



# Formation and estimated cytotoxicity of trihalomethanes and haloacetic acids during ozonation of nonylphenol in bromide-containing water after chlorination process: Impact of ozonation initial pH

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## ARTICLE INFO

Handling Editor: Dr. L.H. Lash

### Keywords:

Nonylphenol  
Trihalomethanes  
Haloacetic acids  
Ozonation initial pH  
DBP cytotoxicity

## ABSTRACT

The presence of nonylphenol (NP) in bromide-containing water contributed to the formation of regulated disinfection by-products (DBPs): trihalomethanes-4 (THM4) and haloacetic acids-5 (HAA5). This study investigates the effects of ozonation pH on the degradation of NP, DBP formation, and DBP-estimated cytotoxicity. The ozonation pH was varied to 5, 7, and 9 to determine the effect of acidic, neutral, and alkaline conditions. The increase of ozonation initial pH improved the NP degradation. Ozonation of all initial pH conditions could decrease TCM, BDCM, and BDCM formation but increase the TBM formation at alkaline conditions. The formation of mono-HAA5 on the other hand, increased at all ozonation initial pH. Ozonation at acidic and neutral initial conditions can reduce the estimated cytotoxicity of the total formation of THM4 and HAA5 by 74.34 % and 93.31 %, respectively. In contrast, DBP's estimated cytotoxicity was raised by 33.72 % upon ozonation at an initial pH of alkaline. According to the study's findings, lowering the cytotoxicity of DBPs in acidic or alkaline environments can be achieved without changing the ozonation's pH. Based on these findings, pH changes are not required to reduce DBP during ozonation of NP-bromide-containing water. Future research on the impact of natural organic matter is recommended to investigate ozonation's capacity to reduce DBP production during ozonation of NP-containing natural water.

## 1. Introduction

Surface water is the most important source of supply of water for humanity. Excessive human activity has polluted surface water with numerous kinds of pollutants, including endocrine-disrupting chemicals (EDCs). There has been considerable concern regarding the occurrence of NP as an EDC in water [1]. The potential for nonylphenol polyethoxylated (NPEO) surfactants, which can degrade into NP in water, is greatly increased by the extensive use of detergent, lubricating oil additives, emulsifiers, and antioxidants [2] making it a very possible source of pollution to water [3]. As one of the contaminants of emerging concern (CEC) [4], NP is classified as anthropogenic organic matter (AOM) since it is created by human activity that is persistent in the environment [5] and may have a hormonal impact on environmental and human health [6]. In polluted water, the presence of NP could reach 60 µg/L [7]. The presence of NP in surface water can be a serious

problem if the polluted water source is used as a source for the water treatment process.

As an essential step in the water treatment process, chlorination can disinfect a surface or substance by eliminating bacteria, and preventing the spread of water-borne illnesses to humans [8,9]. However, carcinogenic DBPs such as THM4 and HAA5 can be formed when chlorine reacts with organic matter [8–10]. The presence of DBPs in chlorinated water has a carcinogenic risk [11]. Common DBPs that are regulated by USEPA about their formation in drinking water are THM4 and HAA5. A large number of DBP such as THM4 and HAA5 are cytotoxic [12]. Studies on epidemiology revealed minor but important associations between disinfected drinking water and negative health consequences, such as bladder cancer [9]. The US Environmental Protection Agency (USEPA) established the maximum contamination limit (MCL) at 80 µg/L for THM4 and 60 µg/L for HAA5 in drinking water [13].

Ozone is a strong oxidant that can degrade organic matter in water

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<https://doi.org/10.1016/j.toxrep.2024.101769>

Received 4 August 2024; Received in revised form 4 October 2024; Accepted 11 October 2024

Available online 16 October 2024

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[14,15], including phenolic compounds [16,17] such as NP [18]. The ozonation process has been reported to reduce the formation of DBPs during chlorine disinfection [8,15]. Ozone breaks NP through electrophilic substitution into intermediates like propylphenol, pentylphenol, and heptylphenol then breaks the benzene ring into alkyl intermediates [19]. Chlorine can react with the intermediate product to DBPs such as THMs and HAAs [20]. The presence of bromide in water affects the speciation of DBPs formed during the chlorination process. Chlorine reacts with bromide to produce hypobromous acid, a radical that can react with organic materials to create brominated DBPs [21,22].

DBP formation reduction by ozonation is influenced by ozonation pH and DBP precursor characteristics [20]. Previous studies have shown that the ozonation process under high pH (alkaline settings) has high hydroxyl radicals ( $\text{OH}\bullet$ ) in alkaline conditions [20,23]. The pH parameters of the ozonation process have also been observed to influence the speciation of DBPs generated during the chlorination of bromide-containing water [8,20]. Under alkaline conditions, the extensive generation of hydrophilic organic matter causes the formation of brominated DBPs, which have precursor properties to brominated DBPs [20].

Previous research also suggests that ozonation of bromide-containing water can impact DBP formation as well as its cytotoxicity [24–26]. A recent study evaluates the molecular characteristics of nontarget brominated disinfection byproducts formed during ozonation in the presence of bromide and ammonium and their potential toxicity implications [24]. A study on low- $\text{H}_2\text{O}_2$ -mediated ozonation of reclaimed water has been reported could increase the brominated DBP formation and DBP cytotoxicity [25]. Also, the pre-ozonation process has been reported could reduce DBP toxicity during the conventional water treatment process using alum coagulation [26].

Studies on NP degradation using the ozonation process have been conducted previously [18,27–29]. However, the impact of the NP ozonation process on DBP formation and its toxicity is still unknown. Understanding the pH's influence on DBP formation can lead to better water treatment practices. This approach could be a simple way to improve water treatment methods in order to meet government standards and protect public health. Given a lack of research on NP degradation and its relationship to DBP creation, this study aimed to investigate the effect of ozonation initially pH on THM4 and HAA5 formation during chlorination. In this study, the initial pH of ozonation was varied at 5, 7, and 9 to represent acidic, neutral, and alkaline conditions. Bromide was also added to the water to determine its effect on the formation of brominated DBPs during the process. The results of this study should provide novel insight into the best way to break down NP in water while identifying its precursor properties to carcinogenic DBPs such as THM4 and HAA5 and evaluating its estimated cytotoxicity. This work not only provides insight into the treatment of NP-containing water but also offers a broader perspective on environmental science and toxicology.

