-1.30)	1.00 (0.86-1.16)
0 -249 mg	186	1,763	1.08 (0.92-1.27)	0.97 (0.82-1.15)
250 – 499 mg	13	133	1.04 (0.58-1.87)	0.91 (0.50-1.64)
>500mg	35	253	1.44 (1.00-2.08)	1.22 (0.84-1.77)
<b>DEP</b>				
0 – 249 mg	183	1,718	1.09 (0.93-1.28)	0.99 (0.83-1.17)
250 -499 mg	11	120	0.99 (0.53-1.86)	0.89 (0.47-1.68)
>500 mg	18	142	1.27 (0.77-2.10)	1.06 (0.63-1.76)
<b>DBP</b>				
0 – 249 mg	8	85	1.05 (0.50-2.19)	0.92 (0.44-1.94)
250 – 499 mg	(n<5)	13	(-)	(-)
>500 mg	17	117	1.53 (0.91-2.58)	1.32 (0.78-2.23)
<b>Enteric phthalate polymers</b>				
Ever exposed	224	2,081	1.11 (0.95-1.29)	1.00 (0.85-1.17)
0 – 4,999 mg	174	1,563	1.16 (0.98-1.37)	1.04 (0.88-1.24)
5,000 -9,999 mg	17	146	1.12 (0.67-1.88)	1.03 (0.61-1.73)
>10,000 mg	33	372	0.89 (0.61-1.27)	0.79 (0.54-1.16)
<b>CAP</b>				
0-1,999 mg	121	1,176	1.06 (0.87-1.29)	0.96 (0.79-1.18)
2,000-3,999 mg	19	199	1.01 (0.62-1.64)	0.88 (0.54-1.43)
>4,000	43	457	0.93 (0.67-1.29)	0.87 (0.62-1.22)
<b>HPMCP</b>				
0-1,999 mg	121	1,176	1.06 (0.87-1.29)	0.96 (0.79-1.18)
2,000-3,999 mg	19	199	1.01 (0.62-1.64)	0.88 (0.54-1.43)
>4,000	43	457	0.93 (0.67-1.29)	0.87 (0.62-1.22)
<b>PVAP</b>				
0-9,999 mg	(n<5)	17	(-)	(-)
10,000-19,999 mg	(n<5)	(n<5)	(-)	(-)
>20.000 mg	(n<5)	21	(-)	(-)

**Table 2** Association between ortho-phthalate exposure or enteric phthalate polymer exposure and the risk of gastric adenocarcinoma within dose strata throughout the period 2004-2015.

*Ortho*-phthalate exposure is specified to diethyl phthalate (DEP) and dibutyl phthalate (DBP) exposure.

Enteric phthalate polymers are specified to cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP) and polyvinyl acetate phthalate (PVAP).

<sup>1</sup>Adjusted for age, calendar time and gender (by matched design). <sup>2</sup> Fully adjusted model, see section 'confounding variables'.

	<b>Cases Exposed/Unexposed</b>	<b>Controls Exposed/Unexposed</b>	<b>Crude OR<sup>1</sup></b>	<b>Adjusted OR<sup>2</sup></b>
All	234 / 1,220	2,149 / 12,482	1.12 (0.96-1.30)	1.00 (0.86-1.16)
<b>Age</b>				
<50 years	18 / 102	152 / 1,050	1.21 (0.71-2.07)	1.04 (0.59-1.82)
50-69 years	97 / 578	917 / 5,882	1.07 (0.85-1.34)	0.93 (0.74-1.18)
>70 years	119 / 540	1,080 / 5,550	1.15 (0.93-1.41)	1.05 (0.84-1.30)
<b>Gender</b>				
Male	165 / 886	1,428 / 9,083	1.18 (0.99-1.41)	1.06 (0.88-1.27)
Female	69 / 334	721 / 3,399	0.98 (0.75-1.29)	0.88 (0.66-1.16)
<b>Stage of Disease</b>				
Localized	31 / 148	279 / 1,552	1.18 (0.78-1.78)	1.07 (0.70-1.65)
Non-localized	165 / 906	1,540 / 9,188	1.09 (0.91-1.30)	0.98 (0.82-1.17)
Unknown	38 / 166	330 / 1,742	1.20 (0.83-1.74)	1.01 (0.68-1.49)
<b>Other subgroups</b>				
Excluding those w. lithium exp	228 / 1,198	2,087 / 12,058	1.09 (0.94-1.27)	0.99 (0.85-1.16)
Excluding those w. diabetes	208 / 1,144	1,945 / 11,750	1.10 (0.94-1.29)	0.98 (0.84-1.16)
Excluding those w. alcohol abuse	217 / 1,148	2,025 / 12,044	1.12 (0.96-1.31)	1.02 (0.87-1.20)
Excluding those w. H.pylori	103 / 765	1,203 / 8,902	1.01 (0.81-1.26)	0.92 (0.73-1.15)

**Table 3:** Subgroup analysis among individuals exposed to ortho-phthalates

<sup>1</sup> Adjusted for age, calendar time and gender (by matched design)

<sup>2</sup> Fully adjusted model, see section 'confounding variables'.

