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Population Exposure to Phthalate-containing Drugs

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Abstract: Phthalates are known endocrine disruptors. Not commonly recognized, phthalates are used as excipients in a number of drug formulations. We aimed to describe the sale of phthalate-containing drugs in Denmark from 2004 to 2015. National data on annual sale of medications (tablets only) were accessed from medstat.dk. Data from the Danish Medicines Agency on phthalate content per tablet were merged with data on total sale for each active substance and drug formulation. We used the 'defined daily dose' (DDD) as the unit of sale and calculated the total amount of phthalate (mg) dispensed per 1000 inhabitants. Specific tablet content was compared with the maximum daily exposure limits defined by regulatory agencies for diethyl phthalate (DEP) and dibutyl phthalate (DBP) of 4.0 and 0.01 mg/kg/day, respectively. Use of phthalate-containing drugs in Denmark was common. We found 154 drug products containing five different phthalates. Two low-molecular-weight phthalates and three high-molecular-weight phthalates were identified, with a total sale of 59.4 and 112 DDD per 1000 inhabitants per day during the study period, respectively. The highest amount of DBP was found in multi-enzymes (24.6–32.8 mg per DDD) and mesalazine (12.5–26.4 mg per DDD). Budesonide, lithium and bisacodyl also exceeded the DBP exposure limit of 0.01 mg/kg/day. Other drugs had high levels of DEP, although not exceeding the exposure limit. Sales of phthalate-containing drugs in Denmark from 2004 to 2015 were substantial, and phthalate exposure from several products exceeded the regulatory exposure limit introduced in 2014.

Phthalates are used as plastic softeners in consumer products like toys, food containers and cosmetics [1]. Not widely recognized, phthalates are also used as excipients in some orally administered drugs, mostly to control release [2]. A recent study found that individuals in long-term treatment with phthalate-containing medications have up to 50-fold higher urine concentrations of phthalate metabolites than the average population [3].

These chemicals are endocrine disruptors [4,5], but the effect of phthalate exposure on human reproduction, development and carcinogenesis remains controversial [6–8]. High-molecular-weight phthalates are considered harmless due to negligible absorption, but absorption of high-molecular-weight phthalates is complex and does not appear to have been systematically studied in human beings. [9]. In response to increased attention to possible harmful effects of phthalates on human health, the European Medicines Agency and the U.S. Food and Drug Administration in 2014 set maximum daily exposure limits for low-molecular-weight phthalates, including diethyl phthalate (DEP) and dibutyl phthalate (DBP). Exposure limits for DEP and DBP were set to 4.0 and 0.01 mg/kg/day, respectively [10]. Despite these recommendations, DBP-containing drugs exceeding the advised exposure limit remain marketed.

In this study, we estimate the sale of phthalate-containing medication in Denmark from 2004 to 2015.

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Method

We obtained overall sales data including both in- and outpatient prescriptions as well as over-the-counter drugs from www.medstat.dk from 2004 until 2015, inclusive.

Data source. Medstat.dk is a public database containing statistics on the annual sale of medication in Denmark [11]. Data are based on recordings from the Register of Medicinal Product Statistics, to which reporting of medication sales in Denmark is mandatory (including to individuals, medical practices, treatment centres and hospitals). Sales are categorized according to the Anatomic Therapeutic Chemical (ATC) index developed by the World Health Organization, as well as a product number used to identify the individual medicine package including product name, administration form, strength and pack size. We only included data on orally administered tablets and capsules. Other orally administered formulations, such as granulate or dispersible tablets, were not included in this study.

