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Methadone Contributes to *N*-nitrosodimethylamine Formation in Surface Waters and Wastewaters during Chloramination

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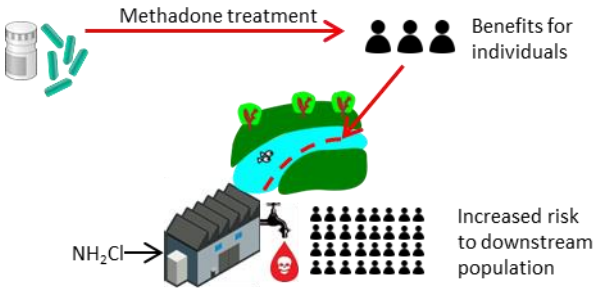

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1 Abstract

N-nitrosodimethylamine (NDMA) is a probable human carcinogen that forms in drinking water as a disinfection by-product. Several specific precursor chemicals present during chloramination are known but cannot account for the total observed NDMA formation potential (FP) in drinking waters. We discovered a pharmaceutical precursor of NDMA with high FP using a liquid chromatography/quadrupole/time-of-flight mass spectrometry (LC/QTOF-MS) screening procedure. The pharmaceutical methadone, which is used to mitigate heroin withdrawal symptoms and is also prescribed for chronic pain, contains a dimethylisopropylamine functional group that reacts to form high amounts of NDMA upon chloramination. In this study, methadone had a molar NDMA yield ranging from 23% to 70% dependent upon chloramine dose (1 to 150 mgCl_2/L) and was responsible for between 1 and 10% of NDMA FP in most raw surface waters in which it was detected and up to 62% of NDMA FP in wastewater. Samples with higher methadone concentrations had greater NDMA FP. We measured a median methadone concentration of 23 ng/L with a range of 1 to 2,256 ng/L among detections, which was consistent with high occurrence rates and environmental persistence for methadone in the published literature for surface waters and wastewaters. A literature review of methadone use, metabolism, and fate in the U.S. resulted in a prediction of low ng/L levels of methadone-associated NDMA FP at drinking water treatment plants (DWTPs) downstream of communities using methadone. Medicinal use of methadone potentially displaces and transforms the health risks associated with heroin use by individuals to possible cancer risk for populations served by downstream DWTPs. This work is among the first to contrast known public health benefits of pharmaceutical-taking patients against the potential exposure of millions of people to physiologically-relevant levels of carcinogenic NDMA in chloraminated drinking water.

2 Introduction

N-nitrosodimethylamine (NDMA) is a disinfection by-product (DBP) of regulatory concern due to its carcinogenic potential and occurrence.[1,2] Health Canada, Massachusetts, and California have set regulatory limits, guidance limits, or notification levels in the 10 to 40 ng/L range.[3-5] NDMA forms in drinking water from a reaction between chloramines and predominantly unidentified organic nitrogen precursors, and these precursors appear to be strongly linked with the presence of treated wastewater.[6,7] While several model compounds produce NDMA upon chloramination,[8-12] either their NDMA yields are low or the occurrence is too low at the point of chloramination to account for NDMA formation.[7,13] The only current options to remove NDMA precursors in drinking water treatment plants (DWTPs) are nonselective control strategies (e.g., activated carbon or pre-oxidation), which are potentially cost prohibitive or confounded by unintended consequences such as formation of other DBPs.[14] Without knowledge of precursor chemical structures and characteristics, mitigation strategies for NDMA formation in DWTPs are difficult to optimize.