## 2. Materials and methods

### 2.1. Chemicals and solution

Certified reference materials for THM4 (including trichloromethane (TCM), bromodichloromethane (BDCM), chlorodibromomethane (CDBM), and tribromomethane (TBM)) and HAA5 (including monochloroacetic acid (MCAA), monobromoacetic acid (MBAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), and dibromoacetic acid (DBAA)), as well as potassium indigotrisulfonate (ozone scavenging agent) and 4-nonylphenol (4-NP) were supplied by Sigma Aldrich (USA). Merck (Germany) supplied the extraction chemicals for THM4 and HAA5, which included methyl tert-butyl ether (MTBE), methanol, sulfuric acid, sodium sulfate, and sodium sulfite. The other chemicals were also acquired from Merck (Germany), including potassium bromide, potassium bromate, sodium bicarbonate, phosphoric acid, pH buffer

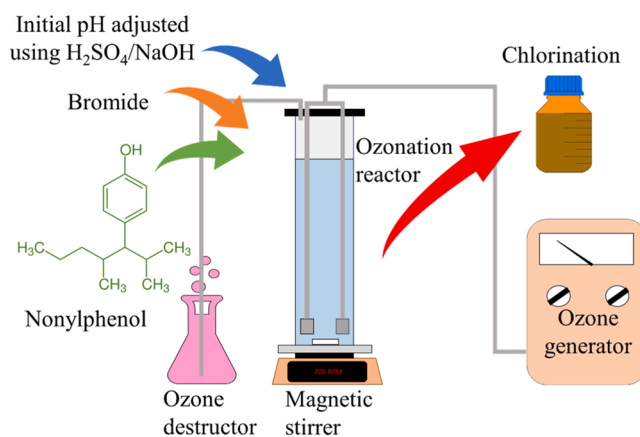


Fig. 1. Schematic diagram of ozonation process of NP-bromide-containing water.

solution, and TOC standard solution. The sodium hypochlorite was provided by Puduk Scientific (local). More details of chemicals used in this study were provided in the supplementary (Table S1).

A stock solution containing 4-NP and bromide was used for the experiment. The formation of THM4 and HAA5 from the chlorination of 4-NP in water was measured at a high concentration since the DBPs formation of 4-NPs is relatively small. After diluting 4-NP at a concentration of 4 mg/L in Milli-Q grade water, the stock solution was agitated for two hours at 35 °C. Additionally, potassium bromide was added to the mixture to reach a 1 mg/L bromide concentration. Details on the preparation of the 4-NP stock solution were provided in Text S1. The DOC concentration,  $\text{UV}_{254}$  absorbance, and SUVA value are 3.24 mg/L,  $0.14 \text{ cm}^{-1}$ , and 0.35 L/mg·m respectively. All solutions were diluted using Milli-Q grade water.

### 2.2. Ozonation processes

The ozonation process was conducted in a 70 mm diameter by 475 mm tall borosilicate batch reactor filled with 800 mL of NP stock solution. Furthermore, two ozone diffusers were positioned 3 cm from the reactor's bottom and connected to a 3g- $\text{O}_3$ /h ozone generator (corona discharge type) (Hypro, China) via a 5 mm PTFE tube (Fig. 1). To ensure that the solution was uniform, a magnetic stirring bar was placed at the bottom of the reactor. The ozonation initial pH conditions were adjusted at 5, 7, and 9 for acidic, neutral, and alkaline initial conditions, respectively, using either 0.1 M of  $\text{H}_2\text{SO}_4$  or NaOH [23]. The initial pH was monitored using a pH meter (Mettler Toledo S20). To simulate the actual conditions of the water treatment process as well as to enable the system to be scaled up for future uses, the buffer solution is not added to the water [30]. Each ozonation time is carried out individually due to the large number of samples required for analysis and ensures the same volume ratio and more accurate calculations at each ozonation time compared to the sampling method [8]. Each process was carried out for 5, 10, 15, 20, 25, and 30 min to assess the best operational conditions from a technological and economic perspective [31] and efficient NP degradation. The room temperature was kept at 25 °C. The rest of the sample was neutralized using  $\text{H}_2\text{SO}_4$  or NaOH solution and prepared for the chlorination process.

### 2.3. Chlorination

The chlorination process of NP was conducted based on our previous study [7]. The process was performed in 100 mL amber glass bottles containing 97 mL samples. The samples were chlorinated with 1 mL of 20 mg/L sodium hypochlorite and buffered at pH 7 with 1 mL of 0.5 M phosphate buffer solution then incubated in the dark for 24 h at 25 °C.

**Table 1**  
Cytotoxicity ( $LC_{50}$  values for CHO cells) of THM4 and HAA5 [12].

DBPs	$LC_{50}$ values (M)
<b>THM4</b>	
TCM	$9.62 \times 10^{-3}$
BDCM	$1.15 \times 10^{-2}$
CDBM	$5.36 \times 10^{-3}$
TBM	$3.96 \times 10^{-3}$
<b>HAA5</b>	
MCAA	$8.10 \times 10^{-4}$
MBAA	$9.60 \times 10^{-6}$
DCAA	$7.30 \times 10^{-3}$
TCAA	$2.40 \times 10^{-3}$
DBAA	$5.90 \times 10^{-4}$

1 mL of 5 % sodium sulfite was added after 24 h. Each process was performed twice. All samples were directly extracted for THM4 and HAA5 analysis.

