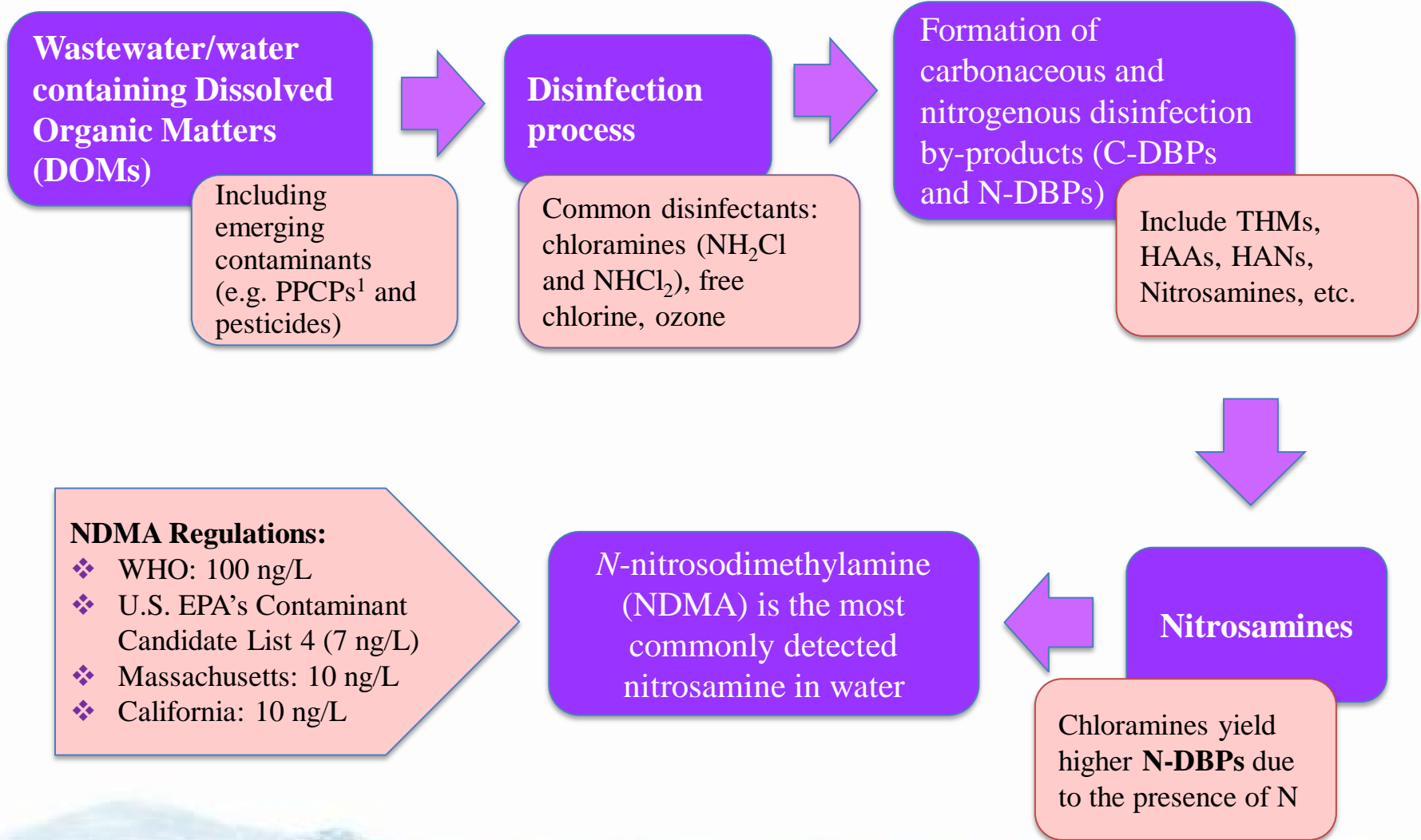


Reactivity and *N*-nitrosodimethylamine formation potential of betrixaban with monochloramine, chlorine, and ozone

Tahereh Jasemizad and Dr. Lokesh P. Padhye

Department of Civil and Environmental Engineering, The University of Auckland,
Auckland, New Zealand