Current research regarding NDMA precursors is limited to applying chloramines to model compounds that contain organic nitrogen. Wastewater is well known to contain higher amounts of NDMA precursors,[6] and thus there has been a significant effort to identify pharmaceutical and personal care products present in wastewater that are NDMA precursors.[11] Other research has focused on agricultural runoff and led to the discovery that diuron, a herbicide, produces NDMA upon chloramination.[15] This approach has led to discovery of multiple NDMA precursors with a range of molar NDMA yields but the occurrence of such compounds in DWTP intakes is either unknown or not great enough to account for a significant fraction of the total NDMA formation potential (FP) of the water.[13] For example, ranitidine has high NDMA yield upon chloramination

but no occurrence, and dimethylamine has high occurrence but is only responsible for low ng/L levels of NDMA due to low NDMA yield. However, both the occurrence of anthropogenic chemicals in the environment[16] and the wastewater content in U.S. surface water are increasing,[17] and therefore it is likely that NDMA precursor loadings will consequently increase. In addition, 22% of the U.S. population was served with chloraminated drinking water in 2010, an increased from 19% in 2007.[18] Thus, discovering NDMA precursors with moderate to high yield that are likely to occur in surface water could lead to targeted treatment strategies that reduce NDMA formation and thus cancer risk to end users of chloraminated drinking water.

Methadone is a pharmaceutical that contains organic nitrogen (tertiary amine) and is typically used to treat heroin addiction but is becoming more commonly prescribed for chronic non-cancer pain and to mitigate withdrawal symptoms associated with prescription opiates (e.g., morphine).[19] In the U.S. in 2009, 4.4 million methadone prescriptions (approximately 1.5/100 U.S. persons) were issued, which includes only methadone distributed for pain relief and not to substance abuse treatment centers.[19,20] In 2013, there were 330,308 persons (approximately 1/1,000 U.S. persons) being treated with methadone for substance abuse, which was 26% of all U.S. substance abuse clients.[21] The 2014 production quota of methadone in the U.S. was 31,875 kg, or approximately 274 mg day^{-1} 1000 U.S. $persons^{-1}$.[22] Methadone use is marginally lower in Europe, where use was reported as 0.3–232,[23] 138,[24] 148[25] (estimated from concentrations in WWTPs), and 97[26] (National Health Service data) mg day^{-1} 1000 $people^{-1}$, in Spain, Belgium, Croatia, and the United Kingdom, respectively. Approximately 28% of ingested methadone is excreted in the urine as unmetabolized drug (although this varies from 10-60% based on patient sex and urine pH).[27-32] EPISuite modeling and occurrence data predict methadone removal in wastewater treatment plants (WWTPs) to be low (27%[33] and 0 to 44%,[23,25,34-37] respectively).

Methadone removal in the environment is also predicted to be slow, having a predicted lifetime of several months.[33] Estimated NDMA FP from methadone in DWTPs downstream of WWTP effluents results in one to tens of ng/L NDMA, which is typical for DWTPs of this nature (See Health Implications). Pre-oxidation and granular activated carbon (GAC) remove methadone well in DWTPs,[34] which is similar to what has been seen previously for NDMA FP reduction.[38,39] Methadone therefore likely has the characteristics (occurrence and environmental persistence) to be a precursor of importance to NDMA formation.

The goal of this research was to identify NDMA precursors in surface water and wastewater that have both high occurrence and high NDMA molar yield. Our approach was to use liquid chromatography/quadrupole/time-of-flight mass spectrometry (LC/QTOF-MS) with accurate mass to identify NDMA precursors via neutral loss fragmentation of the dimethylamine structure, which may form NDMA upon chlorination. If successful, this approach will be useful to identify new NDMA precursors to suggest new treatment techniques or DWTP source water protection strategies. This paper details the approach and identifies methadone, a pharmaceutical that has not been previously reported as a precursor of NDMA in surface water and wastewater.

3 Materials and Methods

A list of reagent chemicals and a description of the analytical methods can be found in the supporting information (SI). Surface waters (n=10) and the secondary effluent of a wastewater treatment plant were collected from across the U.S. and Canada between August 2014 and February 2015. The wastewater plant treated 45,000 m^3/d (roughly 120,000 people at 378 L/d) and was selected because we have conducted research at this facility located near our laboratories for over a decade.[40,41] Samples ranged in organic matter characteristics (dissolved organic carbon from 2.5 to 6 mgC/L and total dissolved nitrogen from 0.4 to 5.4 mgN/L) and in

the potential contribution from upstream wastewater and agricultural sources. The sample locations are known to have relatively high NDMA FP (20 to 600 ng/L) and thus were expected to have high concentrations of NDMA precursors.

