Nitrosamine formation from the oxidation of secondary amines

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Abstract

The nitrosamines are potent carcinogens which can be formed as by-products during water treatment. Much recent research activity has been focussed upon the formation, occurrence and control of N-nitrosodimethylamine (NDMA) in particular. In this study, seven secondary amines were oxidised by chlorine, ozone, and UV-irradiation, with and without post-chloramination, to quantify the effect on the formation of seven nitrosamines, including NDMA. While the yields of nitrosamines ranged from 0.01% for N-nitroso-di-n-butylamine (NDBA) to 2.01% for N-nitrosopyrrolidine (NPYR) under conditions of excess monochloramine at pH 7, yields from other oxidants were zero. Pre-oxidation with chlorine reduced nitrosamine formation by up to 83% compared with chloramination alone. This illustrates that in situations where secondary amines are key precursors, chlorine addition before ammonia during chloramination can be expected to limit nitrosamine formation. UV irradiation at 40 mJ cm^{-2} had little observed impact. Ozonation enhanced NDMA and N-nitrosomethylethylamine (NMEA) formation by subsequent chloramination to 7.48% and 10.15%, respectively.

Keywords: nitrosamine; NDMA; chlorination; chloramination; ozonation

Introduction

The nitrosamines are a group of potent carcinogens (Loeppky and Michejda, 1994), and the discovery of N-nitrosodimethylamine (NDMA) in drinking water (Jobb et al., 1992) has stimulated much research interest and activity. Occurrence of NDMA in drinking water is mainly associated with wastewater ingress into source waters and/or the use of chloramination for secondary (i.e. residual) disinfection. The former is related to heightened levels of DMA and perhaps other precursors found in wastewater; the latter is related to reactions between monochloramine and DMA leading to unsymmetrical 1,1-dimethylhydrazine (UDMH) and subsequently NDMA (Reaction 1 in Figure 1 below, Choi and Valentine, 2002). Other formation pathways involving chlorinated UDMH (Reaction 2, Schreiber and Mitch, 2006) and nitrosation (Reaction 3, Keefer and Roller, 1973) may also play a role.

Reaction 1: NDMA formation via UDMH pathway

$(CH_3)_2NH$ + NH_2Cl → $(CH_3)_2NNH_2$ → $(CH_3)_2NNO$

DMA + monochloramine → UDMH → NDMA

Reaction 2: NDMA formation via chlorinated UDMH pathway

$(CH_3)_2NH$ + $NHCl_2$ → $(CH_3)_2NNHCl$ → $(CH_3)_2NNO$

DMA + dichloramine → chlorinated UDMH → NDMA

Reaction 3: NDMA formation via nitrosation pathway

$(CH_3)_2NH$ + nitrosating agent (e.g. NO^+, HNO_2, N_2O_4) → $(CH_3)_2NNO$

Figure 1: NDMA formation mechanisms.

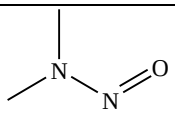
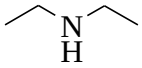
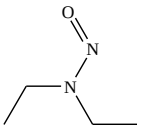
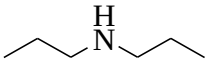
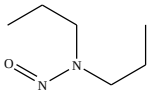
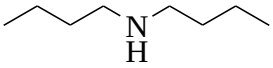
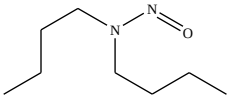
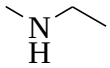
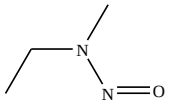
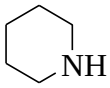
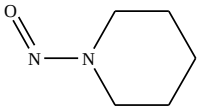
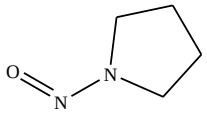
Occurrence of NDMA in chlorinated or chloraminated wastewater at above 1000 ng L^{-1} has been reported, while concentrations above 10 ng L^{-1} in drinking water can be regarded as high (Krasner et al., 2009b; Sacher et al., 2008). The United States Office of Environmental Health Hazard Assessment (OEHHA) has issued a public health limit of 3 ng L^{-1} for NDMA, for example (OEHHA, 2006).