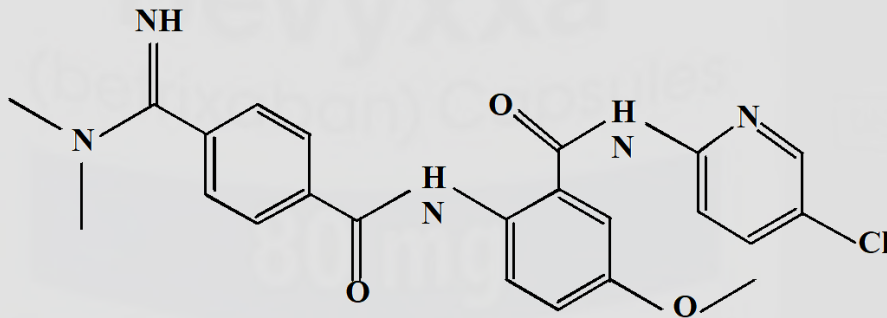
Disinfection and NDMA formation



¹ Pharmaceutical and personal care products

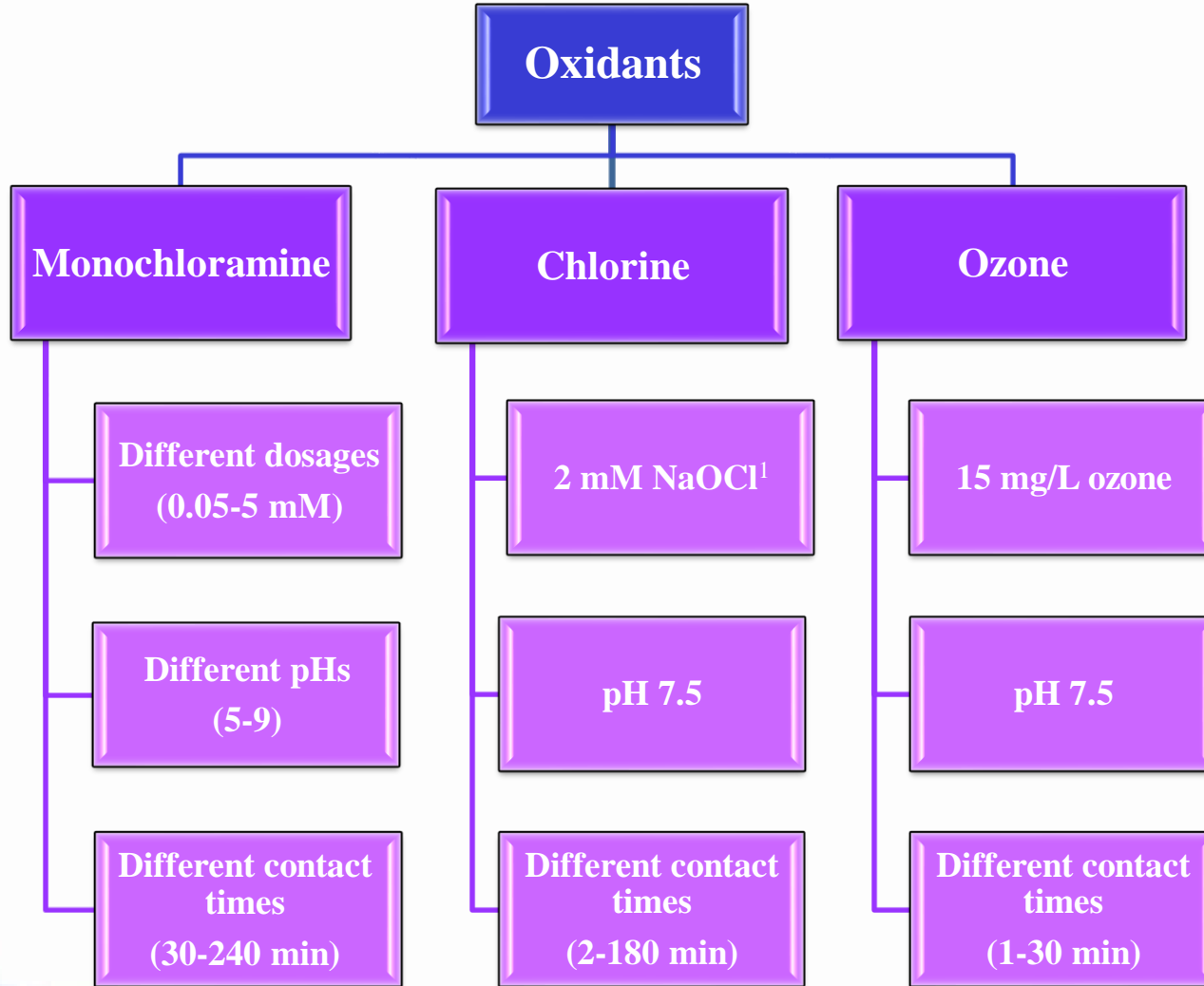
Betrixaban (Bevyxxa)

