

Review

Chlorine Disinfection Byproducts: A Public Health Concern Associated with Dairy Food Contamination

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Abstract: The prevention of human infectious diseases associated with waterborne pathogens is reliant on the effective disinfection of water supplies by drinking water treatment plants and adequately maintained distribution networks. For decades, the chlorination of water has safeguarded public health, where chlorine is broadly applied in both water disinfection and food production facilities, including the dairy industry, from farm to fork. The identification of chlorine disinfection byproducts in water supplies and dairy food produce is of great concern, however, due to their cytotoxic, genotoxic, mutagenic, teratogenic, and potential endocrine-disrupting activity. The association between the trihalomethanes (THMs) and haloacetic acids (HAAs) and tumour formation is documented and has led to the implementation of maximum contaminant levels enforced by the European Union. Furthermore, chlorine resistance in bacterial species is associated with multidrug resistance in clinically relevant pathogens, where antibiotic- and biocidal-resistant genes are also environmental pollutants. Increasing the concentration of chlorine to surmount this resistance will ultimately lead to increasing concentrations of byproducts in both water and food products, exceeding the EU requirements. This article provides insight into chlorine DBPs as a toxicological public health risk and the relationship between chlorine resistance and antibiotic resistance in microbes relevant to dairy food production.

Keywords: chlorine; disinfection byproduct; dairy; toxicology; health risk; carcinogenic



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1. Introduction

Chlorine is an effective biocide with broad-spectrum antimicrobial activity, which is economically viable for broad-scale application. With the addition of water, chlorine is hydrolysed to give hypochlorous acid (HOCl), which dissociates, yielding hydrogen and hypochlorite ions [1]. The application of chlorine as a drinking water disinfectant has been monumental in safeguarding public health from waterborne infectious diseases, including cholera and typhoid. Similarly, chlorine is the most common chemical disinfectant applied in food production facilities to reduce the transmission and occurrence of foodborne infectious disease [2]. Disinfection byproducts (DBPs) have emerged as a toxicity issue associated with the use of disinfectants in water treatment and food production. Over 800 DBPs have been identified in drinking water [3], which are formed when disinfectants react with natural organic matter (NOM), anthropogenic contaminants, and brominated and iodinated compounds present in water sources [4]. Emerging organic micropollutants (EOMPs) are abundant in water systems and include synthetic and naturally occurring chemicals, e.g., pharmaceuticals, personal care products, pesticides, and industrial chemicals, which are a toxicological risk to human and environmental ecosystems [5]. The

