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Veterinary antibiotics used in animal agriculture as NDMA precursors

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HIGHLIGHTS

- NDMA may be formed by the reaction of chloramines with veterinary antibiotics.
- Antibiotics with two dimethylamine groups formed disproportionately more NDMA.
- Agricultural run-off may be a source of NDMA formation.

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ABSTRACT

The formation of carcinogenic *N*-nitrosodimethylamine (NDMA) during chloramination at drinking water treatment plants has raised concerns as more plants have switched from chlorine to chloramine disinfection. In this study, a source of NDMA precursors that has yet to be investigated was examined. Veterinary antibiotics are used in large quantities at animal agricultural operations. They may contaminate drinking water sources and may not be removed during wastewater and drinking water treatment. Ten antibiotics used in animal agriculture were shown to produce NDMA or *N*-nitrosodiethylamine (NDEA) during chloramination. Molar conversions ranged from 0.04 to 4.9 percent, with antibiotics containing more than one dimethylamine (DMA) functional group forming significantly more NDMA. The highest formation for most of the compounds was seen near pH 8.4, in a range of pH 6 to 11 that was investigated. The effect of chlorine-to-ammonia ratio (Cl_2/NH_3), temperature, and hold time varied for each chemical, suggesting that the effects of these parameters were compound-specific.

1. Introduction

N-Nitrosodimethylamine (NDMA) is a disinfection byproduct that can be formed during drinking water treatment. It is preferentially formed by chloramines (Schreiber and Mitch, 2006). The use of chloramines during drinking water treatment has increased in recent years as regulation of chlorine disinfection byproducts has resulted in many treatment plants switching to the use of alternative disinfectants (Seidel et al., 2005). Precursors of NDMA are varied and diverse; however, they are typically secondary, tertiary or quaternary amines (Krasner et al., 2013). Known sources of precursors include certain human pharmaceuticals and personal care products (PPCPs), pesticides and herbicides, soluble microbial products, polymers used during water treatment, and wastewater treatment plant effluent (Shen and Andrews, 2011a; Farré et al., 2016; Sgroi et al., 2014; Hanigan et al., 2015; Park et al., 2015; Chen and Young, 2008; Le Roux et al., 2011).

The U.S. Environmental Protection Agency's (USEPA) Integrated Risk Information System (IRIS) database classifies NDMA and five other nitrosamines as carcinogenic with low ng/L levels being associated with a 10^{-6} lifetime cancer risk. California currently has a notification level for NDMA and two other nitrosamines at 10 ng/L each and a Public Health Goal at 3 ng/L (CDPH, 2009; OEHHA, 2006). Other nitrosamines can be formed during chloramination; however, NDMA was the most frequently detected nitrosamine in drinking water during the USEPA's Unregulated Contaminant Monitoring Rule 2 monitoring program (USEPA, 2012).

NDMA precursors have been found in wastewater-impacted drinking water supplies (Guo and Krasner, 2009). Certain PPCPs in the wastewater discharges are believed to be an important source of the precursors (Shen and Andrews, 2011a). More recently,

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NDMA precursors were found to increase in concentration during runoff events in certain watersheds (Krasner et al., 2015) . During run-off, the percent contribution of wastewater to the steams was lower, based on lower concentrations of the wastewater indicator sucralose, an artificial sweetener. This suggests that other sources of NDMA precursors could be in these watersheds. Combined sewer overflows could be a source of NDMA precursors, but they would also be a source of sucralose. One possible source of NDMA precursors that would be present when NDMA FP is high, but wastewater contribution is low could be veterinary antibiotics from animal agriculture operations.

The majority of all antibiotics distributed in the United States are used on animals farmed for human consumption. In 2011, the U.S. Food and Drug Administration reported that 29.9 million pounds were used on farmed animals or 80.5 percent of the total antibiotics consumed in the U.S. (FDA, 2011; Health and Human Services, 2012). Antibiotics are frequently used in the treatment of disease and as a component of animal feed to serve as growth promoters (Cohen, 1998). The usage of antibiotics in animal feed increased by almost 8 percent from 2009 to 2011 (FDA, 2011, 2009).