- ❖ Approved in 2017 by the FDA for treatment of Venous Thromboembolism.¹
- ❖ Increase in its medical use necessitates understanding its fate in the environment.
- ❖ High water solubility (2.7 mg/mL) and established stability under light and heat would mean that it will persist longer in the aqueous environment and through conventional treatments^{2,3}.
- ❖ According to European Medicines Agency, it is likely to be detected in surface waters and detailed environmental risk assessment is required².



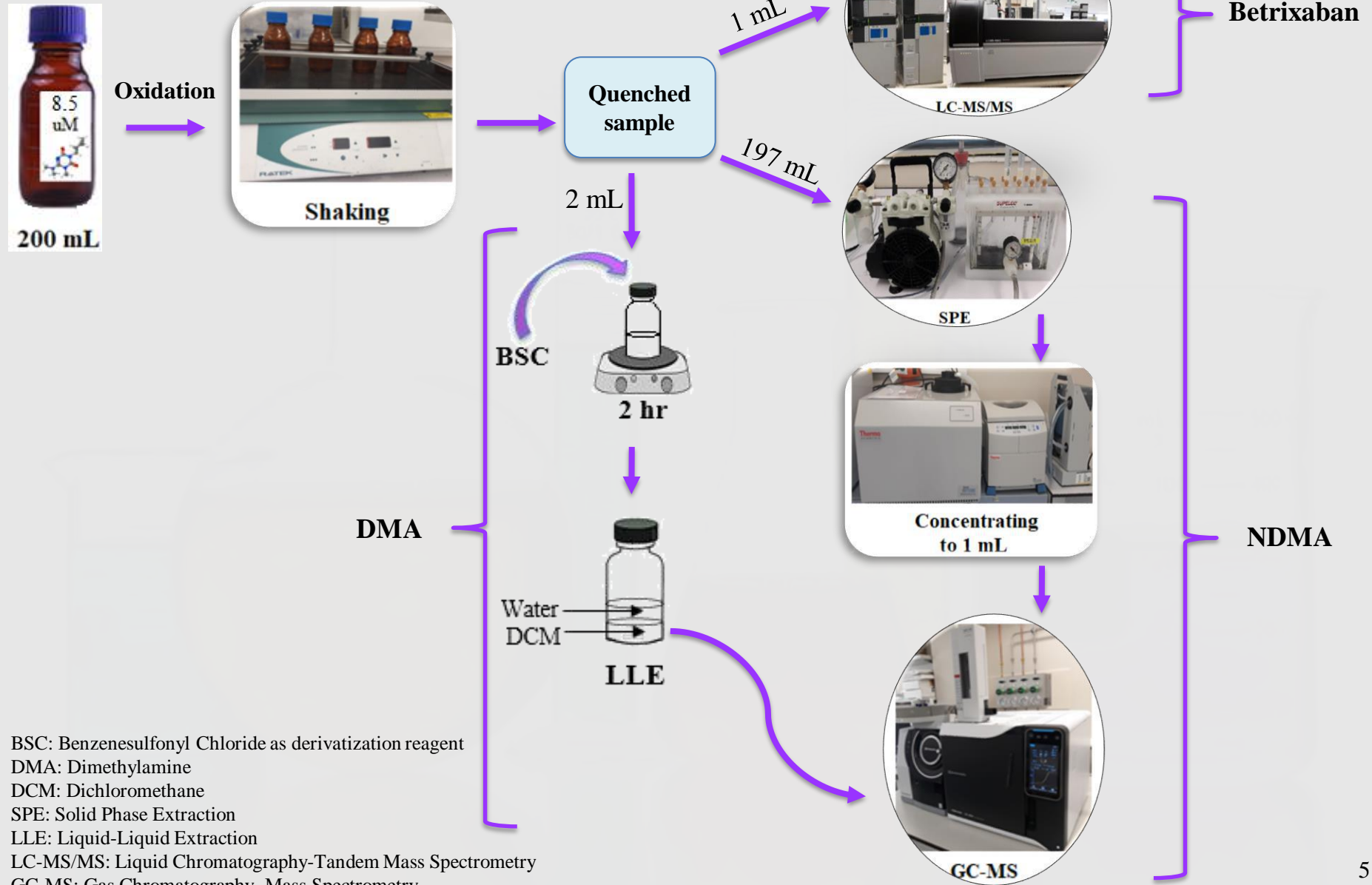
1. Traynor, K. (2017) Betrixaban approved as oral VTE preventive. Am J Health Syst Pharm 74, 1118.
2. Dexxience, European Medicines Agency, 2018.
3. <https://www.drugbank.ca/drugs/DB12364>