formation of DBPs, namely trihalomethanes (THMs), i.e., trichloromethane (CHCl_3), tribromomethane (CHBr_3), bromodichloromethane (CHCl_2Br), and dibromochloromethane (CHClBr_2), chloroform, and bromoform, occurs when chlorine reacts with NOM present in water sources [6]. Additional DBPs formed with the chlorination of water include haloacetic acids (HAAs) and nitrogenous DBPs, including haloacetonitriles (HANs), haloacetamides (HAcAms), and dimethylnitrosamine (NDMA) and halogenated aldehydes (HAs) (Table 1). The nitrogenous DBPs are more toxic than the THMs and HAAs but are not currently regulated in water supplies [7]. Chloroform is the most abundant THM in treated water and is, therefore, often the focus of toxicology studies [8]. These DBPs are known to be a toxicological risk, having cytotoxic, mutagenic, carcinogenic, teratogenic, and neurotoxic activity [9]. The carbonaceous THMs are more prominent in water supplies and are therefore regulated by the World Health Organization (WHO) due to their public health risk. The WHO sets maximum limits of 300, 100, 100, and 60 $\mu\text{g/L}$ for chloroform, bromoform, DBCM, and BDCM, respectively, with a maximum contaminant level (MCL) established by the European Union (EU) of 100 $\mu\text{g/L}$ for total THM concentration in water [10]. The WHO also recommends a residual level of chlorine at 0.2 to 0.5 mg/L in water supplies to maintain disinfection [1]. The US EPA has implemented Stage 1 and Stage 2 Disinfectants and Disinfection Byproducts Rules (DBPRs) and Microbial and Disinfection Byproducts Rules (MDBPs), which assess compliance with the set limits for total THMs and HAAs in water. Research by Shi et al. (2024) shows a positive correlation between high concentrations of THMs in water and an increased risk of cancer, with exposure duration an important variable [11]. Epidemiology studies have mainly focused on a possible relationship between chlorine and increased risk of colorectal cancer (CRC) and bladder cancer [12]. Chlorite (ClO_2^-) and chlorate (ClO_3^-) are DBPs produced when chlorine dioxide (ClO_2), chlorine, and hypochlorite are applied as disinfectants and a contaminant associated with water and dairy food. Importantly, chlorination is not effective at eliminating certain microbial species, including parasites *Giardia*, *Cryptosporidium*, and bacterial species capable of producing endospores, e.g., *Bacillus* species [13]. Furthermore, chlorine exposure has been associated with antimicrobial resistance (AMR) in many pathogenic species [1]. Clinically, AMR is a global public health concern where the increasing prevalence of resistant pathogens is associated with increasing rates of morbidity and mortality [14]. Increasing the concentration of chlorine applied to surmount this resistance will ultimately lead to increasing concentrations of THMs and chlorate in both water and food products, exceeding the EU MCLs. Identifying suitable biocidal solutions as alternatives to chlorine in food production is an ongoing challenge, where the concentration of DBPs in water used in situ also impacts THM and chlorate levels in dairy foods. This article provides insight into chlorine DBPs as a toxicological public health risk and chlorine resistance in microbes relevant to dairy food production. The correlation between chlorine, DBPs, and the proliferation of AMR and antibiotic resistance genes (ARGs) as environmental pollutants is also discussed.

2. Chlorine Disinfectant Byproducts in Water Supplies

The volatile THMs are the most common DBPs formed with the addition of chlorine to water due to a chemical reaction with organic matter naturally present in waterways, such as humic acid (HA) and fluvic acid (FA), quantified in terms of total organic carbon (TOC) (Table 1). The non-volatile HAAs are the second most common DBPs found in water sources. HA constitutes the major portion of organic material present in surface waters, deriving from living or decaying vegetation or microbial decomposition processes. The proportion of humic acid in the TOC of ground and surface water has been estimated to be 71.4 to 82.5%, respectively [15]. Humic acids are more reactive than fulvic acids in terms of DBP formation. TOC acts as a nutrient source for microbial species and can support biofilm

growth in water distribution networks, resulting in infectious health risks [15]. Wastewater, in particular, has concentrations of inorganic ions, EOMPs, and microbial species present, which generate many DBPs, which are ultimately discharged into surface water and downstream drinking water treatment plants [16]. The formation of DBPs is influenced by the chlorine concentration and contact time, temperature, pH, and concentration of inorganic precursors (iodide, bromide ions) present [17]. These water quality parameters vary depending on location, season, and climate. Surface water has less bromide and iodide ions, and so chlorinated byproducts prevail with chlorine disinfection (HOCl/OCl^-). In the presence of bromide and iodide ions, oxidation leads to the formation of hypobromous acid/hypobromite (HOBr/OBr^-) and hypiodous acid/hypiodite (HOI/OI^-), respectively [18]. When exposed to DBP precursors, the formation of chloro-bromo, chloro-iodo, and chloro-bromo-iodo occurs. Removal of organic matter (OM) precursors from water aims to prevent or reduce the formation of THMs and is achieved via coagulation, adsorption, biodegradation, and filtration processes, the removal of bromide ions however, is small in most conventional treatment protocols [18]. The EU has set an MCL of 100 $\mu\text{g}/\text{L}$ combined concentration for the THMs and an MCL of 60 $\mu\text{g}/\text{L}$ for the sum of monochloro-, dichloro-, and trichloro-acetic acid, and mono- and dibromo-acetic acid combined HAAs in drinking water [19]. ClO_2 is often considered a suitable antimicrobial alternative to chlorine as it is not associated with the production of halogenated organic compounds [20]. As a known goitrogen having negative effects on the thyroid gland, chlorate is regulated by the EU (regulation 2020/749) at maximum levels of 0.10 mg/kg in milk products and 0.70 mg/L in chlorinated water [21]. As the health risks associated with DBPs and anthropogenic water pollution emerge, increasing awareness is needed at a global scale to monitor and prevent associated morbidity. Pollution of drinking water is a growing health concern that needs to be aligned with water access, sanitation, and hygiene (WASH) issues as monitored by the WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene (JMP) since 1990 [22]. The United Nations (UN) Sustainable Development Goal (SDG) number 6, Water and Sanitation, aims to “Ensure availability and sustainable management of water and sanitation for all” and to provide safe drinking water by 2030 [23]. The latest WASH report details published in 2023, shows that in 2022 an alarming 27% of the global population do not have access to “safely managed drinking water”, 43% of the global population do not have access to “safely managed sanitation” and 25% of the global population did not have domestic access to basic handwashing facilities [22]. Chlorinated water is used for consumption, domestic use, leisure activities, and in food production, meaning that exposure routes are varied and unquantifiable amongst individuals within populations.