We used the 'defined daily dose' (DDD) as the unit of sale and obtained DDD values for each active substance from the WHO's ATC/DDD index (www.whocc.no). Multi-enzymes (ATC: A09AA02) did not have an official DDD value from WHO's index or a fixed DDD value from WHO's list for combined products. A national DDK (DailyDose DK) was therefore used instead. The DDK was calculated by the Danish Health Data Authority based on Summary of Product Characteristics for each drug product. For multi-enzymes, one DDD was either six capsules of 10,000 EP-e Lipase or four capsules of 25,000 or 40,000 EP-e Lipase [12]. However, for diseases with pancreatic insufficiency, for example cystic fibrosis, the daily dose can greatly exceed the DDK and thus lead to a substantially higher exposure to phthalates.

Phthalate content. Data on phthalate content were obtained from the Danish Medicines Agency, which maintains a database on product composition for all pharmaceutical products marketed in Denmark. For

each drug product, we defined phthalate content as mg of phthalate per tablet or capsule, and per DDD. Five different phthalates were registered – two low-molecular-weight phthalates: dibutyl phthalate (DBP) and diethyl phthalate (DEP); and three high-molecular-weight phthalates: cellulose acetate phthalate (CAP), poly vinyl acetate phthalate (PVAP) and hypromellose phthalate (HPMCP). Market authorization date, marketing and withdrawal dates, as well as start and end dates of phthalate excipient use, were recorded for each drug product.

Drug product – VNR. The drug product number (VNR) is unique for each product marketed in Denmark and will change if strength, package size or other similar parameters change. While a change of excipients does not necessarily imply a change of VNR, there are exact dates recorded for such changes. Data from medstat.dk reflect annual sale and may not be limited to the phthalate-containing period for a given VNR within a year.

We excluded all data with missing information regarding drug product, amount or type of phthalate, or dates of start or end of phthalate period. Further, we disregarded drugs with no recorded sale in the study period.

In years with alterations to the phthalate content of a given drug, we calculated monthly sales by assuming uniform sale figures within 12 months. Further, if the phthalate content was introduced, changed or removed from a product on or before the 15th of a month, it would be counted as an entire month of sales. Any changes occurring after the 15th would be accounted for in the following month.

We calculated the annual sale of phthalate-containing drugs per 1000 inhabitants per day in Denmark for each type of phthalate. Annual population numbers were defined as all inhabitants in Denmark on 1 January each year. We calculated the annual amount of phthalates in milligrams (mg) sold per 1000 inhabitants per day.

Table 1.
Phthalate content. Content per tablet or capsule and DDD for each active substance, and number of DDD sold from 2004 to 2015.