## **Appendix A – Data sources**

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and has been shown to have accurate and almost complete ascertainment of cancer cases. Cancer diagnoses are recorded according to the International Classification of Diseases, version 10 (ICD-10), and the ICD for Oncology (ICD-O-3) for topography and morphology codes.

The Danish National Prescription Registry contains data on all prescription drugs dispensed to Danish citizens since 1995. The data include the type of drug, date of dispensing, and quantity. The dosing information and the indication for prescribing are not available, and no information is available on drug use dispensed at hospital level. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the WHO, and the quantity dispensed for each prescription is given by the number and strength of the pharmaceutical entities (e.g., tablets), as well as the defined daily doses (DDD).

The Danish National Patient Register contains nationwide data on all non-psychiatric hospital admissions since 1977 and on all outpatient contacts since 1995. Discharge/contact diagnoses have been coded according to ICD-8 from 1977 to 1993 and ICD-10 since 1994.

Statistics Denmark administers registries on education and income. The Population Education Register contains information on the highest completed level of education, derived from type and duration of schooling.

The Danish Civil Registration System contains data on date of death and migration to and from Denmark, allowing unambiguous linkage between registries, extraction of population controls, and complete tracking of Danish inhabitants.

## Appendix B – Definitions (confounders and exclusions)

<b>Exclusion criteria</b>	<u>ICD-10 code</u>	<u>ATC-code</u>
Hereditary nonpolyposis colon cancer	C18.8A	
Familial adenomatous polyposis	D12.6F	
NSAID use $\geq$ 2 prescriptions	M01A excl. M01AX	
Any cancer	Any record in the Cancer Registry (except NMSC)	
<b>Confounders/Risk factors</b>		
Use of drugs ( $\geq$ 2 fillings prior to index date)		
<u>Drug</u>	<u>ATC-code</u>	
Aspirin	B01AC06; B01AC30; N02BA01 and N02BA51	
NSAIDs	M01A excl. M01AX	
Menopausal Hormone Therapy	G03C G03D G03F G03HB10	
<b>Prior diagnoses (either a diagnostic code or a drug marker)</b>		
<u>Disease</u>	<u>ICD-10 code</u>	<u>Drug markers</u>
Diabetes type 2	E11-E14, E145D, E891D, G590, G632, G730A, G990C, H280, H360, I792A, M142, N083, O241	A10B ( $\geq$ 500DDD)
COPD	J40-44	R03BB ( $\geq$ 500DDD)
Alcohol-related conditions	F10, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, R78.0, T51, Z72.1	N07BB01, N07BB03, N07BB04 (ever use)
H. pylori infection	B980	P01AB01+ J01FA09+ A02BC (ever use for the combination)
Chronic atrophic gastritis	K294, K295, K297	
Duodenal ulcers	K26	
Pernicious anemia	B510	
<b>Socioeconomic status (education)</b>		
<u>Educational level</u>	<u>Duration of education</u>	
Basic	10 years	
Short/medium	11-13 years	
Long	>13 years	
Missing/unknown	-	

NOTES: NMSC = Non-melanoma skin cancer; COPD = Chronic obstructive pulmonary disease;

NSAID = Non-steroidal anti-inflammatory drugs



## Appendix C

DBP-containing drug products	Indikation*	ATC code	DBP amount used (mg)	Percentage of total DBP use
Mesalazine	Inflammatory Bowel Disease	A07EC02	2,054,348	63,7%
Lithium	Bipolar disease	N05AN01	858,813	26,6%
Multienzymes (lipase, protease etc.)	Exocrine pancreas insufficiency	A09AA02	302,416	9,4%
Bisacodyl	Constipation	A06AB02	7,673	0,3%
<b>Total</b>			3,223,250	100,0%

**Table A1:** DBP-containing orally administered drugs used by the study population: ATC-codes, total amount redeemed and percentages of total use during the period 2004-2015.

\*Indication constituting the majority the utilization in Denmark.

DEP containing drug products	Indication*	ATC code	DEP amount used (mg)	Percentage of total DEP use
Theophylline	Chronic Obstructive Lung Disease	R03DA04	2,054,349	82,9%
Erythromycin	Infections, acne	J01FA01	178,389	7,2%
Verapamil	Atrial fibrillation	C08DA01	99,583	4,0%
Mianserin	Depression	N06AX03	69,278	2,8%
Multienzymes (lipase, protease etc.)	Exocrine pancreas insufficiency	A09AA02	23,790	1,0%
Galantamine	Alzheimerz disease	N06DA04	9,782	0,4%
Diclofenac, combinations	Mild to moderate pain	M01AB55	6,810	0,3%
Ibuprofen	Mild to moderate pain	M01AE01	5,998	0,2%
Bisacodyl	Constipation	A06AB02	4,788	0,2%
Diclofenac	Mild to moderate pain	M01AB05	2,482	0,1%
<b>Total</b>			2,477,627	100,0%

**Table A2:** DEP-containing orally administered drugs used by the study population: ATC-codes, total amount redeemed and percentages of total use during the period 2004-2015.

\*Indications constituting the majority of the utilization in Denmark.