Table 1. Chlorine disinfection byproducts produced in water treatment and associated toxicity.

Category	Disinfectant Byproduct	Toxicity	Exposure Risk
Oxyhalides	Chlorite (ClO_2^-), chlorate (ClO_3^-)	Erythrocyte toxicity, headache, dizziness, and methemoglobinemia. Ingestion may produce gastrointestinal distress, and kidney toxicity [24], reproductive, neurodevelopmental, and endocrine disruptors [20].	Ingestion and inhalation exposure.
Trihalomethanes (THMs)	Chloroform, Bromoform, Dibromochloromethane (DBCM), Bromodichloromethane (BDCM)	Probable carcinogens, acute exposure can lead to adverse health effects, reproductive and developmental issues, headaches, dizziness, central nervous system (CNS) toxicity [25], birth defects, low birth weight, miscarriages, stomach and colorectal cancers [26], neurotoxicity, hepatotoxicity, nephrotoxicity, and reproductive toxicity	Volatile, can evaporate from water, exposure through ingestion, inhalation, skin, risk associated with drinking, cooking, domestic exposure, and swimming pools [25]; MCL of 100 $\mu\text{g}/\text{L}$ applies [19].

Table 1. Cont.

Category	Disinfectant Byproduct	Toxicity	Exposure Risk
Haloacetic acids (HAAs)	Monochloro-, dichloro-, and trichloro-acetic acid, and mono- and dibromo-acetic acid	Carcinogenicity, spontaneous abortions, and birth defects [27].	Non-volatile, ingestion is the main route of exposure; MCL of 60 µg/L applies [19].
Nitrogenous DBPs	Haloacetonitrile (HANs), haloacetamides (HAcAms) and dimethylnitrosamine (NDMA)	Cytotoxicity, genotoxicity in vitro, kidney toxicity, renal tubular swelling, and glomerulus hemorrhage in animal models [7].	Not regulated in drinking water.