#### 2.4. Analytical methods

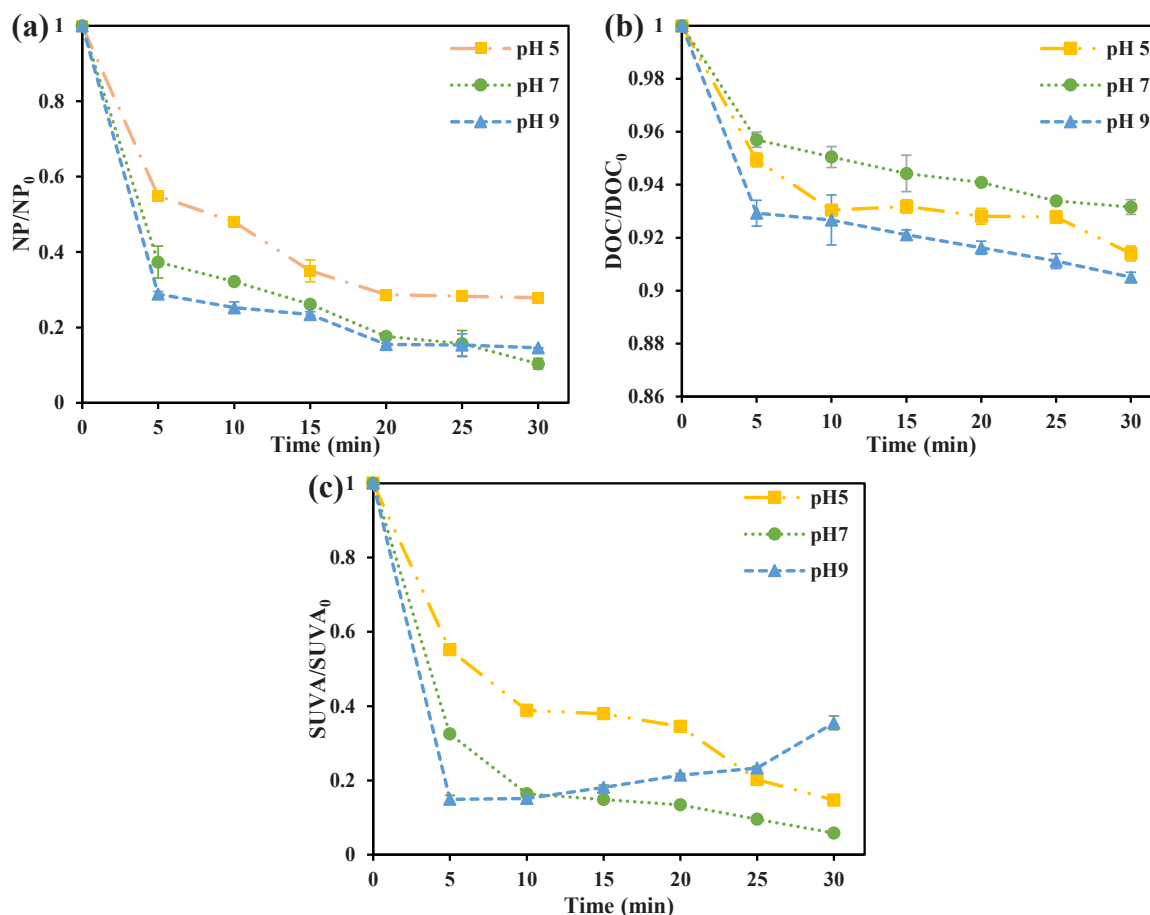
$UV_{254}$  was analyzed using an Agilent Cary 60 UV-Vis spectrophotometer. The ozone residue and bromate formation were respectively examined by indigo colorimetric methods (Methods 4500- $O_3$ ) [32] and fuchsin methods [33] using Lovibond PC Spectro II UV-Vis spectrophotometer. An Elementar Vario TOC analyzer was used for DOC analysis. THM4 and HAA5 were also analyzed using the EPA 551.1 [34] and 552.2 [35] methods by a gas chromatography (GC) Agilent 7890B GC system with an HP-5 column coupled to a micro-electron capture detector ( $\mu$ -ECD). A flame ionization detector (FID) was used to analyze

4-NP using a solid-phase microextraction method [36]. The extracted samples were kept refrigerated at 4 °C for no more than two days before analysis.

#### 2.5. Cytotoxicity calculation

The estimated cytotoxicity of each DBP ( $EC_{DBPs}$ ) was calculated using the median lethal concentration ( $LC_{50}$ ) endpoint exposed to Chinese hamster ovarium (CHO) cells provided by a previous study [12] (Table 1). The dose required to induce 50 % viability of the cells as compared to the concurrent negative control for CHO cells (72 h exposure). All DBPs were tested separately utilizing the same biological system and endpoints, allowing for molecule-by-molecule comparisons of their cytotoxic potency. Based on DBP formation data, estimated cytotoxicity was calculated by dividing the molar concentration of each formed DBP ( $M_{DBPs}$ ) by the provided cytotoxicity ( $LC_{50}$ ) values ( $MLC_{50}$ ) (1). The objective of this evaluation was not to give a direct assessment of the human health impact of DBPs formed during the chlorination of NP ozonation products, but rather to allow a comparison between the unitless DBP-associated chronic cytotoxicity of NP ozonation by product and to determine if any trends exist between these parameters and the DBP-derived cytotoxic nature of NP ozonation by product.