Though drinking water research has mainly concentrated on NDMA, there is potential for the formation of other nitrosamines, especially given the variety of NDMA precursors that have been identified. DMA has been comprehensively examined as a precursor, although its conversion to NDMA is inefficient, with yields of only around 0.5% typical (Mitch et al., 2003). Various synthetic chemicals have been reported as far more reactive precursors. For example, the pharmaceutical ranitidine has a conversion yield of 63% (Sacher et al., 2008), while *N*,*N*-dimethylsulfamide, a degradation product of the fungicide tolylfluanide, has been responsible for the formation of NDMA after ozonation of German groundwaters (Schmidt and Brauch, 2008). Furthermore, NDMA can result from the use of certain polymers or ion exchange resins during water treatment, either from manufacturing impurities or the release of precursors (Kemper et al., 2009; Park et al., 2009).

Various oxidation techniques, including chlorination and ozonation, before chloramination has been reported to effectively reduce NDMA formation, presumably by destroying precursor sites (Chen and Valentine, 2008). However, while insight into the occurrence and control of NDMA has grown in recent years, there remains a need for analogous information about other nitrosamine species. Hence the aim of this study was to investigate the effect of oxidation processes on the formation of seven nitrosamines (including NDMA) from

secondary amines and the implications for drinking water treatment. The secondary amines included in the study (Table 1) were anticipated to form the corresponding nitrosamine upon chloramination by the equivalent pathway that DMA produces NDMA (Reaction 1). The oxidation processes included in the study were chlorination, ozonation, and UV irradiation, each with or without post-chloramination. The following resulting nitrosamines were quantified: N-nitrosomethylethylamine (NMEA), N-nitrosodiethylamine (NDEA), N-nitroso-di-n-propylamine (NDPA), N-nitroso-di-n-butylamine (NDBA), N-nitrosopyrrolidine (NPYR), and N-nitrosopiperidine (NPIP) (Table 1).

Table 1: Structures of secondary amines and corresponding nitrosamines in this study.

Amine	Structure	Nitrosamine	Structure
Dimethylamine (DMA)		NDMA	
Diethylamine (DEA)		NDEA	
Dipropylamine (DPA)		NDPA	
Dibutylamine (DBA)		NDBA	
N-methylethylamine (MEA)		NMEA	
Piperidine (PIP)		NPIP	
Pyrrolidine (PYR)		NPYR	

Methods

All chemicals were purchased at analytical purity or above from Fisher Scientific or Sigma Aldrich and all solutions were prepared in reverse osmosis treated high-purity water (RO water).

Nitrosamine Formation Potential (FP) Tests

Excess monochloramine (1 mM) was added to individual or mixed secondary amines (200 mL of 5 µM solution), with a seven day contact time at pH 7 (phosphate buffer) and 20±2 ºC. This procedure is based upon the NDMA FP test detailed previously which uses a chloramine dose much higher than is employed during drinking water treatment (Mitch et al., 2003). After this period the reactions were quenched with ascorbic acid (1.1 mM) and nitrosamines quantified using the method described below. In order to limit the formation of chlorinated species other than monochloramine, chloramine stock was prepared daily when required at

pH 8 (phosphate buffer), with chlorine added drop-wise to ammonia (0.1 M) at a N/Cl molar ratio of 1.3:1. The solution thus obtained was then left for 1 h in the dark before concentrations of chlorine, monochloramine and dichloramine were measured by the DPD/FAS titration method (APHA et al., 2005).

Other Oxidation Experiments

Mixed secondary amines (each at 5 µM, pH 7) were oxidised by chlorine, ozone and UV irradiation at doses representative of full-scale water treatment with and without post-chloramination under the same conditions as the nitrosamine FP tests. For samples with post-chloramination, the contact times for pre-oxidation were as stated below; otherwise a seven day contact time was used.

During the pre-oxidation experiments, chlorine was dosed at 71 µM (5 mg L^{-1} as Cl_2). After a 30-minute contact time ammonia solution was dosed at a 1:1 N:Cl molar ratio in order to quench free chlorine before excess monochloramine addition (1 mM) as described above. Chlorine concentration was measured by DPD/FAS titration (APHA et al., 2005).

Ozone was dosed at an initial concentration 5 mg L^{-1} with a 30 minute contact time before chloramine addition for the pre-oxidation tests. A stock ozone solution of ~9 mg L^{-1} was prepared by bubbling ozone-enriched air produced with a Trailigaz ozone generator (Ozotech, Burgess Hill, Sussex, UK) through RO water in iced water, with the initial dose achieved by dilution. Ozone concentrations were measured using the Indigo titration method (APHA et al., 2005).