Samples were shipped overnight in coolers with ice packs within 24 hours of collection. Immediately upon arrival, samples were filtered with pre-combusted Whatman GF/D filters (2.7 µm nominal pore size, GE Healthcare, Piscataway, NJ) to remove colloids and particles that may impede solid phase extraction. The filtered samples were stored in a refrigerated (4°C) chamber for a maximum of one week before extraction/isolation.

NDMA FP tests for methadone yield and kinetics (details contained in the SI) were conducted on the filtered water or Milli-Q™ water. A method to capture and elute NDMA precursors was developed, and recovery of precursors into cation exchange (Oasis MCX) isolates ranged from 41 to 168% (coefficient of variance from 0.01 to 1.04). The details of this method are given in the SI and will be the subject of a future publication. One fraction of the isolate was reconstituted into Milli-Q™ water and chloraminated under FP conditions to determine recovery of bulk NDMA precursors (reconstituted NDMA FP / raw water NDMA FP = bulk precursor recovery). A second fraction was used for NDMA precursor identification by LC/QTOF-MS and methadone quantification by gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS). Further details regarding NDMA and methadone quantification as well as a description of the LC/QTOF-MS system can be found in the SI. A blank (Milli-Q™ water) was also isolated to confirm that methadone was not a contaminant leaching from the cation exchange resin, and none was found.

4 Results and Discussion

4.1 Discovery of a new pharmaceutical NDMA precursor: methadone

Methadone, as an NDMA precursor, was discovered in wastewater using a LC/QTOF-MS screening procedure for the presence of dimethylamine, with a diagnostic loss of 45.058 mass units corresponding to the loss of a dimethylamine structure from the molecule (Figure 1). Using data files from the instrument software that were modified with MATLAB®, it was possible to extract ions with the correct diagnostic ion loss of 45.058 from the sample. Using this procedure, an ion with mass of 310.2165 m/z was found in the water sample that had a dimethylamine loss (45.058). The ion gave a formula of $C_{21}H_{28}NO$ (Figure 1), which corresponds to over 800 possible structures in ChemSpider for the neutral molecule.[42] Several accurate mass tools were applied to help determine the structure and identify the unknown, including extraction of diagnostic ions,[43] MS/MS analysis,[43] isotope pattern mass spacing,[44] fragment structural analysis,[45] and database extractions.[46] Figure 1 shows the results of the MS-MS analysis and structural fragments consistent with a putative methadone identification, which was later confirmed with a pure methadone standard by retention time and MS-MS analysis (Figure SI-1) with accurate mass. A more detailed explanation of the screening and MATLAB® procedure will be discussed in a later publication that presents instrumental analytical techniques for unknown NDMA precursors. Next was to confirm that the dimethylamine loss was consistent with a high NDMA formation potential.

