Demographic effects on domestic pharmaceutical emissions in Germany

Effets démographiques sur les émissions domestiques des agents pharmaceutiques en Allemagne

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RÉSUMÉ

L'impact des agents pharmaceutiques sur l'environnement aquatique augmente. Une grande partie des agents est émise avec les eaux usées domestiques (STEP, rejets unitaires de temps de pluie, effluents non traités). L'évolution future de la consommation est liée à l'évolution démographique. En Allemagne, comme dans beaucoup de pays européens, on attend deux tendances simultanées : le vieillissement et la diminution de la population. L'objectif de cette étude est d'évaluer les conséquences de cette tendance sur la consommation et sur l'émission de composants pharmaceutiques. La consommation est calculée sur la base des prescriptions à l'échelle nationale par groupes d'âge et par rapport aux prévisions démographiques pour chaque région allemande. Les résultats sont présentés en charge par km² et en utilisant la valeur PEC/PNEC pour les agents pharmaceutiques choisis. Malgré la diminution de la population, les émissions d'agents pharmaceutiques auront tendance à augmenter. Les résultats sont pourtant très différents selon l'agent spécifique, la situation démographique actuelle et son évolution future. Le facteur majeur est la densité de la population. Dans les régions qui attendent une diminution de la population on peut observer deux tendances : les agents pharmaceutiques principalement consommés par la population âgée vont être émis en quantité supérieure et d'autres, comme les antibiotiques, vont diminuer. Dans les régions en croissance, l'émission de tous les agents pharmaceutiques va augmenter. La valeur PEC/PNEC peut aider à identifier les substances les plus importantes. Pour chaque situation spécifique, il faut toujours prendre simultanément en compte la valeur PEC/PNEC et la charge pour éviter des conclusions erronées.

ABSTRACT

Pharmaceutical compounds are of increasing relevance for the aquatic environment. A large share of these compounds is emitted via domestic waste water (WWTP, CSO, untreated discharges). The future development of consumption and discharge is to a large extent a function of the demographic development. In Germany as in many other European countries, the population is aging and at the same time decreasing. This study intends to quantify the effect of these trends on pharmaceutical emissions. The calculation is based on nationwide data of prescribed pharmaceuticals per age group and demographic forecasts on a district level. The results are given for selected API as square specific loads and as PEC/PNEC values. As a trend, the emissions of pharmaceuticals will increase although the population is decreasing. However, results differ significantly depending on the regarded ingredient, the current demographic status and its further development. Thereby population density is the governing factor. Emission of API predominantly used by elderly people will increase even in regions with decreasing population while others (e.g. antibiotics) will decrease. In areas of growth emission of all pharmaceuticals will increase. PEC/PNEC values can help to screen the most relevant API. For site specific assessments they should always be regarded in conjunction with loads to avoid misleading interpretations.

KEYWORDS

Pharmaceuticals, demography, environmental risk assessment, emission, wastewater
1 INTRODUCTION

Pharmaceuticals in the aquatic environment are subject of an increasing discussion in public and science (Schwarzenbach et al., 2006, Ashauer et al. 2007, Carlsson et al., 2007). Especially the topics of estrogenic disruptors (e.g. Kidd et al., 2007, Burkhardt et al., 2008), the observed increasing antibiotic resistance (Kümmerer and Henninger., 2003) and highly toxic zytostacics are currently in focus.

So far, only few pharmaceutical agents are included in the priority substances list of the European Water Framework Directive (EU, 2008). Resulting from a thorough measurement campaign in the federal state of Saxony (Germany) it has been shown that out of 51 pharmaceutical substances under review 33 were relevant for water bodies (Engelmann & Rohde, 2009). The identified main emission paths were wastewater treatment plants (WWTP), households without sewer connection, agricultural discharges and aquacultures. Storm water effluents and CSO structures have shown to be less relevant. Still they must be evaluated to account for case specific characteristics.

The future development of pharmaceutical use and related emissions must be observed depending on the deep reaching demographic change as foreseen in many European countries. In fact, the population number is in general decreasing while the average age of the population is rising. This leads to a contradictory effect on pharmaceutical consumption, that is decreasing inhabitants and in tendency higher per capita consumption due to obsolescence. In Germany, people above age 65 represent 12 percent of the total population but contribute 43 percent to the sales of pharmaceuticals (Coca et al., 2008). These figures cannot be extrapolated directly to the different active pharmaceutical ingredients (API) since the consumption of selected API is highly age specific. Still the question is imposed if the expected age driven increase of per capita consumption overcompensates the predicted decrease of population.

