

Supporting Information

**Potential for the Formation of N-Nitrosamines During the
Manufacture of Active Pharmaceutical Ingredients: An
Assessment of the Risk Posed by Trace Nitrite in Water.**

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Example calculations for converting NDMA concentrations and conversions into ppb

This calculation is based upon relating the volume of the NDMA forming phase to the mass of the compound that the level of NDMA is to be compared to in ppb ($\mu\text{g}/\text{kg}$). A relative volume (RV) is defined as the volume of solvent that is equivalent to the mass of the reference compound, such that 2 RV in relation to 1 kg of compound equates to a volume of 2 L.

Assuming that all of the nitrosamine formed in a synthesis is retained to the point where a comparison is made, the level of NDMA may be calculated from the concentration of NDMA (or a different nitrosamine in mol/L) and the mass of the product produced (in kg) by using equation S1.

$$ppb \text{ NDMA} = \frac{[NDMA] \times RV_{aq} \times RMM \text{ NDMA} \times 10^6}{\text{Mass of product}}$$

(S1)

From a percentage conversion to NDMA it is first necessary to convert the percentage into a NDMA concentration in mol/L based on the limiting reactant in the formation of NDMA (equation S2).

$$[NDMA] = \frac{\% \text{ Conversion NDMA} \times [\text{Limiting Reactant}]}{100}$$

(S2)

Scenario 1 gives a NDMA concentration of 4.812×10^{-12} M after 24 hours for the reaction of 1 mM DMA with 2.2×10^{-7} M nitrite in 1 M NaCl at pH 3.15 and 25°C. Considering a process in which this reaction is taking place in 10 RV of NDMA forming phase (1.0 M NaCl) and applying equation S1 the level of NDMA in ppb in the reaction product can be calculated: -

$$ppb\ NDMA = \frac{4.812 \times 10^{-12} \times 10 \times 74.08 \times 10^6}{1} = 3.56 \times 10^{-3}$$

The calculation can be carried through multiple processing steps by using the mass of the final product derived from 1 kg of the initial limiting reagent as the mass of the product in equation S1. It may be extended to other nitrosamines by substituting the appropriate relative molecular mass.

Figure S1. Simulated concentration profile for scenario 1b, the nitrosation of dimethylamine (1 mM) by trace NaNO_2 (6.5×10^{-5} M) in aqueous NaCl (1 M) at pH 3.15 and 25°C.

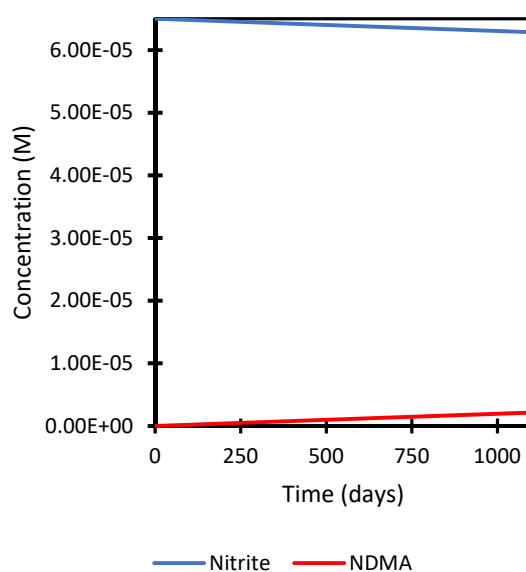


Figure S2. Simulated pH Initial rate profiles showing the contributions of the principal nitrosating species for the nitrosation of dimethylamine (1 M) by water containing trace nitrite (2.2×10^{-7} M) and trace chloride (1 mM) at 25°C.