Phthalate	ATC code	Active substance	Phthalate Content, Mg/DDD	Phthalate Content, Mg/Tbl	DDD/1000 inhabitants/day (% of total sale)
Dibutyl Phthalate	A09AA02	Multi-enzymes	24.6–32.8[1,2]	4.1–8.2[1,2]	0.8 (11%)
	A07EC02	Mesalazine	12.5–26.4[1,2]	4.4–6.66[1,2]	4.1 (15%)
	A07EA06	Budesonide	12.6[2]	4.2[2]	0.0 (<1%)
	N05AN01	Lithium	7.6[2]	1.9[2]	8.2 (64%)
	A06AB02	Bisacodyl	1.42[2]	0.71[2]	8.0 (14%)
	M01AB05	Diclofenac	0.51	0.38	1.2 (2%)
Diethyl Phthalate	A09AA02	Multi-enzymes	43.9	7.32	0.1 (3%)
	J05AF02	Didanosine	12	7.5–12	0.0 (84%)
	M01AE02	Naproxen	10.4	5.22–10.4	1.8 (8%)
	J01FA01	Erythromycin	0.01–10.4	0–3.91	3.3 (51%)
	R03DA04	Theophylline	8.45–8.46	4.23–6.35	5.1 (40%)
	M01AB05	Diclofenac	1.94–6.62	0.97–3.31	0.3 (1%)
	A02BC05	Esomeprazole	4.57	3.05–6.09	0.3 (<1%)
	M01AB55	Diclofenac, comb.	3	1.5	3.5 (39%)
	C08DA01	Verapamil	0.24–2.94	0.04–1.47	5.7 (13%)
	N06AX03	Mianserin	1.05–2.25	0.24–1.4	1.5 (14%)
	N06DA04	Galantamine	2.02	1.01–3.02	1.0 (35%)
	A06AB02	Bisacodyl	0.15–0.9	0.45	10.4 (18%)
	M01AE01	Ibuprofen	0.6–0.8	0.1–0.4	3.5 (1%)
	N06AB03	Fluoxetine	0.2	0.2	0.0 (<1%)
Cellulose Acetate Phthalate	N03AG01	Valproic acid	134–300	15–60	0.5 (3%)
	A09AA02	Multi-enzymes	179	29.9	0.1 (3%)
	A07EC01	Sulfasalazine	96	24	10.4 (61%)
	R03DA04	Theophylline	33.8–56	16.9–49	9.9 (79%)
	M01AE02	Naproxen	41.8	20.9–41.8	1.8 (8%)
	M01AB05	Diclofenac	18.7	9.4	0.3 (1%)
	M01AB55	Diclofenac, comb.	10.8	5.4	1.8 (20%)
	A03AB05	Propantheline	1.4–2.8	0.35–0.71	0.4 (45%)
	R05DB05	Pentoxyverine	1.6	0.4	0.0 (82%)
Hypromellose Phthalate	A09AA02	Multi-enzymes	292–601	48.6–150	2.0 (25%)
	L04AA06	Mycophenolic acid	361–467	42–65	0.0 (7%)
	J01FA01	Erythromycin	78.2–104	25.9–39.1	3.3 (51%)
	N06AX21	Duloxetine	27.5–51.7	12.4–51.7	0.9 (3%)
	A02BC04	Rabeprazole	12–17	6.3–13.8	1.2 (65%)
	B01AC30	Dipyridamole, comb.	12.8	6.4	14.5 (61%)
	B01AC07	Dipyridamole	9.2–9.5	4.6–4.7	51.3 (77%)
	A06AB02	Bisacodyl	1.5–9.1	4.5	9.8 (17%)
	J01FA09	Clarithromycin	5	5	0.0 (1%)
PVAP	N03AG01	Valproic acid	208–263	17.5–69.2	3.2 (17%)

ATC, anatomic therapeutic chemical; PVAP, poly vinyl acetate phthalate; DDD, Daily Defined Dose; Tbl, Tablet.
[1]Range depending on manufacturer and tablet strength.
[2]Exceeding permitted daily exposure limit for DBP for a 70-kg adult (0.7 mg/70 kg/day).

For each phthalate-containing active substance, we calculated the annual sale of both phthalate-containing formulations and overall sale. We characterized the range of specific phthalate content per tablet and DDD throughout the study period. We calculated the total amount sold per day per 1000 inhabitants from 2004 to 2015 for each active substance (table 1A).

Other. All calculations were performed using STATA release 14.0 (StataCorp, College Station, TX, USA).

According to Danish law, studies based solely on register data do not require ethical approval. Furthermore, this study did not need approval from the Danish Data Protection Agency. Data are publicly available, with exception of the product-specific phthalate content.

Results

We identified 393 different drug products containing at least one phthalate from the excipient list from the Danish Medicines

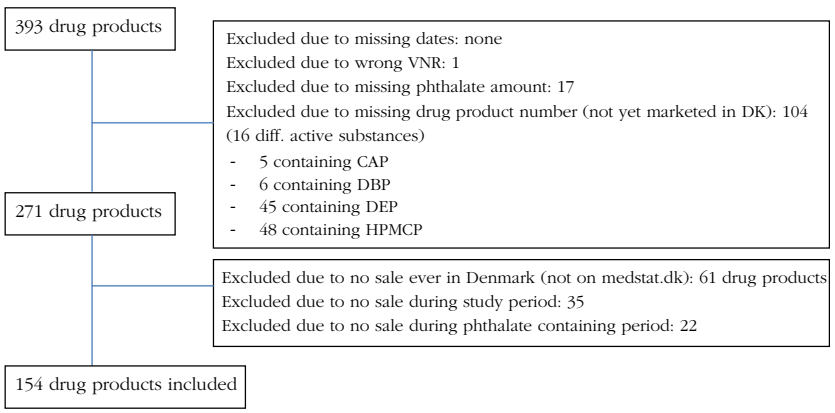

Fig. 1. Exclusions. Flow chart presentation of drug product exclusions.