Experimental parameters



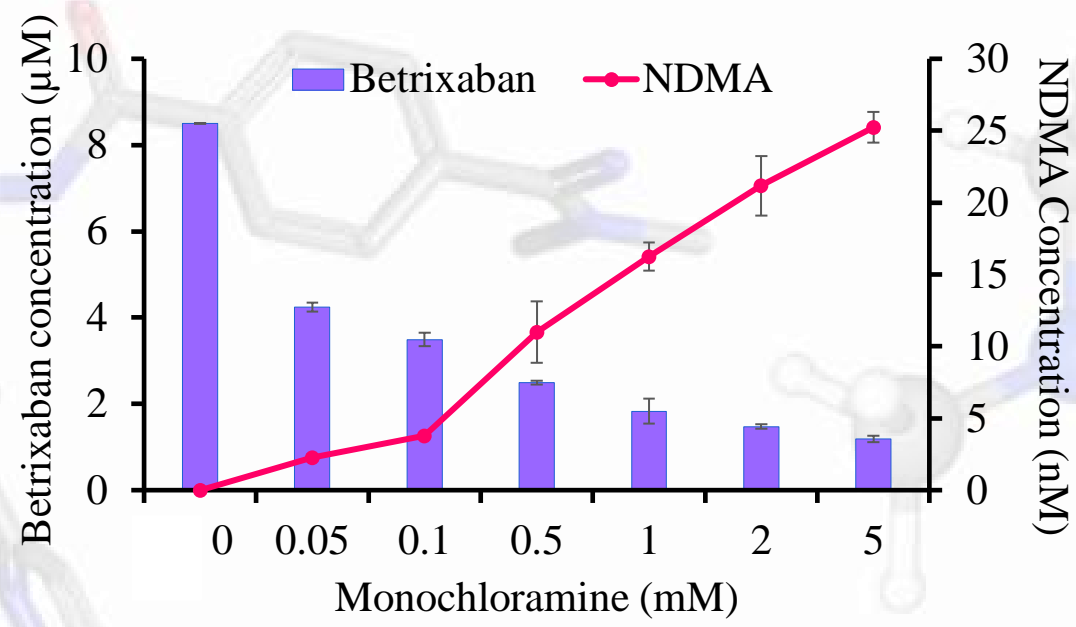
¹ Sodium hypochlorite

Detection methods



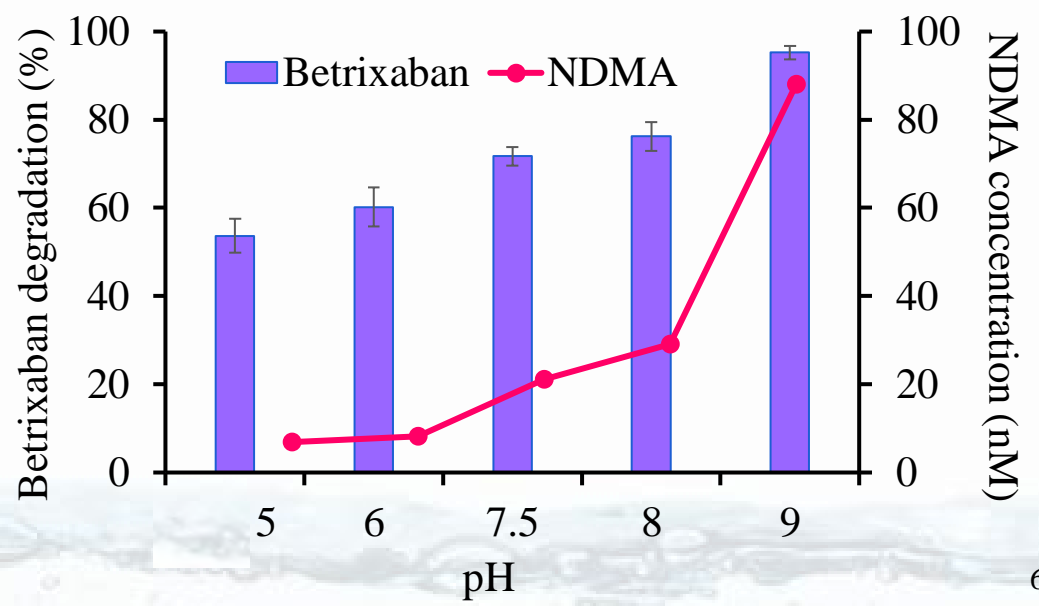
BSC: Benzenesulfonyl Chloride as derivatization reagent
 DMA: Dimethylamine
 DCM: Dichloromethane
 SPE: Solid Phase Extraction
 LLE: Liquid-Liquid Extraction