Therefore the objective for this survey is to predict the future pharmaceutical emission in Germany by domestic wastewater based on sound data. For this, data from the German compulsory health insurance system has been combined with demographic forecasts on district level.

2 METHOD

In Europe, environmental risk assessment (ERA) of pharmaceuticals is mainly based on the exposure models provided by EMEA (2006) and the assessment programme EUSES (EC 2004). The EMEA approach is a crude assessment based on a comparison of Predicted (i.e. modelled) Environmental Concentration (PEC) and a so called Predicted Non-Effect concentration (PNEC). Within the development process of the EMEA guideline various models have been proposed for the PEC assessment. Derived from a comparison among those proposals (including EUSES) Ternes & Joss (2006) suggested an approach for initial exposure assessment as shown by equation 1.

$$ PEC_{SW} = \frac{L}{365 \cdot P \cdot V \cdot D} \cdot (1 - R) $$

In equation 1, \( L \) is the predicted use/prescription amount per year [kg·a\(^{-1}\)], \( R \) is a removal rate (e.g. biodegradation and/or absorption) [-], \( P \) reflects the number of inhabitants of the geographic area considered [cap], \( V \) is the volume of waste water per capita and day [m\(^3\)·cap·d\(^{-1}\)], and \( D \) is factor for dilution of waste water by surface water. It has to be noted that excretion ratios are not considered. If data on degradation are missing, this value is set to zero (Ternes & Joss, 2006).

The PNEC values are extrapolated from a standard set of toxicity tests for the aquatic compartment. These tests are usually assessed for the three trophic levels: algae (producer), daphnia (primary consumer) and fish (secondary consumers), with the lowest concentration being relevant. To account for inter-species variations of differences in sensitivity, intra-species variability and laboratory data to field impact extrapolation an uncertainty factor in the range of 10 to 1000 is applied (EMEA, 2006, Straub, 2002).

To investigate demographic effects equation 1 has been extended by expressing the predicted use/prescription (\( L \)) as function of population, age distribution and age dependent API consumption patterns.
In Germany the yearly number of prescribed daily doses (DDD) per active pharmaceutical ingredient (API) is published annually for all members of the compulsory health insurance. For this study the data of 2007 have been used (Schwabe & Paffrath, 2008). The unit DDD represents the defined mass of a specific API \([\text{mg} \cdot \text{d}^{-1}]\) suggested for standard therapeutical applications of adults according to the Anatomical Therapeutic Chemical (ATC) classification of the WHO, with some national modifications (DIMDI, 2007).

Additionally age specific consumption patterns for the year 2007 specified for 19 age groups are published by Coca et al., 2008. Those consumption patterns are available only on the level of API groups summarising ingredients applied for similar therapeutical indications (e.g. analgetica, sex hormones, gout ingredients). Therefore calculations within this study have been done by the assumption that all API within each group follow the consumption pattern of the overall group. In such cases that a single API is listed by more than one API group (i.e used for different therapeutical indications) the consumption pattern of the respective API group has been applied.

Data on number of population from 1990 and as forecast up to year 2020 on district level with an age resolution of three classes (younger than 20, between 20 and 60, 60 and older) has been used from BBR (2006). The data on original 19 age groups for the pharmaceutical consumption have been aggregated according to these three classes.

The yearly prescribed mass per capita \((a)\) and age group \((i)\) is calculated by relating the age specific ratio of DDD to the number of insured persons \((\text{IP})\) of this age group (equation 2).

\[
a_{i,\text{API}} = \frac{\text{DDD}_{i,\text{API}} \cdot d_{i} \cdot \text{IP}_{\text{total}}}{\sum \text{DDD}_{i,\text{API-group}}} \quad \text{[kg API-cap}^{-1}\text{a}^{-1}] \tag{2}
\]

In 2007, 50.74 Mio. people were insured in the German compulsory health insurance system (KBV, 2008). The age distribution \((d_{i})\) for the respective year over all inhabitants according to the three age groups was 20.0, 55.1, and 24.9 percent.

Assuming the age specific consumption per capita as fixed, the estimated API consumption \((L)\) per district \((j)\) and year \((k)\) is calculated by equation 3. The number of inhabitants and age group \(P_{j,k,i}\) are taken from BBR (2006).

\[
L_{j,k,\text{API}} = \sum_{i=1}^{3} P_{j,k,i} \cdot a_{i,\text{API}} \tag{3}
\]

To assess emission loads for untreated and treated wastewater excretion and WWTP degradation rates have been compiled based on a comprehensive literature review. Excretion rates have been derived from Kümmerer and Henninger (2003), LANUV (2007), LUA (2002), SRU (2007), Winker and Behrendt (2009), Wiegel et al. (2003). Degradation rates have been derived from LUA (2002), LANUV (2007), Wiegel et al. (2003), Winker and Behrendt (2009), Ivasheshkin (2006), Heberer (2002), Schröder (2003).

