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Occurrence and fate of the antidiabetic drug metformin and its metabolite guanylurea in the environment and during drinking water treatment

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ABSTRACT

Metformin, an antidiabetic drug with one of the highest consumption rates of all pharmaceuticals worldwide, is biologically degraded to guanylurea in wastewater treatment plants. Due to high metformin influent concentrations of up to 100 μg/L and its high but incomplete degradation both compounds are released in considerable amounts of up to several tens of μg/L into recipient rivers. This is the first systematic study on their environmental fate and the effectiveness of treatment techniques applied in waterworks to remove metformin and guanylurea from surface water influenced raw waters. The concentrations in surface waters depend strongly on the respective wastewater burden of rivers and creeks and are typically in the range of about 1 μg/L for metformin and several μg/L for guanylurea but can reach elevated average concentrations of more than 3 and 20 μg/L, respectively. Treatment techniques applied in waterworks were investigated by an extended monitoring program in three facilities and accompanied by laboratory-scale batch tests. Flocculation and activated carbon filtration proved to be ineffective for removal of metformin and guanylurea. During ozonation and chlorination experiments with waterworks-relevant ozone and chlorine doses they were partly transformed to yet unknown compounds. The effectiveness of the treatment steps under investigation can be ordered chlorination > ozonation > activated carbon filtration > flocculation. However, most effective for removal of both compounds at the three full-scale waterworks studied proved to be an underground passage (riverbank filtration or artificial groundwater recharge). A biological degradation is most likely as sorption can be neglected. This is based on laboratory batch tests conducted with three different soil materials according to OECD guideline 106. Since such treatment steps were implemented in all three drinking water treatment plants, even traces of metformin and its metabolite guanylurea could not be detected at the end of the treatment trains. Both can only be expected in finished drinking water if surface influenced raw water is used by direct abstraction without underground passage.

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1. Introduction

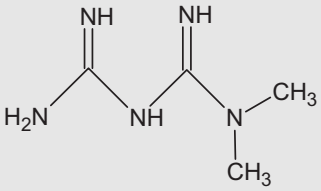
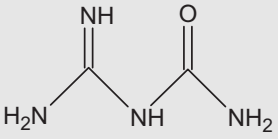
Organic compounds like pharmaceuticals and hormones were detected for the first time in aqueous environmental matrices more than a decade ago. However, the approval and market launch of new compounds, as well as the continuous improvement of sensitive analytical instruments, leaves sparsely investigated and only recently detected compounds. A widely cited biennial review about trends and developments in water analysis for emerging environmental contaminants highlights the enduring actuality of the issue (Richardson, 2009; Richardson and Ternes, 2011). It should be assumed that widely used pharmaceuticals with high prescription rates and consumption volumes are well researched. Interestingly, one of the most prescribed pharmaceuticals by mass, the antidiabetic drug metformin, is still poorly investigated in terms of environmental fate and drinking water relevance. The number of people suffering from diabetes accounts for more than 360 million on a worldwide scale, with about half of them undiagnosed cases. According to the International Diabetes Federation, diabetes caused 4.6 million deaths in 2011 and Type 2 diabetes is increasing in every country (IDF, 2011). In Germany alone prescription rates of metformin almost tripled in the last 10 years to 547 million defined daily doses (DDD) of the pure compound accounting for almost 1100 tons in 2010 (WHO, 2012; Mengel, 2011). Metformin is an orally administered drug with an average dose of 2 g per day (WHO, 2012). The compound is not metabolized in humans and the resorbed fraction (about 70%) is excreted unchanged in urine, the rest in feces (Pentikäinen et al., 1979; Liebl and Martin, 2005). Based on its pharmacokinetics, it is not surprising that high metformin concentrations in wastewater treatment plant (WWTP) influents of 3.5–88 μg/L were predicted for five WWTPs in Virginia/USA (Ottmar et al., 2010). van Nuijs et al. (2010) reported measured concentrations in 18 Belgian WWTPs between 20 and 94 μg/L, which is in the same range as published values for German WWTP influents of 101–129 μg/L (Scheurer et al., 2009, three facilities) and 57 μg/L (Trautwein and Kümmerer, 2011). The two German studies are the only ones reporting the behavior of metformin during wastewater treatment and give similar removal rates of 90% or higher. A recently published article identified guanylurea as the only recalcitrant, aerobic, bacterial degradation product of metformin, but effluent concentrations of guanylurea could not completely account for the removed fraction of metformin (Trautwein and Kümmerer, 2011). For recipient waters, maximum concentrations of the parent drug metformin of 150 ng/L were reported in US streams (Kolpin et al., 2002) and from about 100 ng/L in the lower River Rhine to 1700 ng/L in the Elbe River (Scheurer et al., 2009). The largest screening of metformin was performed in the Rhône-Alpes region, where 71 surface water and 70 groundwater samples were analyzed (maximum concentration of 735 ng/L) (Vulliet and Cren-Olive, 2011). No data at all are reported so far for the environmental fate of guanylurea.

Information about the ecotoxicologigal relevance of both compounds is scarce. For metformin a LC_{50} value of >982 mg/L for *Lepomis macrochirus* and an EC_{50} value of 130 mg/L for *Daphnia magna* were reported (RIVM, 2005; Greenstone LLC, 2009). Caminada et al. (2006) observed no in vitro cytotoxicity for metformin hydrochloride in two tests with fish cell lines at the highest concentration tested (413 mg/L). Guanylurea showed no toxic effects on the bacterial community in a manometric respiratory test at a concentration of 11.9 mg/L (Trautwein and Kümmerer, 2011).

Both metformin and its metabolite are extremely polar compounds (Table 1) which should be very mobile in the aquatic environment. Therefore, a certain degree of drinking water relevance cannot be excluded as they might be present in raw waters used for drinking water production.

This paper provides data on the direct transformation of metformin into guanylurea in WWTPs, the respective effluent concentrations of both compounds and the resulting concentrations in recipient waters. Furthermore, first detailed information based on field studies and laboratory batch tests about the behavior of metformin and guanylurea during drinking water production is given.

Table 1 – Chemical structures of metformin and guanylurea with chemical and molecular formulas and molecular weight.

	Metformin	Guanylurea
Chemical formula		
Molecular formula	$C_4H_{11}N_5$	$C_2H_6N_4O$
Molecular weight in g/mol	129.2	102.1
pK[a]	10.3 and 12.3	8.0 and 13.5

a Calculated using pKa calculation software provided by ChemAxon Ltd. (2012).