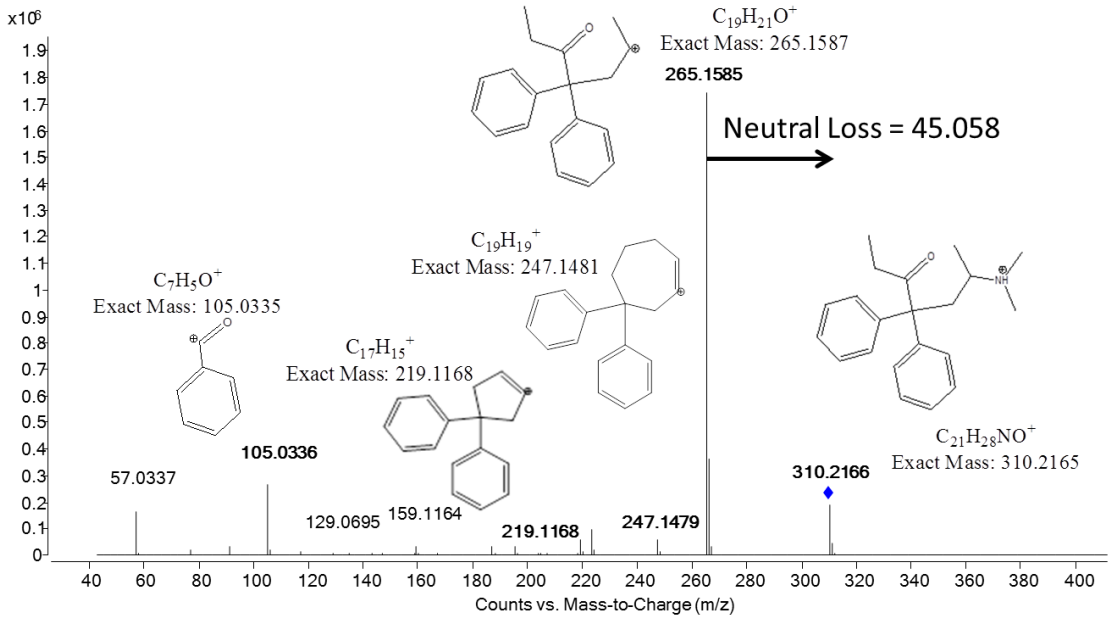

Figure 1 – MS/MS analysis of wastewater sample with putative structures for methadone fragments, which matches MS/MS analysis of a pure standard with less than 1-ppm mass accuracy. Note the loss of a dimethylamine with a neutral loss of 45.058 mass units.

4.2 NDMA formation yield and kinetics from methadone

After confirmation of methadone by the LC/QTOF-MS screening procedure, a methadone standard was purchased, added to Milli-Q™ water, and dosed with monochloramine for varying contact times to determine NDMA formation yield and kinetics (Figure 2). Methadone forms NDMA at low monochloramine doses (1 to 10 $mgCl_2/L$) and at doses typically used in NDMA FP tests (>10 $mgCl_2/L$). At a dose and contact time commonly used in NDMA FP studies (18 $mgCl_2/L$ for 72 hours), methadone had a molar yield of 60%. At this monochloramine dose, NDMA formation from methadone was moderately slow (Figure 2; $K_{app} = 0.035\ M^{-1}\ s^{-1}$ modeled using previously published methods[47,48]) and within the range of previously observed rates for NDMA formation in a wastewater-impacted surface water.[47,48] As the monochloramine contact

time increased from 0 to 72 hr, NDMA formation from methadone increased but did not plateau at longer contact times, meaning that our estimate of 60% yield at 72 hours is potentially a conservative estimate with longer contact times.

In addition to the yield under FP conditions, we investigated whether monochloramine dose would impact the total NDMA formed. In Figure 2, we show that increasing monochloramine dose increased the NDMA yield of methadone (from 23 to 70% at doses of 1 to 150 mgCl_2/L), a phenomenon that has been similarly observed in other natural and engineered (wastewater) water sources recently by our team.[47,48]

Methadone is one of only six compounds known to have a molar yield of NDMA in excess of 50% under 72 hr formation potential conditions; the five others are ranitidine,[11] dimethylisopropylamine,[8] 5-((Dimethylamino)methyl)furan-2-methanol,[9] dimethylbenzylamine,[8,10,49] and N,N-Dimethyl-1-(2-thienyl)methanamine).[8] The other five compounds have not been detected or have not been looked for in wastewater effluents, however published literature reports methadone occurs in both wastewater and surface water.[23,25,34-37,50-53]