2.1. Chlorine Disinfection in Dairy Food Production

The presence of DBPs in dairy food is of concern as dairy production relies heavily on chlorine to ensure effective disinfection of food production equipment, including milk bulk tanks and milking parlours. Furthermore, the dairy industry has a high water consumption, with ca. To make 1 kg of cheese, 5000 L of water is used [28]. Moreover, atmospheric volatilisation of chlorine DBPs can lead to absorption via inhalation, exposing handlers applying chlorine as a disinfectant. As the human population increases, there is an increasing demand for dairy food produce with global milk production currently at 630,000 million L annually, followed by further processing before market [16]. Consequently, there are extensive volumes of waste and effluent produced by the dairy food sector, which is discharged into natural waters, resulting in nutrient and microbial pollution and eutrophication, disrupting natural ecosystems [29]. Dairy effluent contains fat, protein, nutrients including phosphorus and nitrogen, microbial species, chemical biocidal agents, and their DBPs, which ultimately represent an ecotoxicological risk to surrounding waterways [30]. Biocides are used as cleaning in place (CIP) disinfectants for many industrial setups, including food production. CIP uses large quantities of water, chemicals, and energy, with the CIP process using ca. 15% of a company's total water consumption to meet hygiene standards. At a global scale, the processing of dairy foodstuff utilizes ca. 11 L of water per litre of milk processed, where CIP alone requires 28% of this water volume [28]. CIP is a circulatory washing system that runs cleaning and disinfectant liquid through pipes and machines without opening or dismantling the system [28]. Due to its effective broad-spectrum antimicrobial activity, chlorine is applied for CIP in dairy processes as hypochlorite or gaseous chlorine [31]. For decades, chlorine has ensured food safety from microbial infectious risk; however, issues relating to contamination of dairy produce with chlorates, HAAs, and THMs have emerged. In response to this, dairy food producers in the Republic of Ireland implemented a prohibition of chlorine-based chemicals at the farm level and in dairy production facilities in 2021 [32]. Additionally, issues such as chlorine resistance promoting multidrug resistance (MDR) in pathogens and microbial biofilms present in food production facilities mean increasing concentrations of chlorine need to be added to provide satisfactory levels of microbial death [33]. Increasing chlorine concentration to circumvent resistance will undoubtedly lead to higher levels of chlorine residuals and DBPs in dairy production facilities, making it more difficult to comply with the MRLs in place.

2.2. Disinfection Byproducts Detected in Dairy Food

DPBs such as THMs and chlorate enter the food chain as residues via the use of contaminated water in CIP processes or from contact between milk and water [34]. The THM trichloromethane (CHCl_3) or chloroform, which is listed as a Group 2B carcinogen, has been detected in dairy food samples with studies describing greater than 0.176 mg/kg TCM in

dairy products [35]. Studies report the presence of 2 THMs, in particular trichloromethane, and 3 HAAs, mainly dichloroacetic acid, in 56 cheese samples at $\mu\text{g}/\text{kg}$ levels [27]. Studies have shown that the chlorination and chloramination of dairy wastewater increased the aliphatic DBPs concentration to $485.1 \mu\text{g}/\text{L}$ and $26.6 \mu\text{g}/\text{L}$, respectively, from non-detectable levels [16]. The use of chloramine as disinfectant has previously been shown to decrease the formation of HAAs and THMs in water but increases the concentration of nitrogen-containing DBPs, i.e., N-nitrosamines, which are more genotoxic and cytotoxic DBPs [36]. As lipophilic compounds, these THMs can bioaccumulate in milk fat, where HAA is highly soluble in water and can persist in water sources. Importantly, the non-volatile HAAs can persist in milk longer than the volatile THMs due to their lack of volatility and stability in milk at a pH of ca. 6.5 [37]. Research by Cardador and Gallego (2016) detected HAAs dichloroacetic (DCAA) and trichloroacetic (TCAA) in 20% of dairy products tested at concentrations below $2 \mu\text{g}/\text{L}$ [37]. Research has detected chlorate levels of $\geq 0.0020 \text{ mg}/\text{kg}$ in dairy foods and infant milk formula, where a maximum residual level (MRL) of $0.01 \text{ mg}/\text{kg}$ applies for infant food products [32]. Other studies detected chlorates in ca. 73% of samples at concentrations up to ca. $18.70 \mu\text{g}/\text{kg}$ averaging at $7.10 \pm 5.88 \mu\text{g}/\text{kg}$, much below the MRL of $0.1 \text{ mg}/\text{kg}$ imposed by Commission Regulation (EU) 2020/749 in June 2020 for milk, including raw milk and heat-treated milk [34]. The studies of Twomey et al. (2023) detected chlorate in milk ranging from 0.0020 to $0.094 \text{ mg}/\text{kg}$, 0.0022 – $0.024 \text{ mg}/\text{kg}$ in cream, 0.012 – $0.23 \text{ mg}/\text{kg}$ in natural yoghurt, 0.011 – $0.26 \text{ mg}/\text{kg}$ in blueberry yoghurt, 0.01 – $0.50 \text{ mg}/\text{kg}$ in raspberry yoghurt and 0.01 – $0.69 \text{ mg}/\text{kg}$ in strawberry yoghurt [21]. This study concluded that milk, cream, and yoghurt were more frequently contaminated with chlorate, with little to no chlorate detected in butter and cheese. Li et al. (2023) detected chlorate levels of $34.3 \mu\text{g}/\text{kg}$ in infant formula milk powder, with the average dietary intake for infants < 6 months determined to be $0.71 \mu\text{g}/\text{kg}$, respectively [38], which is deemed to be an acceptable level. Research by Nobile et al. (2022) detected chlorates in 73% of raw milk samples at concentrations $\leq 18.70 \mu\text{g}/\text{kg}$ with an average concentration of $7.10 \pm 5.88 \mu\text{g}/\text{kg}$, well below the EU MRL of $0.1 \text{ mg}/\text{kg}$ [34].