Samples were exposed to UV light using a low pressure collimated beam device, which emits at 254 nm. A UV fluence of 40 mJ cm^{-2} was applied. The intensity of the UV light generated by the collimated beam was calculated using an International Light Technologies 1700 radiometer with an SED240 sensor (Reading, UK). The UV fluence calculation followed standard methods described in detail elsewhere (Bolton and Linden, 2003).

Nitrosamine Analysis

Nitrosamines were quantified using solid phase extraction, isotope dilution gas chromatography mass spectrometry, based on the method of Taguchi et al., (1994). In brief, 200 mL of water sample was extracted with 50 mg of carbonaceous polymeric beads (Ambersorb 483, Aldrich) by shaking for one hour at 250 rpm before being filtered onto a glass fibre filter. After air drying for 2 hours, the beads were transferred to a 2-mL amber vial with 400 µL insert. Dichloromethane (methylene chloride) (300 µL) was added to extract the adsorbate. A 5 µL aliquot of methylene chloride extract was injected into a Perkin-Elmer Clarus-500 GC/MS with a programmable large-volume injector and a DB1701 capillary column. *d6*-NDMA was used as the internal standard. Concentrations were calculated using selective ion monitoring at the mass peaks of the analysed nitrosamines. Method and analytical blanks were run for quality assurance. Each sample was analysed in duplicate. The mean average deviation of nitrosamines formed from duplicate samples of the corresponding secondary amine after individual nitrosamine FP tests was 0.11% (Table 2).

Results and Discussion

Formation of nitrosamines from chloramination of individual secondary amines

Yields of nitrosamines resulting from chloramination of the corresponding individual secondary amine ranged from 0.01% for NDBA to 2.01% for NPYR (Table 2). Thus it can be seen how nitrosamine formation via this mechanism is rather inefficient. Formation yields of 1.27% for NDMA from DMA compare with value of 0.49-2.74% (Sacher et al., 2008) and 0.5% (Mitch et al., 2003) reported by other researchers. Values of 2.01% for conversion of PYR to NPYR compares well with equivalent value of 1.84% quantified by Sacher et al. (2008). The formation of 0.13% NPYR and 0.18 % NPIP from chloramination of PIP and DPA respectively was thought to result from the presence of other components of the reaction mixture co-eluting with the nitrosamine peaks.

Based on the magnitude of the conversion yields, NPYR and NDMA are the measured nitrosamines most likely to occur in drinking water, whereas NDBA can be regarded as least likely. This correlates with data from German raw waters, where chloramination of 100 river, groundwater and lake samples under a laboratory nitrosamine FP protocol found NDMA followed by NPYR were the major nitrosamine species, though levels of NDMA were always at least an order of magnitude of higher than other nitrosamines (Sacher et al., 2008). In the same study the authors considered that measured incidence of DEA, which reached 290 ng L^{-1}, combined with conversion yields to NDEA could account for formation of these nitrosamines (Sacher et al., 2008). Conversely, the same did not apply for NDMA and NPYR, suggesting that other precursors are significant.

Table 2: Nitrosamine yields from the chloramination (1 mM, 7 days, pH 7) of individual secondary amines.

	Nitrosamine Molar % Formation Yield						
Precursor	**NDMA**	**NMEA**	**NDEA**	**NDPA**	**NDBA**	**NPYR**	**NPIP**
Dimethylamine (DMA)	**1.27± 0.00**	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
Methylethylamine (MEA)	0.00± 0.00	**0.70± 0.04**	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
Diethylamine (DEA)	0.00± 0.00	0.00± 0.00	**0.46± 0.21**	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00
Dipropylamine (DPA)	0.00± 0.00	0.00± 0.00	0.00± 0.00	**0.86± 0.55**	0.00± 0.00	0.00± 0.00	***0.18*± *0.01***
Dibutylamine (DBA)	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	**0.01± 0.00**	0.00± 0.00	0.00± 0.00
Pyrrolidine (PYR)	0.00± 0.00	0.00± 0.00	0.01± 0.01	0.00± 0.00	0.00± 0.00	**2.01± 0.04**	0.00± 0.00
Piperidine (PIP)	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.00	***0.13*± *0.00***	**0.42± 0.00**
Sum (excluding direct precursor)	**0.00**	**0.00**	**0.02**	**0.00**	**0.00**	**0.13**	**0.20**
Sum (including direct precursor)	**1.27**	**0.71**	**0.48**	**0.86**	**0.01**	**2.42**	**0.62**