Veterinary antibiotics used in large-scale farming operations can contaminate water sources through the disposal of unused or expired compounds, via overland flow runoff, in unsaturated zone transport on fields in which agricultural waste has been applied, and via leaky waste-storage structures (Sarmah et al., 2006). Poor absorption in the guts of farm animals may result in up to 95 percent of a veterinary antibiotic being excreted as the parent compound (Elmund et al., 1971; Magnussen et al., 1991; Beconi-Barker et al., 1996; Hirsch et al., 1999). Additionally, metabolites of antibiotics that still contain dimethylamine functional groups may also be NDMA precursors. Tetracycline, when excreted, contains 5% as its metabolite, Δ-epitetracycline (Agwuh and MacGowan, 2006). This compound still contains a dimethylamine functional group which is capable of completing the NDMA formation reaction and thus, likely, an NDMA precursor itself. Additionally, metabolites of the antibiotic may be capable of being transformed back to the parent compound in the environment (Sarmah et al., 2006). As a result, the occurrence of veterinary antibiotics in the environment, especially near large-scale agricultural operations, is likely.

Antibiotics used in animal agriculture have been detected in surface waters, wastewater treatment plant effluents, and groundwater in North America, Europe, and Australia (Table 1). The stability of tetracycline in animal slurry solutions, even during changes in temperature and aeration through repeated stirring, may result in a large amount of the antibiotic being transferred to the environment via manure application (Winckler and Grafe, 2001). Different physico-chemical properties of veterinary antibiotics impact their ability to sorb to soils or sediments and determine their mobility in soil/water systems. Sorption of antibiotics to clay sorbents can be pH-dependent and may be reduced in the presence of dissolved organic matter, which may increase mobility (Kulshrestha et al., 2004; Aga et al., 2003). The sorption of these compounds to dissolved organic matter may both increase their mobility and decrease their ability to be biodegraded.

Veterinary antibiotics have frequently been found in wastewater treatment plant effluents, as well as drinking water treatment plant influents (Ternes, 1998; Alexy et al., 2006; Miao et al., 2004; Golet et al., 2001; McArdell et al., 2003; Stackelberg et al., 2004; Giger et al., 2003). Antibiotic removal during wastewater treatment is largely dependent on the ability of the individual antibiotic to be biodegraded and to be sorbed by activated sludge. Tests using wastewater bacteria support the idea that many antibiotics are not likely biodegraded during secondary wastewater treatment (Al-Ahmad et al., 1999; Kümmerer et al., 2000; Alexy et al., 2004).

However, antibiotics with higher sorption coefficients, such as tetracyclines, may be substantially removed during the activated sludge process (Kim et al., 2005). Additionally, organic matter in wastewater effluent may become a mode of transportation for sorbed antibiotics (Ternes, 1998). In a study of antibiotics present downstream from a wastewater treatment plant, the concentration of antibiotics or degradation products remained relatively static up to 3 km away from the plant, indicating that the stream served as a transport mechanism and would be an inadequate method for removing compounds (Haggard and Bartsch, 2009).

In drinking water treatment plant studies, PPCPs, including some antibiotics, have been shown to be poorly removed during coagulation or during lime softening (Westerhoff et al., 2005;

Table 1
Concentrations of antibiotics found in the environment.

Antibiotic	Wastewater effluent (ng/L)	Surface water (ng/L)	Ground water (ng/L)	Country	Reference
Clarithromycin	328	65		Switzerland	(Giger et al., 2003)
		600			(Göbel et al., 2007)
	350	380			(Göbel et al., 2007)
	240	260		Germany	(Hirsch et al., 1999)
		37			(Christian et al., 2003)
	38				(Alexy et al., 2006)
		20.3		Italy	(Calamari et al., 2003)
Spiramycin		74.2		Italy	(Calamari et al., 2003)
Tetracycline	20	1		Germany	(Färber and Färber, 2002)
		5		USA	(Arikan et al., 2008)
	300	1200			(Karthikeyan and Meyer, 2006)
		53			(Haggard and Bartsch, 2009)
		110			(Kolpin et al., 2002)
			400		(Krapac et al., 2001)
	977			Canada	(Miao et al., 2004)
	30	35		Australia	(Watkinson et al., 2007)
Oxytetracycline		340		USA	(Kolpin et al., 2002)
		47	388		(Arikan et al., 2008)
		20			(Haggard and Bartsch, 2009)
	20			Australia	(Watkinson et al., 2007)
		32,000		UK	(Kay et al., 2005)
Tetracycline + Oxytetracycline		2000		USA	(Campagnolo et al., 2002)