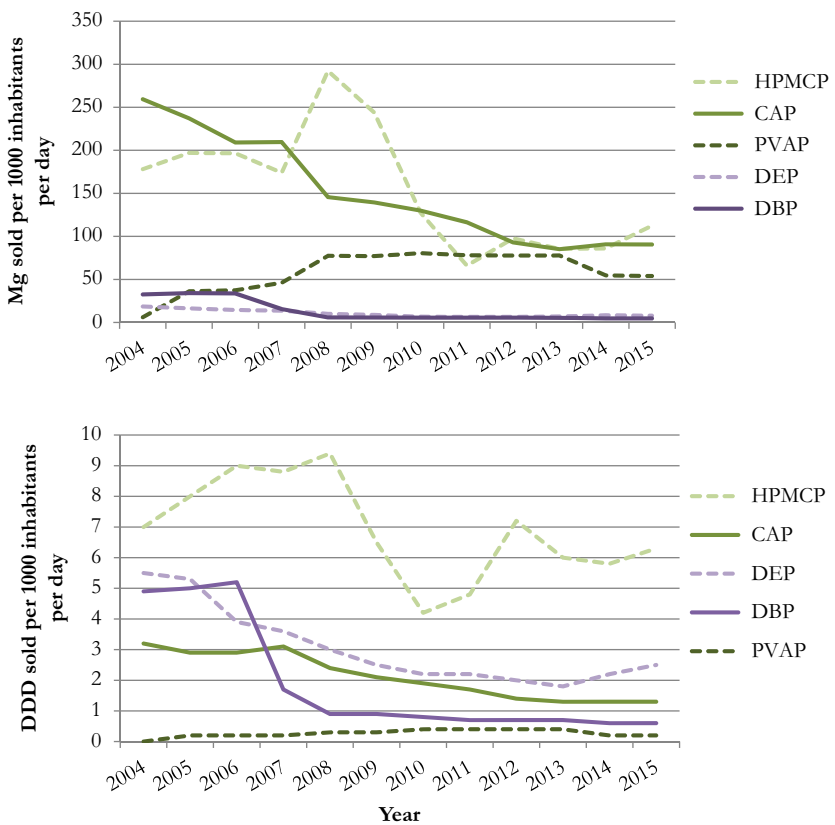

Fig. 2. Annual amount of phthalate sold. 'Total amount of phthalate (mg) (top figure) and DDD (of drugs containing phthalate, bottom figure) sold/1000 inhabitants/day, specified by type of phthalate'.