 LC-MS/MS: Liquid Chromatography-Tandem Mass Spectrometry
 GC-MS: Gas Chromatography- Mass Spectrometry

The effect of monochloramine dosage and pH



Effect of pH

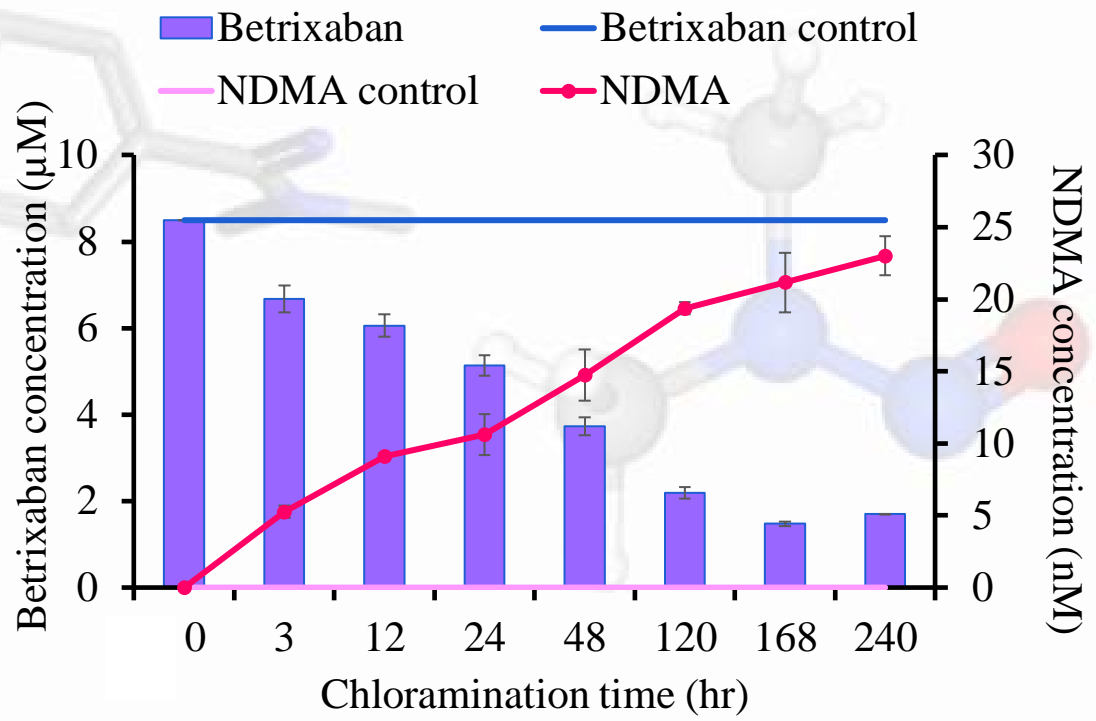
Since NDMA formation is not significant at pH lower than 7 where NHCl_2 dominates, NHCl_2 does not seem to play a critical role in NDMA formation.