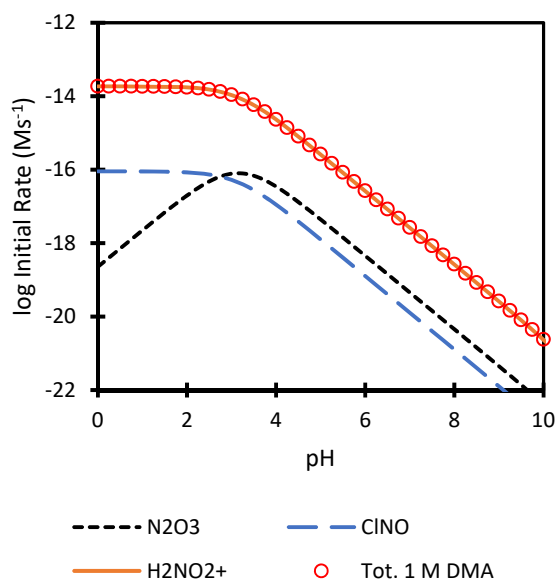
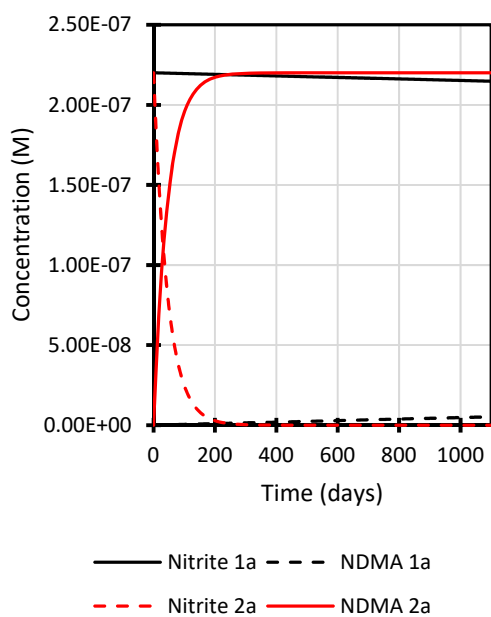


Figure S3. Comparison of the simulated reaction profiles for Scenarios 1a ($[\text{DMA}] = 1 \text{ mM}$) and 2a ($[\text{DMA}] = 1 \text{ M}$) with $[\text{NO}_2^-] = 2.2 \times 10^{-7} \text{ M}$ and trace chloride (1 mM) at 25°C.



NDMA formation calculation example for Scenario 1 using equation 10

$$pK_a \text{ HNO}_2 = 3.15 \Rightarrow K_a = 7.0795 \times 10^{-4}$$

$$pK_a \text{ DMA} = 10.91 \Rightarrow K_a = 1.2303 \times 10^{-11}$$

$$\text{pH} = 3.15 \Rightarrow [\text{H}^+] = 7.0795 \times 10^{-4}$$

$$[\text{NaNO}_2] = 2.2 \times 10^{-7} \text{ M}$$

$$[\text{NaCl}] = 1.0 \text{ M}$$

$$[\text{DMA}] = 0.001 \text{ M}$$

Calculate fractions of HNO_2 and DMA in the reactive forms based on equation 5: -

$$f_{\text{HNO}_2} = \frac{[\text{H}^+]}{[\text{H}^+] + K_{a \text{ HNO}_2}} = \frac{7.0795 \times 10^{-4}}{2 \times 7.0795 \times 10^{-4}} = 0.5$$

$$f_{\text{DMA}} = \frac{K_{a \text{ DMA}}}{[\text{H}^+] + K_{a \text{ DMA}}} = \frac{1.2303 \times 10^{-11}}{7.0795 \times 10^{-4} + 1.2303 \times 10^{-11}} = 1.7334 \times 10^{-8}$$

Calculate initial rate of NDMA formation via N_2O_3 using equation 5: -

$$\begin{aligned} \text{Init. Rate}_{\text{N}_2\text{O}_3} &= k_{\text{N}_2\text{O}_3} \times K_{\text{N}_2\text{O}_3} \times [\text{HNO}_2]_T^2 \times f_{\text{HNO}_2}^2 \times [\text{DMA}]_T \times f_{\text{DMA}} \\ &= 1.2 \times 10^8 \times 3 \times 10^{-3} \times (2.2 \times 10^{-7})^2 \times (0.5)^2 \times 0.001 \times 1.7334 \times 10^{-8} \\ &= 7.55 \times 10^{-20} \text{ Ms}^{-1} \end{aligned}$$