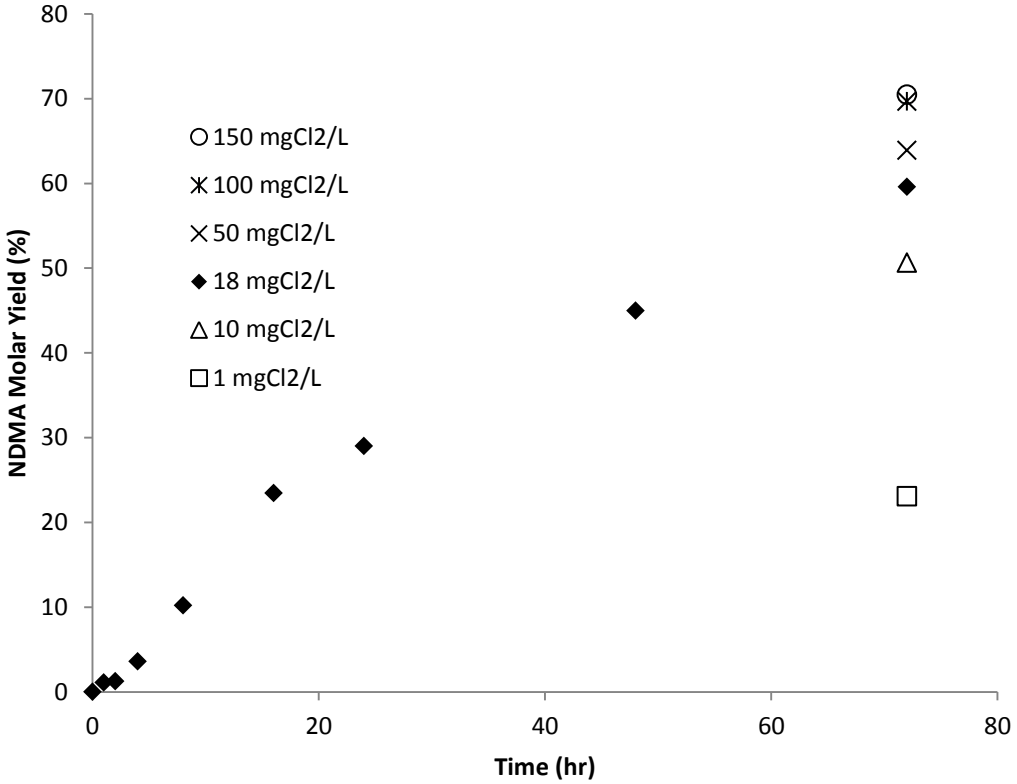

Figure 2 – NDMA yield from methadone at various contact times and doses. The matrix was Milli-Q™ water borate buffered at pH 8. The data points shown are averages of duplicates with relative deviation <8%.

4.3 Occurrence of methadone and contribution to NDMA formation

Organic matter from a secondary wastewater effluent sample was isolated using cation exchange (Oasis MCX) in triplicate to search for the DMA structure. After discovering methadone in extracts from a WWTP sample by LC/QTOF-MS (Section 4.1), we quantified methadone in the extracts by GC/MS and found that concentrations ranged from 32 to 2,256 ng/mL (Figure 3). Because methadone can degrade in the inlet of a GC,[54] we used LC/MS to confirm our quantification and the results agreed well. Furthermore, although our extraction

method was similar to published methadone extraction procedures,[36,50] our goal during method development was to screen samples for dimethylamine structures. Therefore, an isotopically-labeled methadone was not used to quantify losses during solid phase extraction. Consequently, our estimations are likely conservative and inherently variable. When exposed to 18 mgCl_2/L monochloramine (the same as that used in our FP tests on the raw water), methadone had a 60% molar yield to NDMA at 72 hr. Using this yield, methadone contributed up to 323 ng/L (assuming 100% recovery across SPE) to the NDMA FP of this water, or up to 62% of the total NDMA formation potential of the non-methadone spiked reconstituted wastewater isolates (reconstituted NDMA FP of 525 ng/L for this extract). We note that two of the methadone extracts contributed 1 to 13% of NDMA formation with one extract contributing 62%.