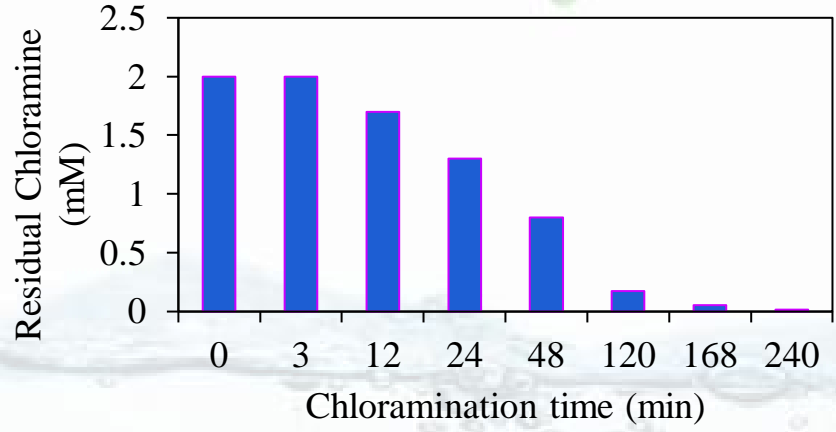
The effect of contact time

DMA

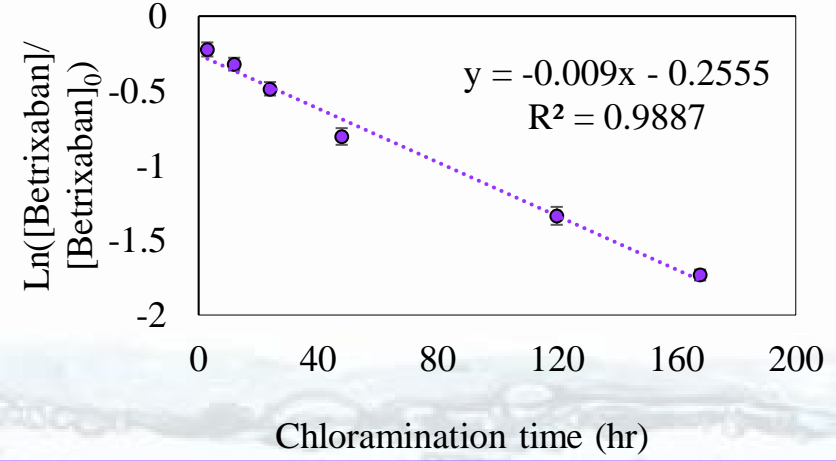
The formation of DMA from betrixaban in the presence of NH_2Cl , at pH 7.5, during 24 hr was more than in the absence of NH_2Cl .