$$EC_{DBPs} = \frac{M_{DBPs}}{M_{LC50}} \quad (1)$$



**Fig. 2.** Effect of ozonation pH on the degradation of: (a) NP, (b) DOC, and (c) SUVA ( $NP_0$ : 4 mg/L).

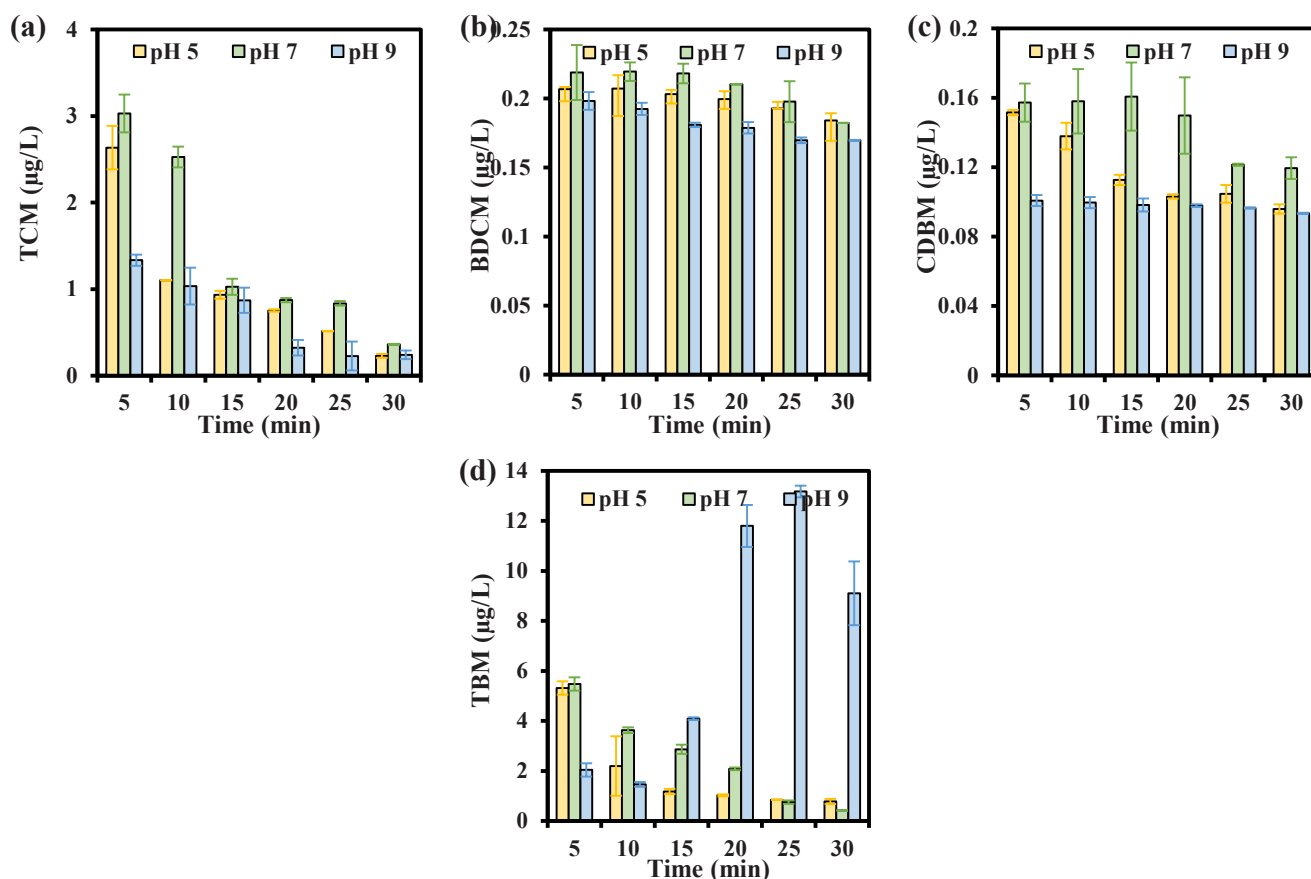


Fig. 3. Effect of initial pH on THM4 formation during ozonation of NP containing water: (a) TCM, (b) BDCM, (c) CDBM, and (d) TBM (NP<sub>0</sub>: 4 mg/L, Cl<sub>2</sub>: 20 mg/L, Br<sup>-</sup>: 1 mg/L).

### 3. Results and discussion

#### 3.1. NP degradation

Fig. 2a shows the effect of the ozonation pH process on the degradation of 4-NP in bromide-containing water. The 4-NP concentration decreased significantly at the first 5 min and continued to degrade at a lower rate with the increase of time. There were no significant 4-NP concentration changes after 20 min. Ozonation at the acidic initial condition (pH 5) had a lower degradation of 4-NP compared with neutral (pH 7) and alkaline (pH 9) initial conditions. Furthermore, after

20–30 min, the NP degradation in neutral and alkaline settings is comparable, with the neutral condition outperforming the alkaline condition after 30 min of ozonation. This could be attributed to measurement error caused by the low concentration of remaining NP. Previous research shows that the breakdown of dissolved organic matter (DOM) through ozonation is pH-dependent [20]. Alkaline environments enhance ozone reactivity and decomposition to OH•, increasing ozone consumption [21] that may improve NP degradation. Although alkaline ozonation conditions result in better NP degradation, neutral conditions are chosen to be more efficient for water treatment processes when compared to other initial pH levels. The pH of natural water was nearly neutral. Increasing the pH incurs additional costs due to the inclusion of chemicals.

At all initial pH conditions, ozonation on average only degraded 7–10 % of the DOC (Fig. 2b). NP degradation indicates the degradation of NP into lower molecular weight DOM, while DOC degradation indicates the mineralization of DOM into inorganic carbon such as CO<sub>2</sub> [37]. At alkaline initial condition, the lowest SUVA value was achieved at 5 min of ozonation and the value increased again between 5 and 30 min (Fig. 2c). This condition might occur since at alkaline initial condition, ozone reacted with hydroxyl ion to form hydroxyl radical (OH•) that was more reactive to phenolic compound than the ozone itself [8,20]. The oxidation process not only breaks the aromatic ring but also forms new 5 (furan) and 6 (benzene) heterocyclic rings [38]. These rings have chromophore properties [39] that might increase the SUVA value. The SUVA index has been used to determine the degree of hydrophobicity and its relationship with the molecular size of organic molecules in a water sample [40].

Ozonation may degrade the presence of NP in water. However, the ozonation technique is not cost-effective because of the lengthy period

Table 2

THM4 and HAA5 formation potential of 4-NP in bromide containing water.

