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Population Exposure to Phthalate-Containing Drugs

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Abstract: Phthalates are known endocrine disruptors. Not commonly recognised, 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 1,000 inhabitants. Specific tablet content was compared with the maximum daily exposure limits defined by regulatory agencies for diethylphthalate (DEP) and dibutylphthalate (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 1,000 inhabitants per day during the study period, respectively. The highest amount of DBP was found in multienzymes (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 recognised, 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 a 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 humans. [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 diethylphthalate (DEP) and dibutylphthalate (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.

Method

We obtained overall sales data including both in- and out-patient 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). Multienzymes (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 were calculated by the Danish Health Data Authority based on Summary of Product Characteristics for each drug product. For multienzymes, one DDD was either 6 capsules of 10,000 EP-e Lipase or 4 capsules of 25,000 or 40,000 EP-e Lipase [12]. However, for diseases with pancreatic insufficiency, e.g. 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.

Data analysis

Analyses were performed separately for low- and high-molecular-weight phthalates. Results for the three high-molecular-weight phthalates CAP, PVAP and HPMCP are presented in Appendix 2-3.

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 1,000 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 1,000 inhabitants per 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 1,000 inhabitants from 2004 to 2015 for each active substance (Table 1).

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 Agency. Of these, 104 products had no marketing approval in Denmark, 1 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 5 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 (6 active substances) containing DBP of which 20 (5 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 1,000 inhabitants per day were sold, distributed over 5 active substances. The sale of DBP-containing drugs peaked in 2006 with 33.7 mg per 1,000 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 1,000 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 1,000 inhabitants per day in 2004 (spread over 12 active substances) to 7.9 mg per 1,000 inhabitants per day in 2015 (8 active substances) (Fig. 3a).

For results on the high-molecular phthalates, see Fig. 3b and Table 1(continued).

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.

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 dataset contains sales only, and we cannot from these data estimate cumulative exposure at an individual level. The present data is a conservative estimate of exposure, as a number of drugs containing phthalates were reformulated following 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 bodyweight 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.