The excreted load \((L_{\text{ex}})\) and the effluent load of a conventional biological treatment plant \((L_{\text{eff}})\) have been calculated using equation 4 and 5.

\[
L_{\text{ex},j,k,\text{API}} = L_{j,k,\text{API}} \cdot r_{\text{ex}} \tag{4}
\]

\[
L_{\text{eff},j,k,\text{API}} = L_{\text{ex},j,k,\text{API}} \cdot \left(1 - r_{\text{deg}}\right) \tag{5}
\]

The resulting Predicted Effluent Concentration with and without treatment, PEC and PEC*, are derived by dividing the respective load by total water consumption of each district (equation 6 and 7). Total water consumption per district \((j)\) and year \((k)\) is based on the specific drinking water demand \(q\) (in 2004) and inhabitants \(P_{j,k}\) (Statistisches Bundesamt, 2009). In contrast to equation 1, no fixed dilution factor has been applied. The influence of extraneous water has not been considered.
Finally the environmental relevance has been asssed by the ratio of PEC to published PNEC (compiled for a literature review (Borkmann, 2008)). By omitting a fixed dilution factor the ratio itself represents a necessary dilution in unpolluted water to reach a harmless environmental concentration. The described procedure has been applied on 34 API for which the required data were available.

3 RESULTS

For the sake of simplicity results from three representatives out of all API are exemplarily discussed. Additionally three districts (Erding, Börde and the city of Gera) with significantly different demographic situations have been selected out of 413.

The hormone Estriol is prescribed for different purposes and so listed twice as sex hormone for birth control and as gynaecologic drug to mitigate hormone deficiency of mainly elderly women. Amoxicillin is an antibiotic with a homogeneous consumption pattern across age groups. Bezafibrat is an antilipidemic drug and is representing a typical ingredient predominantly used by elderly people. For exact numbers regarding consumption patterns see table 1.

Among all districts in Germany Erding (near Munich) is the district with the expected highest population growth until the year 2020. In contrast, Gera is facing a decrease of more than 30 percent from 1990 and 2020. The population number of district Börde is expected to remain constant. True for all districts is an increase of people older than 60 years resulting in an increase of mean age. The applied specific water consumption in 2004 for Erding, Gera, and Börde was 122, 107, and 184 L\( \text{cap}^{-1} \text{d}^{-1} \) respectively (Statistisches Bundesamt, 2009).

<table>
<thead>
<tr>
<th>Active ingredient group</th>
<th>No. of prescribed DDD (2007)</th>
<th>relative per capita consumption compared to mean [Mio.]</th>
<th>Age group</th>
<th>0 - &lt; 20</th>
<th>20 - &lt; 60</th>
<th>&gt; 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex hormones</td>
<td>6.5</td>
<td>2.17</td>
<td>0.67</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecologics</td>
<td>205.0</td>
<td>0.16</td>
<td>0.63</td>
<td>2.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics, Antiinfecting drugs</td>
<td>78.4</td>
<td>1.12</td>
<td>0.95</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antilipidemic drugs</td>
<td>18.0</td>
<td>0.00</td>
<td>0.49</td>
<td>2.93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Total consumption of selected in ingredients groups and its distribution over age groups

<table>
<thead>
<tr>
<th>API</th>
<th>API group</th>
<th>DDD</th>
<th>max</th>
<th>min</th>
<th>min</th>
<th>max</th>
<th>min</th>
<th>max</th>
<th>Excretion</th>
<th>elimination at WWTP</th>
<th>PNEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estriol</td>
<td>Sex hormones, Gynecologics</td>
<td>0.0002</td>
<td>33</td>
<td>33</td>
<td>50</td>
<td>94</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Antibiotics, Antiinfecting drug</td>
<td>1.0</td>
<td>98</td>
<td>50</td>
<td>17</td>
<td>64</td>
<td>0.0037</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bezafibrat</td>
<td>Antilipidemic drug</td>
<td>0.6</td>
<td>50</td>
<td>47</td>
<td>9</td>
<td>99</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Input parameters for Estriol, Amoxicillin and Bezafibrat

The used input parameters of the three API are listed in table 2. The minimal and maximal values can differ over a wide range. This applies especially to PNEC values which are often selected differently in the literature. Here, the lowest value for Amoxicillin (Kümmerer, 2008) is derived from the EC\(_{50}\) value.
for the Algae species *M. aeruginosa*, where the highest value (Thompson, 2005) is derived from quantitative-structure activity relationships (QSAR), a method applied when neither NOEC nor acute toxicity values are available. The uncertainty related to PNEC values will probably be reduced with increasing application of the long term toxicity tests suggested by EMEA (2006). However, with regard to potential antagonistic and synergistic effects of mixtures of compounds it becomes questionable if a generally applicable and widely accepted set of PNEC value for certain pollutants can be agreed and satisfactorily applied to assess their environmental relevance for a specific water body (Silva et al., 2002).