	Mean	SD
DOC (mg/L)	3.24*	N.A.
UV <sub>254</sub> (cm <sup>-1</sup> )	0.14	0.001
SUVA (L/mg·m)	4.35	0.03
<b>THM4</b>		
TCM (µg/mg)	3.72	0.491
BDCM (µg/mg)	0.23	0.008
CDBM (µg/mg)	0.24	0.037
TBM (µg/mg)	8.05	0.266
Cytotoxicity THM4 (× 10 <sup>-6</sup> )	11.60*	0.66
<b>HAA5</b>		
MCAA (µg/mg)	16.68	0.137
MBAA (µg/mg)	7.10	0.616
DCAA (µg/mg)	13.83	0.128
TCAA (µg/mg)	3.09	0.137
DBAA (µg/mg)	6.38	0.089
Cytotoxicity HAA5 (× 10 <sup>-6</sup> )	5.61*	0.46

NP: 4 mg/L, Br<sup>-</sup>: 1 mg/L, Cl<sub>2</sub>: 20 mg/L.

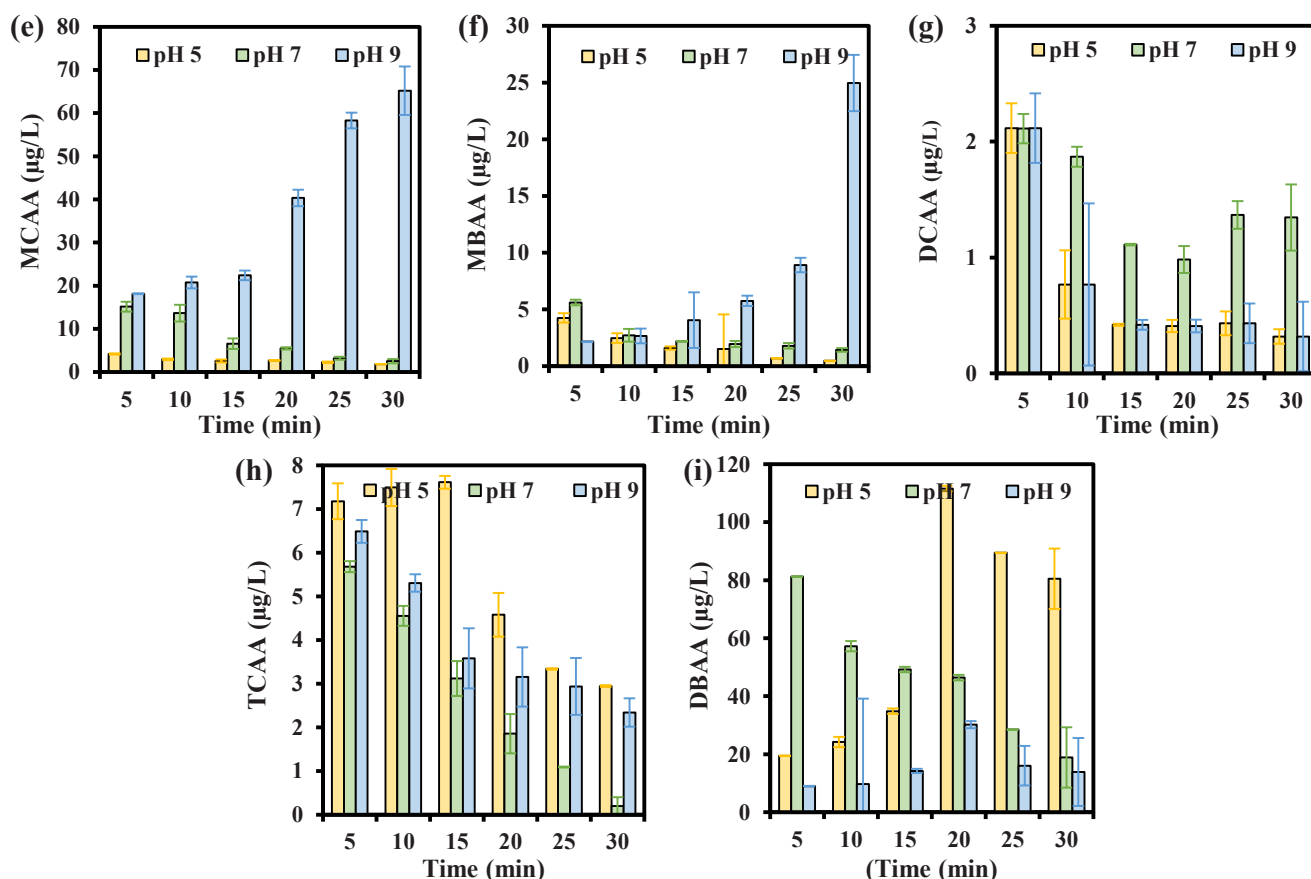


Fig. 4. Effect of initial pH on HAA5 formation during ozonation of NP containing water: (a) MCAA, (b) DCAA, (c) TCAA, (d) MBAA, and (e) DBAA (NP<sub>0</sub>: 4 mg/L, Cl<sub>2</sub>: 20 mg/L, Br<sup>-</sup>: 1 mg/L).

(30 min) required for effective NP removal. Other ozonation approaches, such as catalytic ozonation or advanced oxidation, may be required to improve NP degradation. Because the 30 min ozonation process could not completely remove NP from water, changing the ozonation initial pH was not cost-effective for NP removal.

### 3.2. Effect of ozonation on THM4 formation

THMs are a typical type of DBP discovered in organic matter-containing chlorinated water. Because the ozonation process converts high molecular weight DOM into low molecular weight DOM [41], understanding THMs precursor properties of ozonation by-product is essential. Fig. 3 shows the effect of ozonation of NP-containing water on the THM4 formation. Initial DBP formation and its calculated cytotoxicity of NP stock solution were provided in Table 2. After 5 min ozonation, the formation of TCM, a chloro-THM4 (Cl-THM4), was lower than from untreated 4-NP stock solution (Fig. 3a). Longer ozonation time at all initial pH conditions tended to result in lower TCM, with no significant differences between pHs for 30 min ozonation. Ozonation at alkaline conditions had high ozone reactivity and decomposition to OH• that are reactive to the phenolic group [20]. Because the phenolic and aromatic groups were precursors of TCM [42], the decrease in TCM formation might occur more quickly. On the other hand, because of the poor ozone reactivity [43], the decrease in Cl-THM4 production ozonation was slow under acidic conditions [21].