References


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

<table>
<thead>
<tr>
<th>Phthalate</th>
<th>ATC code</th>
<th>Active substance</th>
<th>Phth. Content, Mg/DDD</th>
<th>Phth. content, Mg/Tbl.</th>
<th>DDD/1,000 inhabitants/day (% of total sale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibutyl Phthalate</td>
<td>A09AA02</td>
<td>Multienzymes</td>
<td>24.6 - 32.8&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4.1 - 8.2&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.8 (11 %)</td>
</tr>
<tr>
<td></td>
<td>A07EC02</td>
<td>Mesalazine</td>
<td>12.5 - 26.4&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4.4 - 6.66&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4.1 (15 %)</td>
</tr>
<tr>
<td></td>
<td>A07EA06</td>
<td>Budesonide</td>
<td>12.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0 (&lt;1 %)</td>
</tr>
<tr>
<td></td>
<td>N05AN01</td>
<td>Lithium</td>
<td>7.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.2 (64 %)</td>
</tr>
<tr>
<td></td>
<td>A06AB02</td>
<td>Bisacodyl</td>
<td>1.42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.71&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.0 (14 %)</td>
</tr>
<tr>
<td></td>
<td>M01AB05</td>
<td>Diclofenac</td>
<td>0.51</td>
<td>0.38</td>
<td>1.2 (2 %)</td>
</tr>
<tr>
<td>Diethyl Phthalate</td>
<td>A09AA02</td>
<td>Multienzymes</td>
<td>43.9</td>
<td>7.32</td>
<td>0.1 (3 %)</td>
</tr>
<tr>
<td></td>
<td>J05AF02</td>
<td>Didanosine</td>
<td>12</td>
<td>7.5 - 12</td>
<td>0.0 (84 %)</td>
</tr>
<tr>
<td></td>
<td>M01AE02</td>
<td>Naproxen</td>
<td>10.4</td>
<td>5.22 - 10.4</td>
<td>1.8 (8 %)</td>
</tr>
<tr>
<td></td>
<td>J01FA01</td>
<td>Erythromycin</td>
<td>0.01 - 10.4</td>
<td>0 - 3.91</td>
<td>3.3 (51 %)</td>
</tr>
<tr>
<td></td>
<td>R03DA04</td>
<td>Theophylline</td>
<td>8.45 - 8.46</td>
<td>4.23 - 6.35</td>
<td>5.1 (40 %)</td>
</tr>
<tr>
<td></td>
<td>M01AB05</td>
<td>Diclofenac</td>
<td>1.94 - 6.62</td>
<td>0.97 - 3.31</td>
<td>0.3 (&lt;1 %)</td>
</tr>
<tr>
<td></td>
<td>A02BC05</td>
<td>Esomeprazole</td>
<td>4.57</td>
<td>3.05 - 6.09</td>
<td>0.3 (&lt;1 %)</td>
</tr>
<tr>
<td></td>
<td>M01AB55</td>
<td>Diclofenac, comb.</td>
<td>3</td>
<td>1.5</td>
<td>3.5 (39 %)</td>
</tr>
<tr>
<td></td>
<td>C08DA01</td>
<td>Verapamil</td>
<td>0.24 - 2.94</td>
<td>0.04 - 1.47</td>
<td>5.7 (13 %)</td>
</tr>
<tr>
<td></td>
<td>N06AX03</td>
<td>Mianserin</td>
<td>1.05 - 2.25</td>
<td>0.24 - 1.4</td>
<td>1.5 (14 %)</td>
</tr>
<tr>
<td></td>
<td>N06DA04</td>
<td>Galantamine</td>
<td>2.02</td>
<td>1.01 - 3.02</td>
<td>1.0 (35 %)</td>
</tr>
<tr>
<td></td>
<td>A06AB02</td>
<td>Bisacodyl</td>
<td>0.15 - 0.9</td>
<td>0.45</td>
<td>10.4 (18 %)</td>
</tr>
<tr>
<td></td>
<td>M01AE01</td>
<td>Ibuprofen</td>
<td>0.6 - 0.8</td>
<td>0.1 - 0.4</td>
<td>3.5 (1 %)</td>
</tr>
<tr>
<td></td>
<td>N06AB03</td>
<td>Fluoxetine</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0 (&lt;1 %)</td>
</tr>
</tbody>
</table>

---

a) Range depending on manufacturer and tablet strength  
b) Exceeding permitted daily exposure limit for DBP for a 70-kg adult (0.7 mg/70 kg/day)  
DDD (Daily Defined Dose); Tbl Tablet
### Table 1 (continued): Phthalate content

Content per tablet or capsule and DDD for each active substance, and DDD sold from 2004 until 2015.