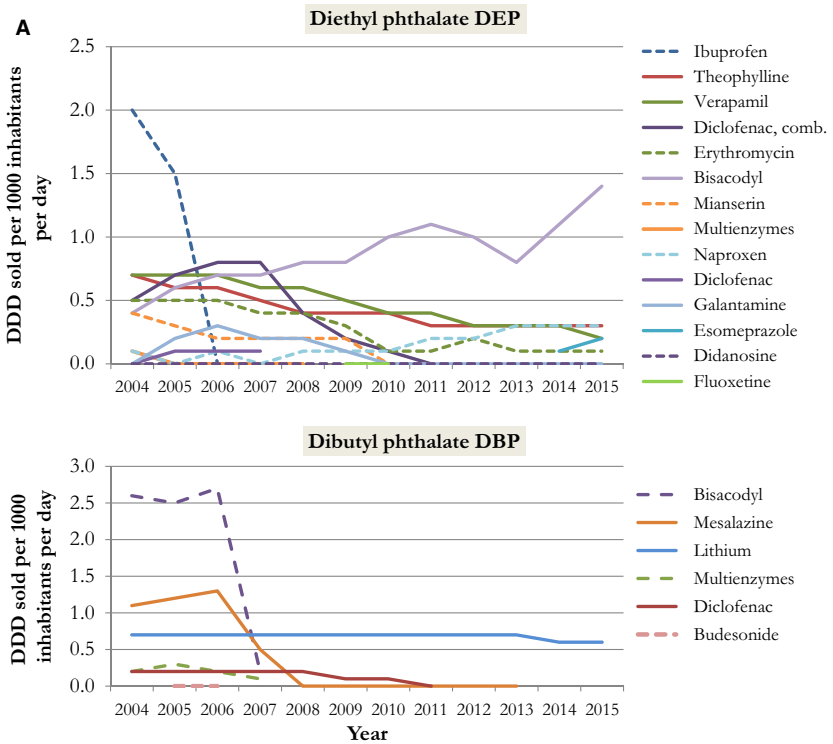

Fig. 3. (A) Amount of DDD sold. DDD sold per 1000 inhabitants per day in Denmark containing low-molecular-weight phthalates. (B) Amount of DDD sold. DDD sold per 1000 inhabitants per day in Denmark containing high-molecular-weight phthalates.

Agency. Of these, 104 products had no marketing approval in Denmark, one had been allocated an incorrect product number, and 17 were excluded due to missing information about phthalate content, see fig. 1 for flow chart. This left us with phthalate data on 271 different drug products. However, 60 products had never been sold in Denmark, and 57 additional products did not have any registered sale during the study period or the phthalate-containing period. Twenty-seven new products containing phthalates were marketed, while phthalates were added to 26 products already marketed in Denmark after 1 January 2004. Forty phthalate-containing products were removed from the Danish market, and 46 products had phthalates removed from their excipient composition during the study period. In the end, we included 154 drug products containing five different phthalates distributed over 27 different single substances. For the 27 identified active substances, we identified a total of 1068 drug products (with or without phthalate) with sale records during the study period. Overall sale of phthalate-containing drugs has declined since 2007 (fig. 2).

We identified 23 drug products (six active substances) containing DBP of which 20 (five active substances) exceeded the maximal daily exposure level of 0.01 mg/kg/day (assuming an intake of 1 DDD/day and a 70-kg adult). See table 1 for results on single substance level. In 2004, 32.5 mg DBP per 1000 inhabitants per day were sold, distributed over five active substances. The sale of DBP-containing drugs peaked in 2006 with 33.7 mg per 1000 inhabitants per day. DBP was removed from all but one product during the study period (fig. 3A). The remaining product (a lithium tablet) containing 7.6 mg of DBP per DDD, sold 4.7 mg per 1000 inhabitants per day in 2015. This formulation accounted for 56.7% of all lithium sold in Denmark in 2015.

Fourteen active substances contained DEP. None of these exceeded the daily exposure limit of 4.0 mg/kg/day (assuming an intake of 1 DDD/day and a 70-kg adult) (table 1). Sale records for DEP-containing drugs went from 18.5 mg per 1000 inhabitants per day in 2004 (spread over 12 active substances) to 7.9 mg per 1000 inhabitants per day in 2015 (eight active substances) (fig. 3A).

For results on the high-molecular phthalates, see fig. 3B and table 1.

Discussion

This is the first population-wide study that quantifies exposure to phthalates from prescription drugs. We demonstrate a substantial sale of low-molecular-weight phthalate-containing products in Denmark, which for lithium, erythromycin and didanosine comprise more than 50% of all sold DDDs. Some patients have been exposed to low-molecular phthalates from their medication to an extent that exceeds current regulatory guidelines. More than 50% of DDDs sold of sulfasalazine, theophylline, pentoxyverine, erythromycin, rabeprazole, dipyridamole combinations and dipyridamole contained high-molecular-weight phthalates.