Similar to Cl-THM4, ozonation at all initial pH conditions lowered the formation of bromochloro-THM4 (Br-Cl-THM4) from the untreated 4-NP stock solution. The BDCM formation was slightly reduced by 21.5 %, 20.7 %, and 26.9 %, respectively, for 30 min ozonation at acidic, neutral, and alkaline initial conditions (Fig. 3b). CDBM formation

was reduced by 61.1 %, 51.5 %, and 62.1 %, respectively for 30 min ozonation at pH 5, 7, and 9 (Fig. 3c). Because CDBM is a Br-Cl-DBPs, the presence of bromide ions influenced its formation [44]. More bromine was incorporated into the water when the bromide-to-chlorine ratio was higher [45].

At neutral and acidic initial conditions, the TBM formation decreased significantly by 90.3 % and 94.8 %, respectively. The formation of bromo-THM4 (Br-THM4) had a different pattern compared with Cl-THM4 and Br-Cl-THM4 at alkaline ozonation initial condition. Similar to other THM4, TBM formation was reduced after 5 and 10 min ozonation at all pH initial conditions (Fig. 3d). The fluctuation might be caused by the formation of Br-DBPs precursor shifting into bromate, as indicated by bromate formation, when the ozone exposure increased under alkaline initial conditions [46]. The transition from hydrophobic to hydrophilic fractions, which were more reactive with bromine than chlorine, also contributed to the formation of Br-DBPs [44]. Although TBM formation increased under alkaline initial pH conditions, the overall initial pH condition of the ozonation process of NP-bromide-containing water could significantly decrease THM4 formation.

### 3.3. Effect of ozonation on HAA5 formation

Fig. 4 shows the effect of ozonation of NP-containing water on the HAA5 formation. After ozonation at acidic and neutral initial pH, the formation of chloro-HAA5 (Cl-HAA5) decreased compared with untreated 4-NP stock solution. The Cl-HAA5 formation was reduced with longer ozonation time for both initial pHs, albeit the reduction was higher and occurred from shorter ozonation time for acidic initial pH. After 30 min of ozonation at pH 5, MCAA (Fig. 4a), DCAA (Fig. 4b), and



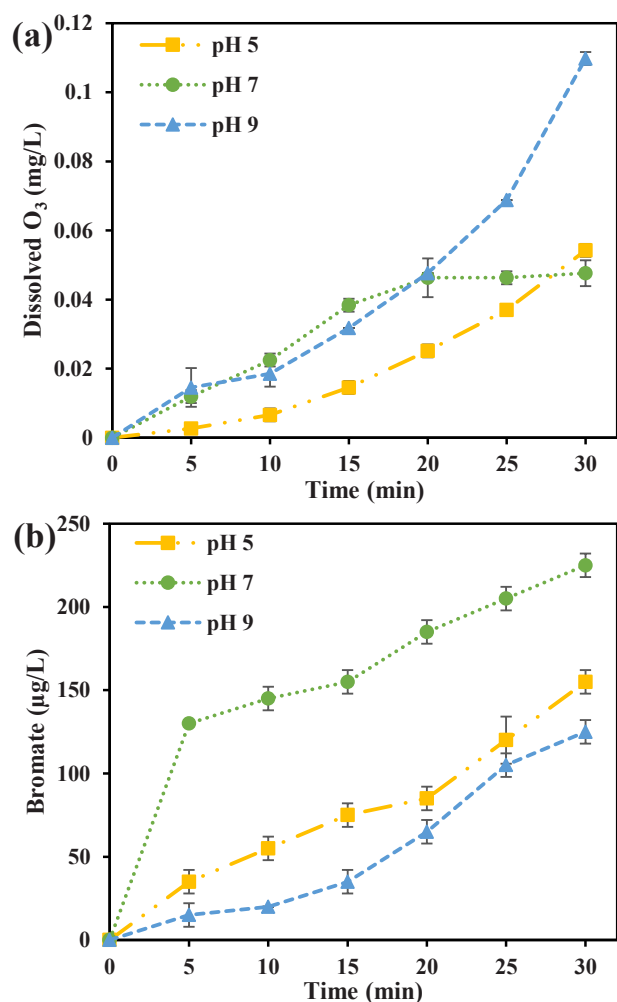


Fig. 5. Effect of NP ozonation initial pH on: (a) dissolved O<sub>3</sub>, and (b) bromate formation.

TCAA (Fig. 4c) formation was reduced by 85.0 %, 96.7 %, and 90.6 %, respectively. Conversely, even though 5 min ozonation at alkaline pH reduced the formation of DCAA (84.4 %) and TCAA (31.3 %), longer ozonation time tended to increase all three Cl-HAA5 formations. The MCAA, DCAA, and TCAA formation was increased by 200.90 %, 80.68 %, and 53.83 %, respectively, after 30 min ozonation at initial pH

9. High ozone decomposition at alkaline initial conditions might increase the DOM hydrophilicity that prompted the rise in HAA5 production [47].

Bromide causes the formation of more reactive bromine species, resulting in the formation of more Br-HAA5. 4-NP ozonation process at different pHs resulted in different trends of bromo-HAA5 (Br-HAA5) formation. The formation of MBAA tended to decrease with longer ozonation time at all initial pH conditions (Fig. 4d). On the other hand, ozonation increased DBAA formation (Fig. 4e). The highest increase was different for each pH: 18-folds for 20 min ozonation at initial pH 5, 13-folds for 5 min ozonation at initial pH 7, and 30-folds for 20 min ozonation at initial pH 9. According to Hua and Reckhow [47], brominated DBPs are formed as a result of an increase in DOM hydrophilicity. Mono- and di-HAA5 have different bromine incorporation properties [48]. As the ozonation period increased, the amount of dissolved ozone rose as well (Fig. 5a). When bromide-containing water is ozonated, ozone may react with the bromide to create bromate, which causes an increase in bromate content (Fig. 5b). The increase of bromate formation might impact the decrease formation of MBAA ( $P < 0.05$ ), which considerably is a mono-HAA5 [46]. The presence of HAA5 which contains two halogen ions (di-HAA) is frequently highlighted due to its high creation during the chlorination process in water treatment [49]. The formation of di-HAA is more dependent on the presence of DOM [50].