Kinetics of initial nitrosamine formation

The relatively slow rate of nitrosamine formation was shown by 24 hour kinetics experiments (Table 3). Nitrosamine yields after 24 h represented some 18-58% (median = 30%) of 7 day yields, with NDBA and NDPA the two species at the lowest end of this range and NPIP the highest. A similar pattern emerges from analysis of zero-order rate constants used to quantify

initial nitrosamine formation over 24 h. NDBA showed the slowest formation, at a rate of 1.95 x 10^{-4} µM h^{-1} and NDMA exhibited the highest rate of the aliphatic nitrosamines, at 8.25 x 10^{-4} µM h^{-1}. Meanwhile, NPIP had the highest rate of all species at 15.28 x 10^{-4} µM h^{-1}. Overall, excluding NMOR, the aliphatic nitrosamines were slower to form than the cyclic. It should be noted that while initial formation data over 24 h followed zero-order behaviour, this may not apply over longer reaction periods or different reactant concentrations. A kinetic model for NDMA formation by the UDMH pathway has been developed previously (Choi and Valentine 2002). It is based upon the premise that all reactions, except oxidation of UDMH to NDMA, can be described by second order kinetics. This model suggests that in the presence of excess monochloramine NDMA formation should be proportional to precursor concentration. Conversely, other authors have found NDMA formation does not vary significantly with nitrogen content of the analysed water (Najm and Trussell, 2001).

Table 3: Nitrosamine yields and rate constants from the oxidation of mixed secondary amines.

	Nitrosamine molar % formation yield or formation rate constant						
	NDMA	**NMEA**	**NDEA**	**NDPA**	**NDBA**	**NPYR**	**NPIP**
Chloramination							
7 day formation yield	1.32± 0.08	0.70± 0.26	0.36± 0.09	1.49± 0.34	0.05± 0.05	2.29± 0.69	1.22± 0.43
24 h zero-order rate constant (µM h^{-1} x 10^{-4})	8.25 (R^2 = 1.00)	5.15 (R^2 = 0.99)	3.79 (R^2 = 0.98)	5.13 (R^2 = 0.97)	1.95 (R^2 = 0.73)	9.86 (R^2 = 0.71)	15.28 (R^2 = 0.99)
24 h yield as % of 7 day yield	30	35	49	18	22	29	58
Other oxidation methods (7 day formation yields)							
Chlorination	0.00± 0.01	0.00± 0.00	0.00± 0.00	0.00± 0.01	0.00± 0.01	0.00± 0.00	0.00± 0.01
Ozonation	0.00± 0.01	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.01	0.00± 0.00	0.00± 0.00
UV irradiation	0.00± 0.01	0.00± 0.00	0.00± 0.00	0.00± 0.00	0.00± 0.05	0.00± 0.00	0.00± 0.00

NR = not reported

Formation of nitrosamines from chloramination, chlorination, ozonation and UV irradiation of mixed secondary amines

While nitrosamine formation from chloramination of the mixed secondary amines was broadly similar to the cumulative total from individual precursors (Tables 2 and 3), chlorination, ozonation and UV irradiation produced no nitrosamines (Table 3). Given the association between monochloramination and nitrosamine formation this is perhaps expected, however, formation of NDMA from other disinfectants has been shown in previous work (Andrzejewski et al., 2008; Mitch and Sedlak, 2002). In particular, ozonation of DMA has been shown to result in a 0.33% conversion to NDMA, possibly from a nitrosation mechanism (Andrzejewski et al., 2008), with maximum NDMA yield at pH 10.5 with an initial DMA concentration of 36 mg L^{-1}. Since the current study was conducted at neutral pH and with an amine level of 5 µM, negligible conversion to nitrosamines can be anticipated. Furthermore, reactions between DMA and nitrite resulting in NDMA can be enhanced by the

presence of free chlorine (Choi and Valentine, 2003). Again, given nitrosamine formation tests were undertaken without nitrite addition in the present work, this pathway was not expected to be relevant.