It must be noted that the detection of DBPs in dairy food is hindered by the complex biological matrix, which contains fat, protein, and immunoglobulins, amongst other components. Conventional laboratory equipment, namely gas chromatography (GC), liquid chromatography (LC), and ion chromatography (IC), often combined with mass spectrometry, is used to determine DBPs in water [39] but must be optimized to counteract the biological matrix present in dairy products.

2.3. Toxicology Risks of DBPs

Research studies have demonstrated the toxicology relationship between THMs and hepatotoxicity, nephrotoxicity, embryo toxicity, and congenital disabilities, where low concentrations are considered mutagenic and possibly carcinogenic [40]. Following exposure, THMs are absorbed and bioaccumulate in adipose tissues, organs, including the liver, kidney, and lungs [8]. After absorption, these elements tend to bioaccumulate in adipose tissue. The key enzymes involved in their detoxification or metabolism include cytochrome P450 (CYP2E1) and glutathione S-transferase (GSTZ1 and GSTT1) [41]. THMs have short half-lives ranging from minutes to hours; a steady state concentration is believed to be present, however, due to the frequency of exposure and movement out of adipose tissue in vivo (Table 2) [42]. Epidemiological studies have shown the association between chlorine and bladder and rectal cancer and patient mortality, where DPB concentrations are elevated in water sources [43]. Chlorine DBPs have also been associated with stomach, brain, pancreas, lung, and liver cancers, where epidemiological studies have also shown their relationship to animal and human reproductive issues, including infertility [44]. DCAA and dibromoacetic