### 3.4. DBP formation mechanism

Fig. 6 illustrates a possible mechanism for THM4 and HAA5 precursor formation in the NP ozonation process. During the ozonation process in water, hydroxide ions cause the ozone to break down to OH•, hence the pH of the water is crucial [21]. In a water solution, ozone reacts by two different mechanisms: first, it directly and selectively reacts with particular functional groups (double bonds, nucleophilic sites) of the organic compound that has to be broken down; second, it responds through reactive oxygen species (ROS) produced during ozone breakdown [51,52]. When direct ozonation reactions take place, a significant portion of the interactions between most aromatic compounds and ozone take place at the benzene ring, resulting in the formation of phenolic compounds or ring cleavage [28]. More polar intermediates are formed when ozone is added to or attacks the aromatic ring [28]. Direct oxidation of ozone was very selective for certain functional groups known as the Criegee mechanism as well as unsaturated aromatic and aliphatic molecules [53]. The cleavage of unsaturated bonds and benzene rings was facilitated by the indirect oxidation of OH• because of its strong oxidation capacity and absence of selectivity [54].

In an indirect reaction, the alkyl chain might be attacked by the OH•, breaking down the NP into intermediates like propylphenol,

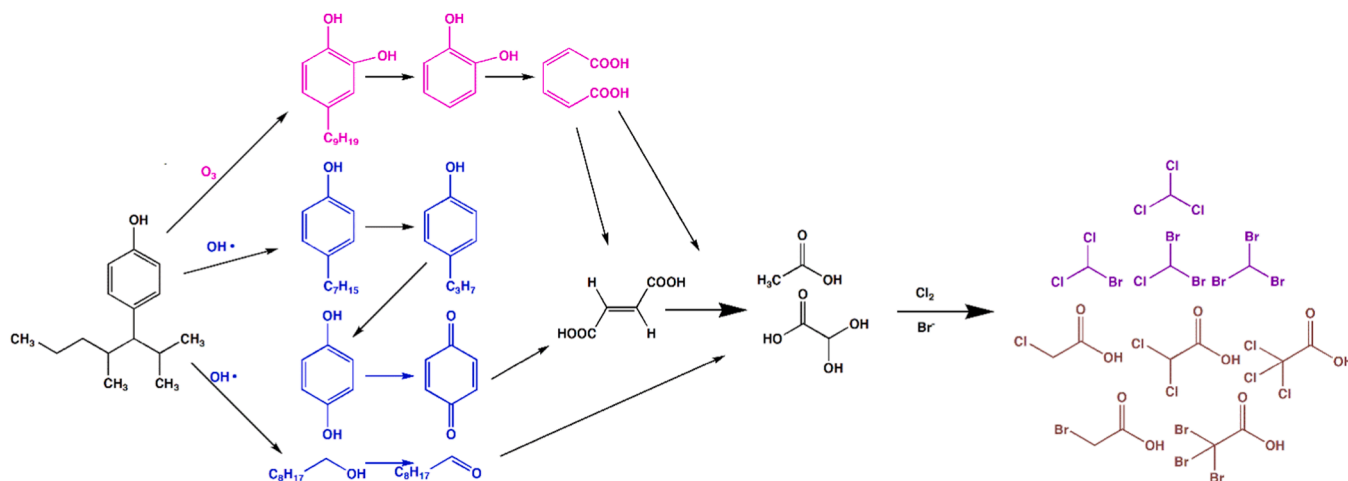


Fig. 6. Proposed mechanism of THM4 and HAA5 precursors formation during NP-Bromide-containing water ozonation processes.

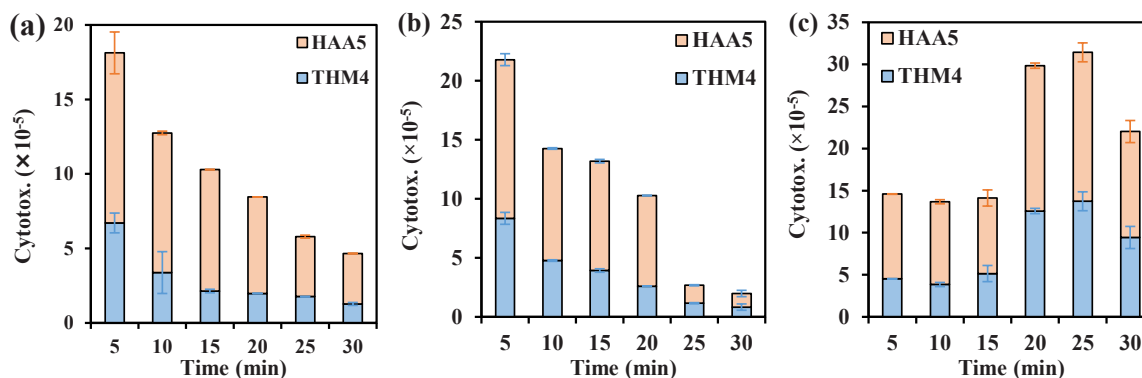


Fig. 7. Effect of ozonation initial pH on estimated DBPs' cytotoxicity of THM4 and HAA5 during ozonation of NP: (a) pH5, (b) pH 7, and (c) pH 9,.

pentylphenol, and heptylphenol [19]. Additionally, the benzene could be attacked by the  $\text{OH}\cdot$ , resulting in the formation of alkyl intermediates such nonanal and nonanol [19]. According to theory, the reaction of the EDC such as NP with radical species and ozone does not result in the full mineralization of the compounds under normal water treatment circumstances [28].