We also isolated 10 surface water samples for DMA structure searches by LC/QTOF-MS, and methadone was quantifiable in five of these sample isolates (SW 3, 5, 6, 7, and 9 in Table SI-1). The contribution to NDMA FP ranged from <1 to 3% of the reconstituted isolates (Figure 3). In general, isolates with greater methadone concentrations formed more NDMA when reconstituted into Milli-Q™ water. One sample had unusually high NDMA FP in the raw water (>500 ng/L); this sample is known to be heavily impacted by wastewater and had the greatest contribution of NDMA FP from methadone, albeit still relatively low (1 to 3%). Five surface water samples had no detectable methadone.

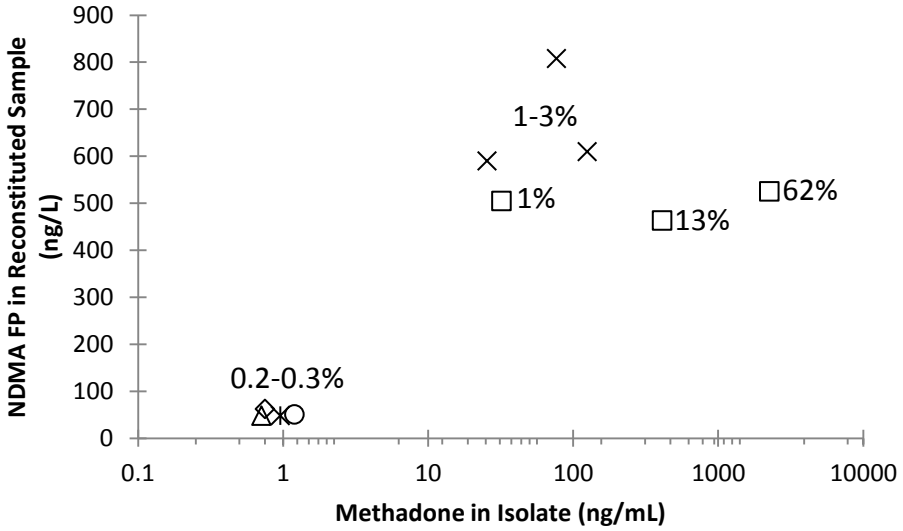

Figure 3 – Percent contribution of methadone to NDMA FP in six water sources. Methadone recovery across SPE was unknown. Squares and Xs show a wastewater and a surface water, respectively, with triplicate extractions and quantification (GC/MS). Other symbols represent four surface waters that were extracted in triplicate, but only a single sample was used for quantification (LC/MS).

Because our sampling campaign and methods were not initially developed to specifically identify and quantify methadone, we searched the literature for methadone occurrence data (Table 1). Available data regarding methadone occurrence is primarily from Europe with only two studies in the U.S. reporting concentrations. Methadone occurred in all WWTP influents except when the limit of quantification (LOQ) was insufficiently low (LOQ = 45 ng/L in one study for WWTP influent samples), and methadone was poorly removed through conventional WWTPs (37%,[23] 42%,[35] 44%,[36] 0%,[37] 0-16%,[34] and 26%[25]). The finding that methadone is poorly removed in WWTPs agrees well with the predicted removal by EPISuite (27%).[33] It should be considered that methadone is metabolized to 2-ethylidene-1,5-dimethyl-3,3-

diphenylpyrrolidine (EDDP). This metabolite has been reported as two to three times more abundant in wastewater than the parent compound,[23,34-36] and the NDMA FP of the metabolite EDDP is unknown, although it is likely to be low based on demethylation and cyclisation of the N. Methadone is generally ubiquitous in surface waters, occurring in all European samples except those of a state controlled park, and ranged in concentration from non-detectable to 55 ng/L. Only two studies published concentrations in the U.S.; both studies were from WWTPs and reported lower concentrations than Europe. Based on this literature review and a molar yield of 60%, the contribution to NDMA formation in surface and wastewater from methadone could be in the low ng/L and the hundreds of ng/L, respectively. We conclude that methadone is a potentially important precursor as NDMA typically forms at roughly the same order of magnitudes as these preliminarily calculated values.