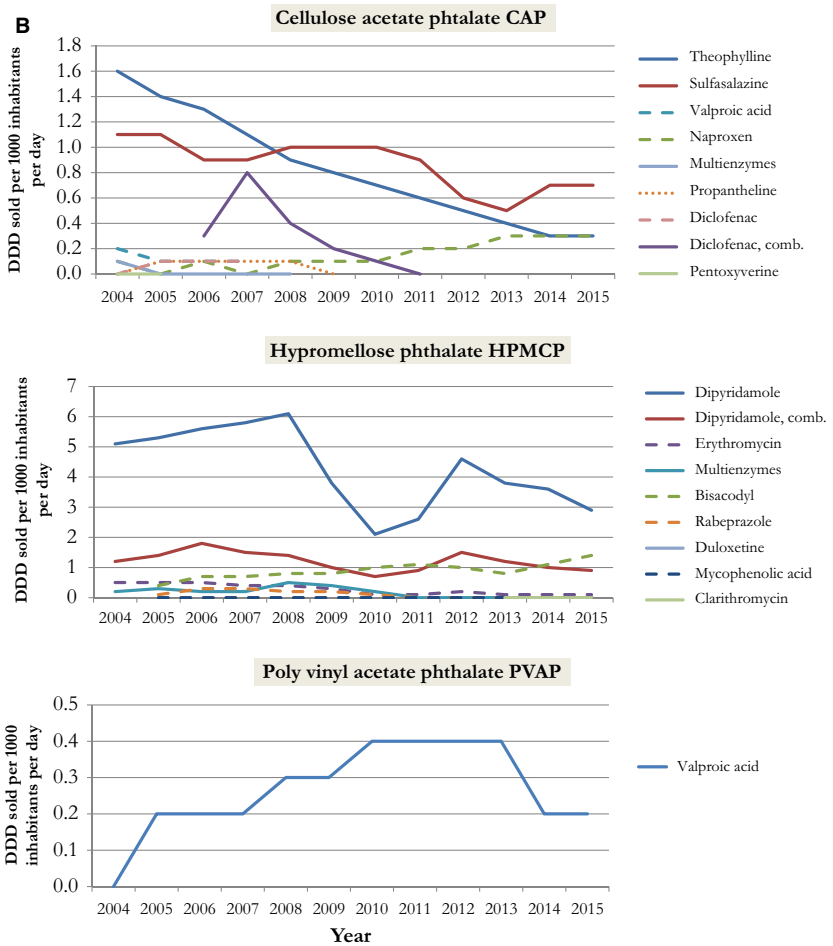

Fig. 3. Continued.

The strength of our study is that it comprises complete nationwide sales data and accounts for product-specific composition with respect to phthalate type and quantity. The main weakness is that the data set contains sales only, and we cannot from these data estimate cumulative exposure at an individual level. The present data are conservative estimate of exposure, as a number of drugs containing phthalates were reformulated after a legislative proposal, aiming to minimize the use of phthalates in medicine, in 2007.

Our results suggest that phthalate exposure from drugs is not negligible compared with environmental exposure. Based on Danish, US and German data, it is estimated that the average adult population exposure of DEP from environmental sources is between 2.3 and 12 μg/kg body-weight daily [13–15]. Especially, patients who are treated with lithium in a formulation containing DBP as excipient are exposed to levels of DBP that exceed regulatory guidelines. As low-molecular-weight phthalate exposure is of concern with respect to adverse effects on human reproduction, consequences of exposure during pregnancy [4,5,16] and potential carcinogenic effects [6–8], we believe that our findings warrant further epidemiological studies based on individual exposure levels.

Conclusion

Sales of phthalate-containing drugs in Denmark from 2004 to 2015 were substantial, and phthalate exposure from several products exceeded the regulatory exposure limit introduced in 2014.

Conflict of interest

None to declare.

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