Calculate initial rate of NDMA formation via H_2NO_2^+ using equation 6: -

$$\begin{aligned} \text{Init. Rate}_{\text{H}_2\text{NO}_2^+} &= k_{\text{H}_2\text{NO}_2^+} \times [\text{HNO}_2]_T \times f_{\text{HNO}_2} \times [\text{DMA}]_T \times f_{\text{DMA}} \times [\text{H}^+] \\ &= 7000 \times 2.2 \times 10^{-7} \times 0.5 \times 0.001 \times 1.7334 \times 10^{-8} \times 7.0795 \times 10^{-4} \\ &= 9.45 \times 10^{-18} \text{ Ms}^{-1} \end{aligned}$$

Calculate initial rate of NDMA formation via ClNO using equation 7: -

$$\text{Init. Rate}_{\text{ClNO}} = k_{\text{ClNO}} \times K_{\text{ClNO}} \times [\text{HNO}_2]_T \times f_{\text{HNO}_2} \times [\text{DMA}]_T \times f_{\text{DMA}} \times [\text{H}^+] \times [\text{Cl}^-]$$

$$= 3.1 \times 10^7 \times 1.1 \times 10^{-3} \times 2.2 \times 10^{-7} \times 0.5 \times 0.001 \times 1.7334 \times 10^{-8} \times 7.0795 \times 10^{-4} \times 1.0$$

$$= 4.60 \times 10^{-17} \text{ Ms}^{-1}$$

Sum the individual initial rates to give the total initial rate of NDMA formation: -

$$\text{Init. Rate} = 7.55 \times 10^{-20} + 9.45 \times 10^{-18} + 4.60 \times 10^{-17}$$

$$= 5.553 \times 10^{-17} \text{ Ms}^{-1}$$

Calculate the concentration of NDMA formed in 24 hours using equation 10: -

$$[\text{NDMA}] = \text{Init. Rate} \times \text{time}$$

$$= 5.553 \times 10^{-17} \times 24 \times 60 \times 60 = 4.80 \times 10^{-12} \text{ M}$$

$$\% \text{HNO}_2 \text{ converted} = \frac{4.80 \times 10^{-12}}{2.2 \times 10^{-7}} \times 100 = 0.0022\%$$

Berkeley Madonna model used to simulate NDMA formation

METHOD RK4

STARTTIME = 0
STOPTIME=10000000
DT = 100

; I Ashworth, December 2019
; Model for rate of nitrosamine formation by N2O3, CLNO & H2NO2+ in aqueous media at 25°C

INIT R2NH = 0.001
INIT NO2 = 6.5e-5

CL = 1

INIT NITROSAM = 0

KNA = 7.079E-4 {Ka of nitrous acid at 25°C}
KECLNO = 1.1E-3 {association constant of CLNO, M-2}
KRCLNO = 3.1E7 {approximate rate constant for secondary amine nitrosation by CLNO, M-1s-1}
KEN2O3 = 3E-3 {association constant of N2O3, M-1}
KRN2O3 = 1.2E8 {typical rate constant for secondary amine nitrosation by N2O3, M-1s-1}
KRNO = 7000 {approximate rate constant for NO+ nitrosation, M-2s-1}
PKA = 10.91 {pKa of secondary amine}
KA=10^(-PKA)
PH = 3.15 {pH of reaction 3.15 is the maximum for N2O3 based nitrosation}
H=10^(-PH)

; pH speciation models

fH = H/(H+KNA) {f HNO2 in protonated form}
fN = KA/(H+KA) {f R2NH in free base form}

; Kinetic model

RXN1 = KRCLNO*KECLNO*H*R2NH*NO2*CL*fH*fN {Nitrosation by CLNO}
RXN2 = KRN2O3*KEN2O3*R2NH*NO2*NO2*fH*fH*fN {Nitrosation by N2O3}
RXN3 = KRNO*H*R2NH*NO2*fH*fN {Nitrosation by H2NO2+}

D/DT(R2NH) = -RXN1-RXN2-RXN3
D/DT(NO2) = -RXN1-RXN2-RXN3
D/DT(NITROSAM) = RXN1+RXN2+RXN3