acid (DBAA) have demonstrated neurotoxicity in rat studies, with exposure to THMs inducing autistic like behaviour in test mice [44]. The International Agency for Cancer Research (IARC) has listed DCAA as a possible human carcinogen (group 2B) [45]. Research showed that THMs associated intrauterine growth retardation was impacted by a polymorphism where affected newborns without the hepatocyte detoxifying enzyme CYP2E1 variant were at increased risk [46]. Research by Yang et al. (2016) investigated the impact of CYP2E1, GSTZ1, and GSTT1 polymorphisms and blood concentrations of THMs on semen in 401 men and concluded that such polymorphisms may impact semen quality [41]. More recently, studies have demonstrated endocrine-disrupting activity, having decreased the levels of testosterone, androgen receptors in male testis, increased miscarriage rates, and follicle-stimulating hormone with reduced oestradiol and progesterone in female mice [47]. DCAA and TCAA may warrant recognition as endocrine-disrupting chemicals (EDCs) due to their impact on embryonic development and male and female gonadal development, where TCAA has a long half-life of ca. 6 days [48]. The brominated THMs BDCM and DBCM have increased lipophilicity and genotoxicity potential. With oral dosing of the rat species, BDCM was hepatotoxic at 400 mg/L and nephrotoxic at 200 mg/L [8]. In the rat species, DBCM was not associated with carcinogenicity, developmental toxicity, but did cause infertility in generational studies [49]. CHBr₃ has demonstrated the greatest mutagenic and cytotoxic potential among the brominated THMs in rodent, human, and bacterial test cells, with bacterial mutagenicity occurring at low concentrations of ca. 0.2 mg/L [50]. In vivo mouse studies show that THMs have a lethal dose in 50% of subjects (LD₅₀) of 707–1550 mg/kg for mice and 250–500 mg/kg and 300–700 mg/kg for children and adults, respectively [49]. Chloroform is the most prevalent THM in treated water and has demonstrated genotoxic effects on human lung cells at concentrations of 11.9 mg/L, which is significantly lower than yeast test cells, where 5600 mg/L was deemed genotoxic [51]. Chloroform is associated with carcinogenesis by non-genotoxic methods, where chloroform causes decreased methylation and overexpression of proto-oncogenes [52]. Chloroform is lipid soluble and results in central nervous system (CNS) toxicity, GABA receptor activation, and rapidly enters many organs such as the liver, kidneys, heart, and brain due to the ease with which it can transverse membranes [53]. Chlorate inhibits the uptake of iodine and produces methaemoglobin and has a tolerable daily intake (TDI) of 3 µg chlorate/kg body weight [54]. The HAAs, TCAA, and DCAA have demonstrated liver tumorigenic activity in rats and mice, where dichloroacetic acid may disrupt intracellular signalling pathways and trichloroacetic acid impacts peroxisome proliferation [52]. DCAA and TCAA were teratogenic and induced developmental and reproductive issues, reduced sperm count, low birthweight, and reproductive damage in mice and rats [55]. HAAs are believed to negatively impact male steroidogenesis, the internal testicular structure, and spermatogenesis according to toxicology studies [56]. Studies show that concentrations four times less than the LD₅₀ for HAAs resulted in testicular toxicity, testis atrophy, destruction of seminiferous tubules, and loss of germ cells in vitro and in vivo [47]. The studies of Zhang et al. (2024) determined that DCAA reduced sperm count and motility in men regardless of exposure route, with greater impact observed in leaner men (BMI < 25 kg/m²) [55]. HAAs are also associated with developmental issues of the testes and ovaries and production of sex hormones, including estrogen, testosterone, luteinising hormone, and follicle-stimulating hormone, and disrupt thyroid function [47]. Indeed, HAAs have weak estrogenic and androgenic activity. The studies of Sun et al. (2020) established a potential susceptible risk period for small for gestational age, low birth weight, and preterm birth with exposure to DBPs at 23 to 35 weeks of pregnancy [42].

With increasing issues of infertility and cancer prevalence at a global scale, it is imperative that the exact impact and mechanisms of toxicity of DBPs are established. At

present, studies are hindered by the experimental models applied, including differences in experimental parameters, THM type, concentration, exposure route, exposure time, and environmental factors. Additionally, toxicity studies primarily focus on single DBPs, where exposure to complex mixtures or DBPs is more realistic in terms of water and food contamination. Investigation into the synergistic effect of the non-regulated DBPs is also overlooked in terms of toxicology risk assessment. Due to their pharmacokinetic profiles, HAAs are often considered as biomarkers for exposure to DBPs, with epidemiological studies focusing on blood concentrations of DCAA and TCAA and corresponding health issues [57]. The reproducibility of such experiments, however, is impacted by many variables, including individual exposure routes, geographic location, initial concentration of DBPs in the water, and must be optimized for population-level studies. Epidemiology studies assessing toxicity risk, including the reproductive impact of THMs and HAAs, are likely impacted by confounders such as trimester of pregnancy, alcohol consumption, smoking, and polymorphisms in essential metabolic enzymes, e.g., CYP2E1. To reduce the presence of DBPs in water sources, environmental waterways, and human exposure, minimisation strategies are employed, including the removal of TOC, pH control, application of alternative disinfectants [58] e.g., ultraviolet (UV) radiation [59], reducing chlorine residual and contact time, membrane filtration, and the use of activated carbon absorption [58,60]. The Republic of Ireland introduced a chlorine ban in dairy food production in 2021 to reduce the presence of DBPs in dairy food to meet the requirements of the MRLs for export [32]. An excellent article assessing the impact of this ban is provided by Twomey et al. (2024), which shows a reduction in THM and chlorate levels in milk samples post-ban implementation [32]. Rinsing milking parlour equipment and bulk milk tanks with clean water to remove chlorine residues post-CIP is implemented to meet MRLs in place. The impact of such strategies, however, must be assessed in terms of microbial risk, where chlorine residual and contact time, for example, are important parameters for microbial death.