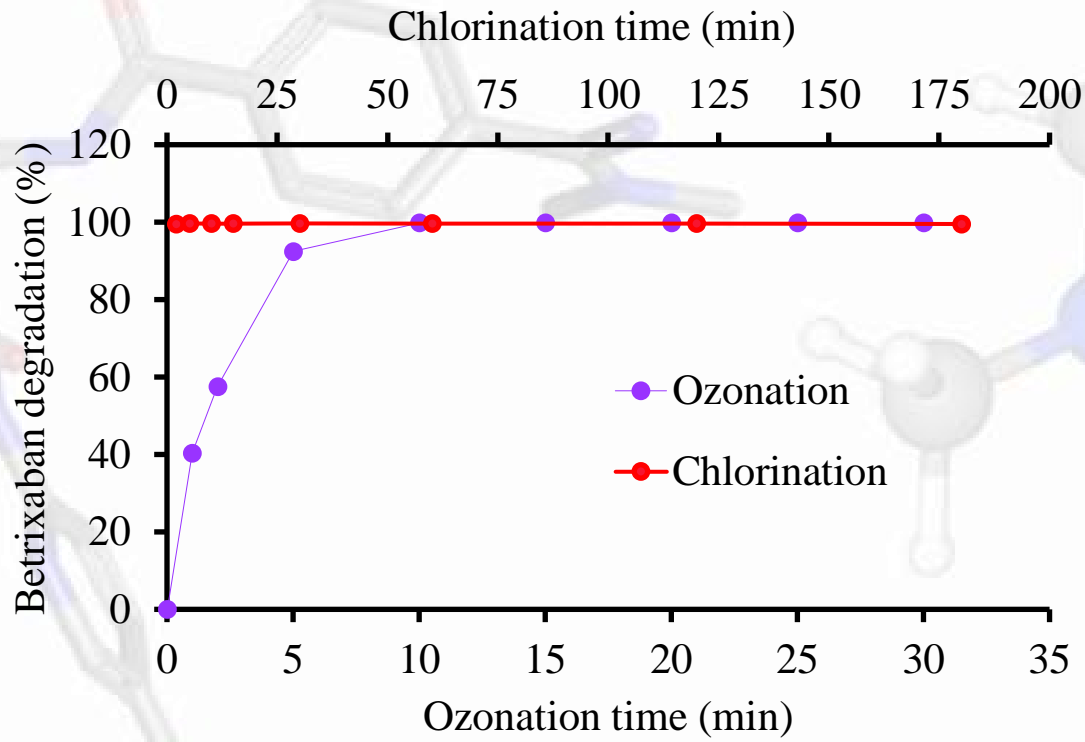
Residual monochloramine



Pseudo-first-order kinetic

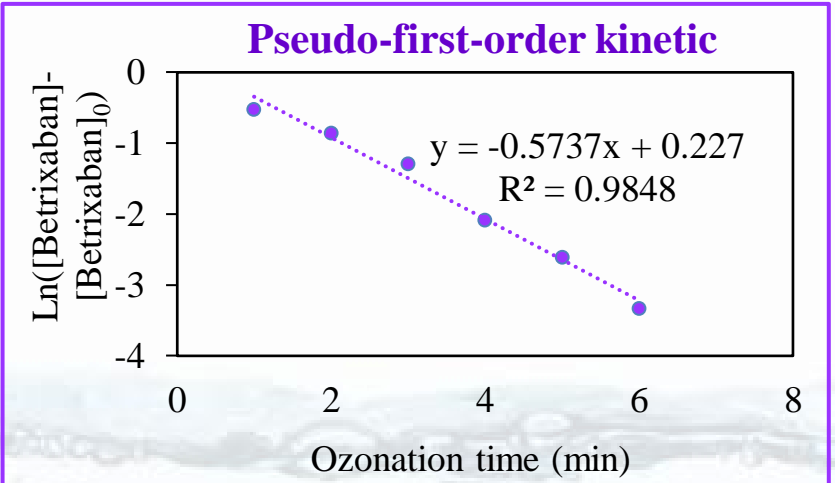


Chlorination and ozonation

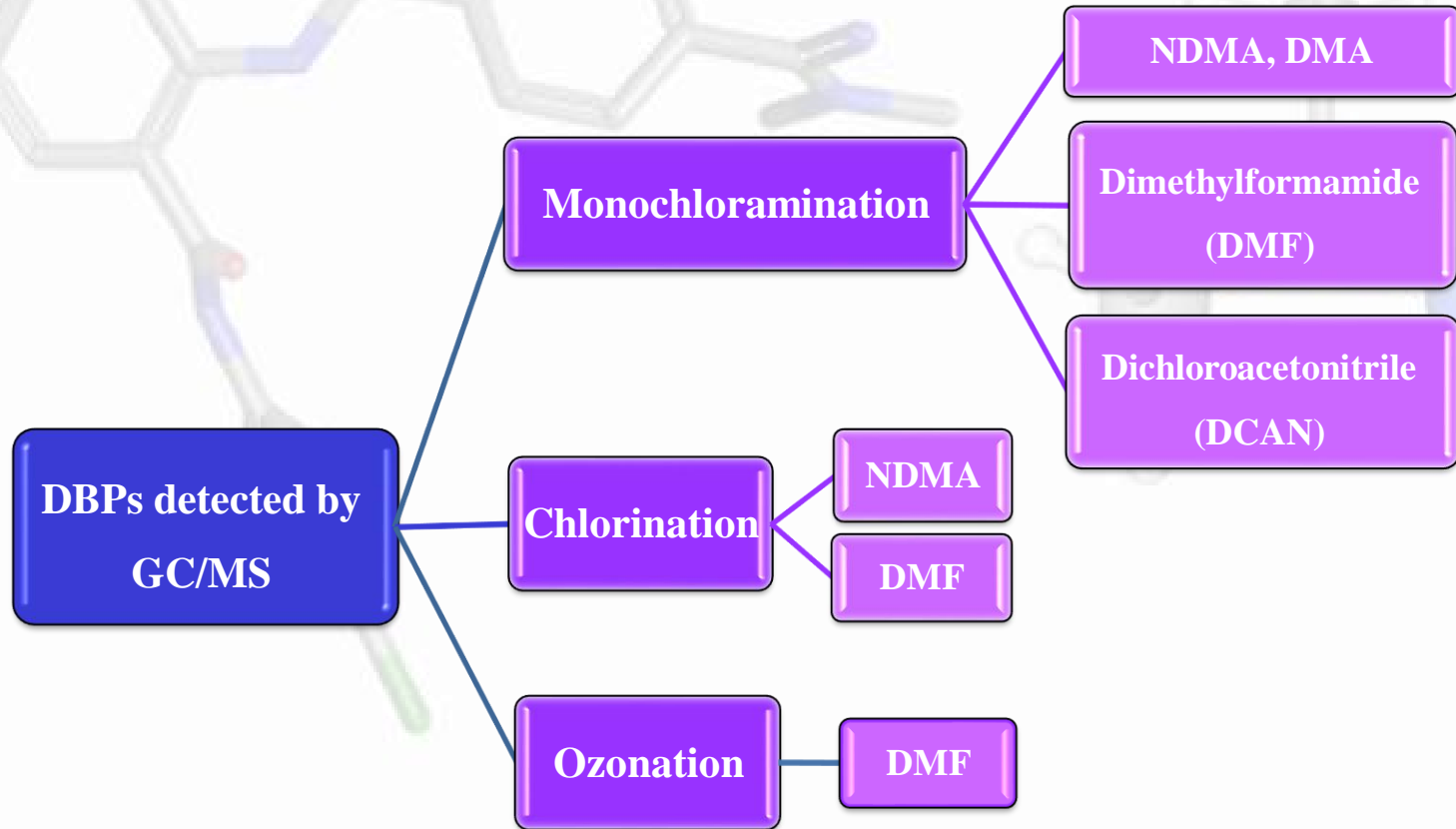


Chlorination

NDMA formation was observed during chlorination of betrixaban, with a low yield (0.014%). No NDMA formation was observed during ozonation.



By-products formation





Conclusions

- ❖ Betrixaban degradation and NDMA formation increased by increasing monochloramine dosage, monochloramine contact time, and pH.
- ❖ The maximum NDMA yield of >1% was observed at pH 9 upon monochloramination, while the yield was ~0.3% at circumneutral pH.
- ❖ NDMA yield of 0.014% was observed upon chlorination of betrixaban; whereas no NDMA formation was observed upon ozonation of betrixaban.
- ❖ DMF was detected as a DBPs during betrixaban monochloramination, chlorination, and ozonation. DCAN was only detected during monochloramination of betrixaban.
- ❖ The efficiency of oxidants in degrading betrixaban followed the trend: chlorination>ozonation>monochloramination.
- ❖ The kinetic studies revealed the pseudo-first-order reaction kinetics for reaction of betrixaban with NH_2Cl and ozone.

❖ **Dr. Lokesh P. Padhye**

Senior lecturer

Civil and Environmental Engineering

Faculty of Engineering

The University of Auckland

ORCID ID: <http://orcid.org/0000-0003-4743-7245>



❖ **Tahereh Jasemizad**

PhD candidate

Civil and Environmental Engineering

Faculty of Engineering

The University of Auckland

ORCID ID: <http://orcid.org/0000-0003-1084-5018>



Thank you