Influence of pre-oxidation on nitrosamine formation after chloramination

Relative to chloramination alone, levels of NMEA, NPIP, NDEA and NDPA were reduced by 57%, 70%, 77% and 83% respectively by the chlorination-chloramination disinfection scenario (Figure 2). Reductions were more modest for the other nitrosamines, with the equivalent reductions in NDBA, NDMA, and NPYR formation being 32%, 21%, and 5%, respectively. For the majority of nitrosamines, UV irradiation before chloramination resulted in slight concentration changes relative to chloramination alone, though most of these differences can be accounted for by experimental error. The exception to this trend was NDMA, where the conversion yield increased from 1.32±0.08% to 2.18±0.30%. For the combination of ozonation followed by chloramination, production of NDBA was reduced by 75% relative to chloramination alone. Conversely, for the other nitrosamines increases were observed, the most emphatic being for NMEA and NDMA, where yields were 7.48% and 10.15% respectively, compared with 0.70% and 1.32% for chloramination by itself. For the remaining nitrosamines the pattern was intermediate between these extremes, with no change in NPIP, while NDEA, NDPA, NPIP and NPYR production increased to yields of 2.70%, 4.17% and 3.60% with pre-ozonation.

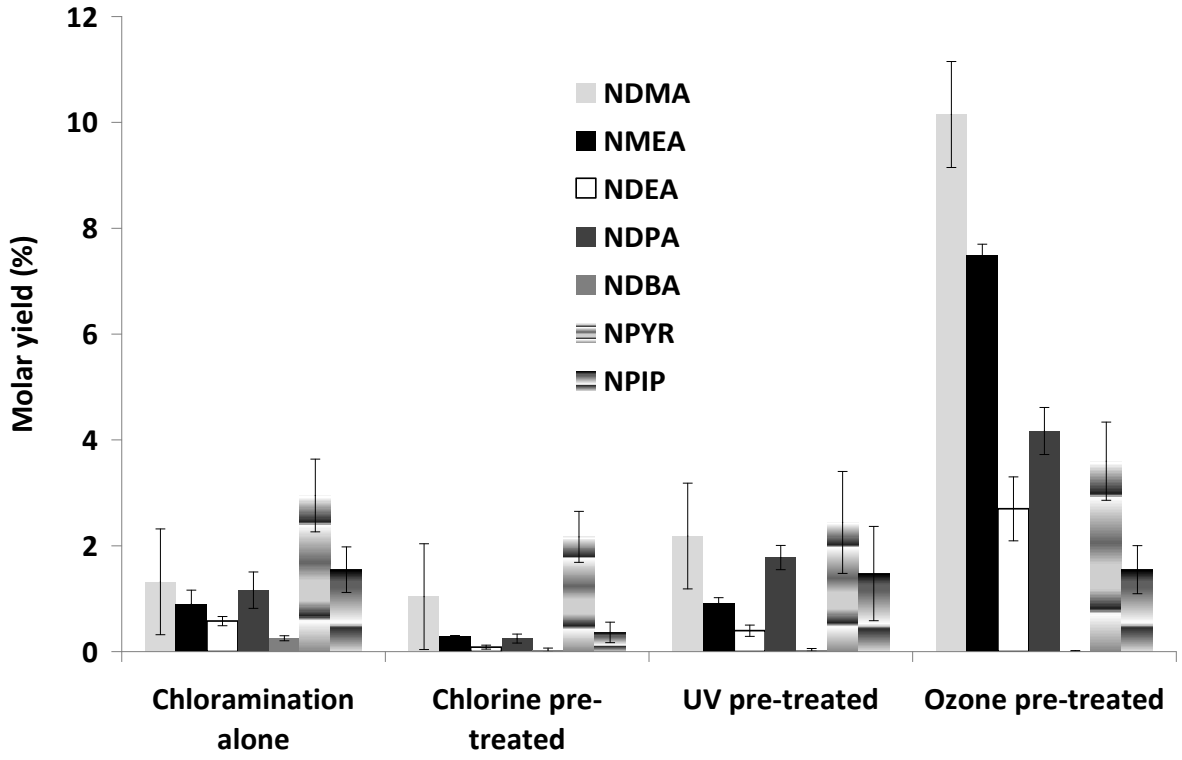


Figure 2: The effect of pre-oxidation on nitrosamine formation from post-chloramination of secondary amines.