Table 2. Variables impacting the formation of DBPs in chlorine-treated water and toxicity following exposure.

Outcome	Factor/Variable	Comment
DBP formation	Ph	Formation of DBPs is pH-dependent; pH impacts the type and amount of DBPs, THMs concentration decreases, and HAAs increase as pH decreases. More acidic pHs produce less chloroform [52], and increasing pH leads to the formation of THMs (pH 9.5).
	Temperature	Increasing temperature increases DBP formation, e.g., an increase from 10 to 30 °C produces a 15–25% increase.
	Presence of organic material and industrial contaminants	THMs and HAAs are produced from reactions of humic and fulvic substances with chlorine [52]. Humic acids are more reactive than fulvic acids.
	UV in the presence of bromide and chlorine	Concentrations of THMs, HAAs, and brominated DBPs increase in the presence of TOC and UV at 254 nm [61,62].
	Chlorine concentration	Production of THMs and HAAs increased with the increase of chlorine dosage, e.g., 20 µg/L THMs produced with 3 mg/L chlorine vs. 10 µg/L at 0.5 mg/L chlorine [63].
	Contact time	Rapid formation in <5 h, 90% formed within 24 h.
	Location	Impacted by geographical location, urban industrial activity, and rural farming activity.

Table 2. Cont.

Outcome	Factor/Variable	Comment
DBP mammalian toxicity	Lipid solubility	THMs are lipid soluble, brominated, and have increased lipophilicity [8]; chloroform is lipid soluble, and HAAs are water soluble. THMs bioaccumulate in fatty tissue.
	Presence of nitrogen	Nitrogen-containing DBPs, i.e., N-nitrosamines, are more genotoxic and cytotoxic [36].
	Pharmacokinetics—ADME	Cytochrome P450 (CYP2E1), glutathione S-transferase (GSTZ1 and GSTT1) metabolize THMs, reducing toxicity. Polymorphisms in these genes impact toxicity [41].
	Half-life	Half-life of TCAA is 2.1 to 6.3 days, BDCM half-life of 0.45–0.63 min, THMs have half-lives of minutes to hours [42].
	Volatility	HAAs are the main non-volatile DBPs [37], while THMs are volatile.
	Endocrine-disrupting action	HAAs have weak oestrogenic and androgenic activity.
	Exposure route	Bathing and swimming showed a considerably increased risk in a bladder cancer study [46].