<table>
<thead>
<tr>
<th>ATC code</th>
<th>Active substance</th>
<th>Phth. Content Mg/Tbl</th>
<th>Phth. Content Mg/DDD</th>
<th>DDD/1,000 inhabitants/day (% of total sale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N03AG01</td>
<td>Valproic acid</td>
<td>134 – 300</td>
<td>15 - 60</td>
<td>0.5 (3 %)</td>
</tr>
<tr>
<td>A09AA02</td>
<td>Multienzymes</td>
<td>179</td>
<td>29.9</td>
<td>0.1 (3 %)</td>
</tr>
<tr>
<td>A07EC01</td>
<td>Sulfasalazine</td>
<td>96</td>
<td>24</td>
<td>10.4 (61 %)</td>
</tr>
<tr>
<td>R03DA04</td>
<td>Theophylline</td>
<td>33.8 – 56</td>
<td>16.9 - 49</td>
<td>9.9 (79 %)</td>
</tr>
<tr>
<td>M01AE02</td>
<td>Naproxen</td>
<td>41.8</td>
<td>20.9 - 41.8</td>
<td>1.8 (8 %)</td>
</tr>
<tr>
<td>M01AB05</td>
<td>Diclofenac</td>
<td>18.7</td>
<td>9.4</td>
<td>0.3 (1 %)</td>
</tr>
<tr>
<td>M01AB55</td>
<td>Diclofenac, comb.</td>
<td>10.8</td>
<td>5.4</td>
<td>1.8 (20 %)</td>
</tr>
<tr>
<td>A03AB05</td>
<td>Propantheline</td>
<td>1.4 - 2.8</td>
<td>0.35 - 0.71</td>
<td>0.4 (45 %)</td>
</tr>
<tr>
<td>R05DB05</td>
<td>Pentoxyverine</td>
<td>1.6</td>
<td>0.4</td>
<td>0.0 (82 %)</td>
</tr>
<tr>
<td>A09AA02</td>
<td>Multienzymes</td>
<td>292 – 601</td>
<td>48.6 - 150</td>
<td>2.0 (25 %)</td>
</tr>
<tr>
<td>L04AA06</td>
<td>Mycophenolic acid</td>
<td>361 – 467</td>
<td>42 - 65</td>
<td>0.0 (7 %)</td>
</tr>
<tr>
<td>J01FA01</td>
<td>Erythromycin</td>
<td>78.2 – 104</td>
<td>25.9 - 39.1</td>
<td>3.3 (51 %)</td>
</tr>
<tr>
<td>N06AX21</td>
<td>Duloxetine</td>
<td>27.5 - 51.7</td>
<td>12.4 - 51.7</td>
<td>0.9 (3 %)</td>
</tr>
<tr>
<td>A02BC04</td>
<td>Rabeprazole</td>
<td>12 – 17</td>
<td>6.3 - 13.8</td>
<td>1.2 (65 %)</td>
</tr>
<tr>
<td>B01AC30</td>
<td>Dipyridamole, comb.</td>
<td>12.8</td>
<td>6.4</td>
<td>14.5 (61 %)</td>
</tr>
<tr>
<td>B01AC07</td>
<td>Dipyridamole</td>
<td>9.2 - 9.5</td>
<td>4.6 - 4.7</td>
<td>51.3 (77 %)</td>
</tr>
<tr>
<td>A06AB02</td>
<td>Bisacodyl</td>
<td>1.5 - 9.1</td>
<td>4.5</td>
<td>9.8 (17 %)</td>
</tr>
<tr>
<td>J01FA09</td>
<td>Clarithromycin</td>
<td>5</td>
<td>5</td>
<td>0.0 (1 %)</td>
</tr>
<tr>
<td>N03AG01</td>
<td>Valproic acid</td>
<td>208 – 263</td>
<td>17.5 - 69.2</td>
<td>3.2 (17 %)</td>
</tr>
</tbody>
</table>

- a) Range depending on manufacturer and tablet strength
- DDD (Daily Defined Dose); Tbl Tablet
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Figures

Figure 1: Exclusions. Flow chart presentation of drug product exclusions.

- 154 drug products included
- 393 drug products
- 271 drug products
- 93 drug products

Excluded due to missing dates: None
Excluded due to wrong VNR: 1
Excluded due to missing phthalate amount: 17
Excluded due to missing drug product number (not yet marketed in DK): 104

- 5 containing CAP
- 6 containing DBP
- 45 containing DEP
- 48 containing HPMCP

- 271 drug products
- Excluded due to no sale ever in Denmark (not on medstat.dk): 61 drug products
- Excluded due to no sale during study period: 35
- Excluded due to no sale during phthalate containing period: 22

154 drug products included

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Figure 2: Annual amount of phthalate sold. “Total amount of phthalate (mg) (top figure) and DDD (of drugs containing phthalate, bottom figure) sold/1,000 inhabitants/day, specified by type of phthalate”. 
Figure 3a: Amount of DDD sold. DDD sold per 1,000 inhabitants per day in Denmark containing low-molecular-weight phthalates.

**Dicetyl Phthalate DEP**

**Dibutyl Phthalate DBP**
Figure 3b: Amount of DDD sold. DDD sold per 1,000 inhabitants per day in Denmark containing high-molecular-weight phthalates.