The dramatically enhanced formation of NDMA and NMEA by ozonation followed by chloramination of mixed secondary amines is notable, especially since previous work has shown that pre-ozonation decreases NDMA FP (Chen and Valentine, 2008; Lee et al., 2007),

although ozonation of DMA has been found to result in yields of NDMA up to 0.33% in another study (Andrzejewski et al., 2008). This is also interesting given that ozonation alone produced negligible nitrosamines (Table 3). Although no mechanism was suggested during the previous studies, formic acid, formaldehyde, nitrates and nitrites were identified though not quantified in the post-reaction mixture. Previous to this study, the mechanisms of reactions between amines and ozone were elucidated by Elmghari-Tabib and co-workers (1982). Reactions between secondary amines and ozone produce (primary) hydroxylamines and aldehydes, the latter are subsequently oxidised to the carboxylic acids (Elmghari-Tabib et al., 1982). In fact, further reactions are possible with these products, since primary hydroxylamines can themselves be oxidised to produce aldehydes and nitrate. As recently suggested nitrite can also be liberated as an end product of this pathway (Yang et al., 2009), something supported by the aforementioned post-reaction analysis of Andrzejewski et al. (2008). This explains how reactions between DMA and ozone can lead to NDMA production by a nitrosation mechanism, given nitrate does not directly form nitrosamines (Sacher et al., 2008). Of the selected amines, the rate constant for reaction between DMA, DEA, PYR and PIP and ozone were found to be 33.5, 9.6, 23.2 and 36.2 $M^{-1}s^{-1}$ respectively (Pietsch et al., 2001). Thus it is probable the higher formation of NDMA and NMEA was controlled by the higher reactivity of DMA and MEA relative to the other amines during nitrosation, rather than their greater stability in the presence of ozone.

It has also been demonstrated through previous studies how the nitrosation of DMA is enhanced by free chlorine, possibly due to the formation of a highly reactive intermediate such as N_2O_4 produced during oxidation of nitrite to nitrate (Choi and Valentine, 2003). It is possible that an equivalent process resulted in heightened NDMA and NMEA formation in this study. In contrast to conventional nitrosation and the UDMH pathway, chlorine-enhanced nitrosation occurs rapidly inside one hour (Choi and Valentine, 2003). These authors observed that the combination of monochloramine and nitrite did not have the same impact on NDMA formation as free-chlorine and nitrite. Furthermore, the chlorine-enhanced reaction was inhibited with ammonia addition, presumably as this led to chloramine formation. However, as previously described, monochloramine can also oxidise nitrite to nitrate (Margerum et al., 1994), though since the first step is much slower than the reaction between free-chlorine and nitrite this may consequently produce less of the reactive intermediate (Choi and Valentine, 2003). It should be noted, however, that these reactions were only followed over 24 hours (Choi and Valentine, 2003) rather than the 7 days considered in this study. Overall, the presented data shows how exposure to free chlorine before chloramination reduced concentrations of all nitrosamines, especially NDEA and NDPA. This illustrates that in situations where secondary amines are key precursors, chlorine addition before ammonia during chloramination can be expected to limit nitrosamine formation.

Conclusions

- After exposure to excess monochloramine for 7 days, yields of nitrosamines from selected secondary amines ranged from 0.01 – 2.01%. These values suggest that to achieve a final nitrosamine concentration of 10 ng L^{-1}, for example, initial levels of secondary amine in the range of 353 ng L^{-1} for PYR to 82 µg L^{-1} for DBA are required.

- The combination of ozonation followed by chloramination dramatically increased formation of NDMA and NMEA from mixed secondary amines relative to chloramination alone. This enhanced nitrosamine production can be rationalised by

ozonation of amines liberating nitrite, which is then oxidised by monochloramine and/or free chlorine to a reactive intermediate which partakes in a nitrosation reaction with secondary amines.

- Exposure to chlorine before chloramine addition was an effective way of limiting nitrosamine formation for most of the nitrosamines, with conversion yields from secondary amines being reduced by 5-83% relative to chloramination alone, with NPYR and NDPA representing the respective extremes of this range.

Acknowledgements

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