Table 1 – Summary of methadone occurrence in surface water and WWTP influents (inf).

Water source	Source type	Frequency >LOQ (*n*)[a]	Methadone occurrence (ng/L)
Spain[23]	Surface	94% (32)	<0.04 – 18
United Kingdom[36]	Surface	100% (6)	10/18[b]
Switzerland[35]	Surface	97% (25)	<0.2 – 5
Northern and central Italy[50]	Surface	100% (11)	0.2 – 10
Near Madrid, Spain[51]	Surface	100% (14)	8 – 55
L'Albufera National Park in Spain[52]	Surface	31% (16)	<0.01 – 0.84
Spain[23]	WWTP inf	100% (15)	3 – 1531
United Kingdom[36]	WWTP inf	100% (7)	88/171[b]
Switzerland[35]	WWTP inf	100% (5)	42 – 202
Netherlands[37]	WWTP inf	0% (32)	<45
New York State, U.S.A.[34]	WWTP inf	93% (14)	<LOQ[c] – 54.6
Czech Republic[55]	WWTP inf	100% (14)	13 – 19
U.S.A.[53]	WWTP inf	100% (7)	5 – 62
Zagreb, Croatia[25]	WWTP inf	100% (27)	25 – 94

[a]*n*: number of samples
[b]Mean/max are shown as no range was given.
[c]LOQ between 1 and 10 ng/L

4.4 Health implications

Methadone has clear benefits as a medicinal tool. However, it is poorly removed in WWTP (<50%), relatively persistent in the environment (months),[33] and has the potential to contribute to the increased cancer risk associated with nitrosamines in chloraminated drinking water. For example, a community of 100,000 people could contain 1,500 chronic pain treatment and 100 substance abuse treatment methadone users.[19-21] Notably, the number of prescriptions of methadone to treat chronic pain is 1.5 orders of magnitude greater than for substance abuse treatment in the U.S. and potentially avoidable using other prescription drugs. At the minimum recommended dose of 7.5 mg/d,[19] the community will consume 12 g/d of methadone, of which approximately 28% is excreted as the parent drug in urine.[27-32] These are conservative estimates of doses and excretion, and if applied to the total number of methadone users in the U.S. given in

the introduction, only half of the U.S. production of methadone is accounted for. A typical wastewater production rate is 378 L day^{-1} $person^{-1}$, resulting in 90 ng/L methadone entering this theoretical WWTP, where it is partially removed (27%).[33] If <10% is removed in the receiving stream with 40% dilution[56] (non-WW origin), a downstream DWTP practicing chloramination could produce roughly 5 ng/L NDMA FP from methadone in the river (60% molar NDMA FP yield). Notably, this theoretical potable water treatment plant would form NDMA in concentrations that are typical of chloraminating DWTPs using wastewater impacted surface water as the water source (median of 35 ng/L in one study).[57]

This is among the few examples showing a direct relationship between a pharmaceutical that improves human welfare and the formation of a carcinogen during drinking water disinfection. The closest example is a personal care product (triclosan) that has the potential to form trihalomethanes during chlorination, but the relative formation of trihalomethanes was concluded to be minor.[58] The medicinal use of methadone potentially displaces and transforms the health risks for individuals associated with heroin use and chronic pain to cancer risk for entire populations served by downstream DWTPs. The health risk associated with heroin use is high, and the risk associated with consumption of low levels of NDMA is relatively low but is spread across a greater population.

5 Acknowledgements

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Environmental Mass Spectrometry acknowledges Agilent Technologies, Inc., for instrument support, especially Jerry Zweigenbaum and Craig Marvin.

6 Supporting Information Available

The supporting information contains a table of NDMA data for reconstituted and raw water samples, a MS/MS spectra of pure methadone and methadone in the wastewater sample, and additional materials and methods. This information is available free of charge via the Internet at http://pubs.acs.org/journal/estlcu.

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