To account for uncertainties, predictions are calculated as range of extremes. PECmax is calculated with maximal excretion rates and minimal elimination rates and PECmin with the opposite assumptions. The same applies for PEC/PNEC ratios ranging from PECmin/PNECmax as optimistic prediction to PECmax/PNECmin as worst case.

For the time span from 1990 to 2020 the development of emission loads *L* per square kilometre for the selected API and districts are shown in figure 1. Due to an increase of inhabitants above 60 years for all considered districts an increase of Bezafibrat loads is expected in all three cases. For the city of Gera the increasing obsolescence clearly more than compensates the decreasing number of inhabitants regarding Bezafibrat.

The effect of demographic composition on emission load of sex hormones is expected to follow the development of younger people, sexual active people. However, sex hormones are not only applied for birth control but also as gynaecologic for elderly people. This way the reduction of Estriol is far less than the expected from the decrease of young and mid-age group in the case of Gera. In Börde and Erding the load increases by 30% and 80%, respectively.

Since the consumption of Antibiotics is nearly equally distributed throughout all age groups its development correlates directly with the population number. As expected it increases in Erding, decreases in Gera and varies only to small extent in the district Börde.

Calculated loads per square kilometer for the selected pharmaceuticals (in 2007) and predicted changes until 2020 for all 413 districts of Germany are plotted in figure 2. It is obvious that population density is the most relevant factor for the degree of emission. Hot spots are major cities and the densely populated Rhein-Ruhr-region. Rural areas are less concerned. As illustrated above, the relative development varies between observed API. Amoxicillin reflects the absolute population.

![Figure 1: Development of emissions per square kilometre for selected API in districts](image-url)
dynamics. Generally, the emission tends to decrease. In the areas of growth (larger coastal cities, Bavaria, and Baden-Württemberg) a slight increase can be expected. The corona around Berlin shows the ongoing expansion from the capital into the outer districts. Estriol and Bezafibrate loads increase in all cases even in regions with decreasing population. In growth regions aging and increasing population number superimpose and result in significant higher emissions.

Summarising the calculated nationwide range of PEC/PNEC values for all 34 investigated API are shown in Figure 3. Each API is represented by two box plots, a grey coloured box referring to PEC to PNEC ratios in 2007 and above a white coloured box referring to expected PEC to PNEC ratios in 2020.
Figure 3: Average PECmax/PNECmin and PECmin/PNECmax values for Germany in 2007 and predicted for 2020

It is obvious that crossing the minimal and maximal extremes for PEC and PNEC changes the ranking regarding relevance. The uncertainty of the input parameters leads in some cases to some orders of magnitude difference. Focussing on the safety oriented PECmax/PNECmin the emission of hormones, antibiotics and analgesics are most critical. In the German average the consumption of antibiotics will slightly decrease, hormones and analgesics are in tendency increasing. However, in the German average the effect of demography is rather low. If discussing advanced treatment technologies to eliminate pharmaceuticals in WWTPs the approach may help to screen for potential actual and future hot spots and key substances.

4 CONCLUSIONS

The applied method allowed a distinct prognosis on pharmaceutical ingredient emissions taking in to account boundary conditions on district level. Regarding the area specific loads, it can be distinguished between the hot spots with high population density and in opposite rural areas. The expected demographic development does not change this picture significantly. In fact, the current hot spots are often the centres of growth with increasing population whereas the rural areas loose inhabitants. However even for areas with further decrease of population the emission of some pharmaceuticals will increase due to obsolescence. Only areas with currently high average age and advancing decrease of population will actually emit less pharmaceuticals.

PEC to PNEC ratios with predefined fixed dilution factors do not consider specific local conditions. Here, rural regions with low specific water consumption would be identified as more severe than areas with high population density. In this study PEC to PNEC ratios are preliminary used to normalise the data and to achieve a ranking of environmental relevance.

For German conditions it can be summarised that advancing obsolescence tends to compensate the decrease of inhabitants, resulting in a further increase of pharmaceutical emissions.

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