The THM4 and HAA5 precursor properties of NP [7] and another organic compound [55] have been reported previously. A phenolic compound such as hydroquinone and simple aliphatic compounds such as acetic acid both have precursor properties to form THM4 during the chlorination process [55]. The precursor characteristics of the intermediate product formed during certain times of the ozonation process of NP affect the formation of THM4 and HAA5.

### 3.5. DBPs cytotoxicity assessment

Fig. 7 shows the effect of ozonation initial pH estimated cytotoxicity of THM4 and HAA5 formation. The estimated cytotoxicity caused by THM4 formation decreased after ozonation processes at acidic and neutral initial pH (Fig. 7a–b), with longer ozonation time resulting in lower cytotoxicity. However, only 5–15 min and 30 min ozonation at alkaline conditions decreased the estimated cytotoxicity of THM4, while 20 and 25 min ozonation did not have an effect (Fig. 7c). Although did not have any obvious trend, the estimated cytotoxicity from HAA5 formation has similar decreasing of estimated cytotoxicity with THM4 ozonation process (Fig. 7a–c).

The total estimated cytotoxicity of THM4 and HAA5 formations can also be seen in Fig. 7. Ozonation at neutral initial conditions has the best cytotoxicity removal followed by acidic initial conditions. After 30 min processes, ozonation at acidic (Fig. 7a) and neutral (Fig. 7b) initial conditions can decrease the estimated cytotoxicity of the total amount of HAA5 and THM4 formation by 74.34 % and 93.31 % respectively. Conversely, DBPs' estimated cytotoxicity was raised by 33.72 % upon ozonation at an initial pH of alkaline (Fig. 7c). Since THM4 has the highest cytotoxicity compared to HAA5 [12], the total THM4 and HAA5 estimated cytotoxicity has a similar trend with THM4 in all research scenarios. Based on the results of this study, pH adjustment of ozonation under acidic or alkaline conditions is not required to reduce the cytotoxicity of DBPs.

Individually, most HAA5 have higher cytotoxicity than THM4 [12]. Br-DBPs such as DBAA and TBM are also reported to have higher cytotoxicity than Cl-DBPs such as TCM and TCAA [12]. The high formation of HAA compared to THM in almost all ozonation pH conditions causes a significant increase in cytotoxicity as ozonation time increases. The presence of bromide in water triggers the formation of Br-DBPs which also increases the cytotoxicity of the DBPs formed. Moreover, the ozonation process converts phenolic compounds into low molecular weight and hydrophilic organic matter which has higher precursor properties to the formation of brominated-DBPs compared to Cl-DBPs

[20]. The cytotoxicity level of DBPs formed during the chlorination process varies with ozonation conditions due to variances in ozonation by-products as DBP precursors. Choosing the right conditions will have an impact on public health issues.

The proposed processes successfully reduced the regulated DBPs' estimated cytotoxicity. However, the anthropogenic organic matter could not only form THM4 and HAA5 but also other toxic DBPs [56] and cytotoxicity is not the only source of toxicity of DBPs [57]. DBPs are cytotoxic, genotoxic, carcinogenic, neurotoxic, mutagenic, and teratogenic in the majority of cases [9]. Furthermore, several DBPs are developmental toxic [58] and limit growth [59]. Investigation of other toxic DBP formations from NP chlorination shall be conducted in future studies. Although THM4 and HAA5 exhibit varied levels of cytotoxicity, the more the DBP formation, the greater the toxicity. Lowering the cytotoxicity level can be accomplished by focusing the research scenario on low-cytotoxicity DBP formation (e.g., Cl-DBPs) or reducing all DBP formation. Since neutral initial pH conditions have a strong ability to remove cytotoxicity, altering the ozonation initial pH was not necessary for this research scenario.

## 4. Conclusions

The ozonation process has successfully reduced the NP-bromide-containing water. The pH rise improved NP degradation during the ozonation process. Ozonation reduces the THM4 formation but increases the TBM formation at an alkaline initial condition. On the other hand, the ozonation process under alkaline initial conditions tends to increase the formation of mono-HAA5 and decrease the formation of di-HAA5. The increase of DBP formation, notably at longer process time, indicates the formation of DBP precursors as a result of NP degradation. Neutral initial pH was the best ozonation condition due to their DBP formation reduction and economical aspect. After 30 min processes, ozonation at acidic and neutral initial conditions can reduce the estimated cytotoxicity of the total formation of THM4 and HAA5 by 74.34 % and 93.31 % respectively. On the other hand, ozonation at an alkaline initial pH increased DBP estimated cytotoxicity by 33.72 %. This finding can guide the water treatment plant operator in optimizing NP degradation and minimizing DBP formation. Furthermore, understanding the DBP-estimated cytotoxicity reduction may assist in mitigating public health concerns during the ozonation treatment of NP-bromide water. The findings of this study indicate that reducing the cytotoxicity of DBPs does not need adjusting the pH of ozonation under acidic or alkaline environments.

### CRediT authorship contribution statement

**Muammar Qadafi:** Conceptualization, Methodology, Investigation, Data analysis, Writing – original draft, Project administration. **Raden Tina Rosmalina:** Supervision, Conceptualization, Methodology. **Hanny**

**Meirinawati:** Methodology, Data analysis, Investigation. **Widyarani:** Conceptualization, Supervision, Writing – review & editing. **Diana Rahayuning Wulan:** Conceptualization, Supervision, Writing – review & editing.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgment

This research was funded by Riset dan Inovasi untuk Indonesia Maju (RIIM), National Research and Innovation Agency (No. 82/II.7/HK/2022) and Lembaga Pengelola Dana Pendidikan (LPDP) Republic of Indonesia. The authors thank E-Layanan Sains (ELSA) for providing the facilities and scientific support from Advanced Characterization Laboratories Bandung, National Research and Innovation Agency, Indonesia.

### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.toxrep.2024.101769](https://doi.org/10.1016/j.toxrep.2024.101769).

### Data availability

Data will be made available on request.

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