3. Chlorine-Associated Antimicrobial Resistance

The use of chlorine in dairy food production is associated with the contamination of milk products with chlorine residuals and DBPs, which may exceed the established MCLs in place. Furthermore, the broad-spectrum application of chlorine and antibiotics in food production has resulted in the emergence and proliferation of antimicrobial resistance and environmental contamination with antibiotic-resistant genes (ARGs) [33]. Therefore, the presence of AMR species, antibiotic residues, and ARGs in dairy food production has come under investigation [64]. The WHO and the EU have implemented MRLs for antibiotics in animal food products intended for human consumption, where an MRL of 100 µg/kg applies for tetracycline, oxytetracycline, and/or chlortetracycline in milk [65,66]. The presence of AMR pathogens [67] and ARGs in water distribution networks and food production facilities is a serious public health risk. Exposure of microbes to chlorine and its DBPs is believed to trigger oxidative stress, regulatory proteins that cause gene expression of ARGs, the intake and accumulation of antibiotics, and gene mutations leading to AMR, ultimately causing bacterial antibiotic resistance [66]. Chlorine exposure also increases the concentration of reactive oxygen species (ROS), enhances membrane permeability, and activates efflux pumps conferring resistance to antibiotics [68,69]. *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Salmonella* spp., *Listeria monocytogenes*, and enteropathogenic *E. coli* are the most common pathogens found in raw milk and associated dairy products and are present in dairy production facilities [67]. Resistance or a reduced susceptibility to biocidal agents may be intrinsic in certain species or acquired via gene sharing similar to antibiotic resistance mechanisms, where plasmids and efflux pumps play a prominent role [68] (Table 3). Chlorination at concentrations of 2–4 mg/L promotes AMR by promoting the expression of efflux pumps, resulting in chlorine resistance [69]. Biocide-resistant genes (BRGs), including the *intl1* gene, *qac*, and *cepA* genes, have been identified in many pathogenic species [70]. Microbial species present can spread ARGs via horizontal gene transfer (HGT) of mobile genetic elements, e.g., integrons, insertion sequences, promoting the emergence of MDR species [71]. Such ARGs persist in water post microbial death and are more difficult to remove than the microbes themselves [72]. Studies have demonstrated that disinfectants provide a selective pressure that enables the uptake of BRG and ARGs

and promotes AMR [73]. In the presence of sub-toxic chlorine concentrations, certain species also become chlorine tolerant [61,62] and possess both chlorine resistance and MDR or even pandrug resistance (PDR) (resistance to all clinically available antibiotics). Biofilms present in water networks provide a protective environment for microbial species where the exopolysaccharide (EPS) matrix prevents chemical penetration, allowing for microbial survival and growth [65], conferring AMR on microbial species. Biofilms of certain species can form in the presence of chlorine residual concentrations in water distribution systems [74]. Furthermore, HGT of ARGs and plasmids is common amongst these biofilm species and leads to the emergence of MDR and PDR phenotypes [74]. Biofilm-forming PDR pathogens commonly associated with water contamination include Gram-negative *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *E. coli* [75]. *E. coli*, for example, is a common microbial contaminant of water and acts as a fecal contamination indicator as recommended by the EPA. Diarrheagenic *E. coli* is the leading cause of waterborne gastroenteritis globally, where its robust virulence factors allow for extra-intestinal infections and immune survival [76]. Studies have identified chlorine resistance up to 1.5 ppm in *P. aeruginosa* isolated from water networks carrying the *intI1* gene, where *P. aeruginosa* is highly MDR and a prolific biofilm formerly classified as a high priority pathogen by the WHO [77] and a clinically relevant ESKAPE (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species) pathogen [78]. The ESKAPE pathogens are a global public health risk due to their significant MDR, morbidity, and mortality [70]. *P. aeruginosa* is a prolific biofilm former in oligotrophic environments and a psychotropic organism, allowing it to persist in water distribution networks and dairy food production facilities. Microbes that are chlorine tolerant, or chlorine injured, may be difficult to culture in vitro as they are physiologically damaged, leading to inaccurate assessments of their presence in treated water [72]. Chlorine-injured bacteria may be considered viable but non-culturable bacteria (VBNC). In unfavourable environmental conditions, bacteria, including *E. coli* and ESKAPE pathogens, can enter a VBNC state as a survival mechanism [79]. VBNC pathogens, including *Listeria* and *Campylobacter*, are present in dairy food production facilities [80]. Chlorine disinfection and residual chlorine levels in wastewater have been associated with a VBNC state in *E. coli*, demonstrating the risk associated with antimicrobial residues [81]. Additionally, VBNC *E. coli* will hinder the detection of this species as per the requirements of the WHO water contamination indicator organism protocols. The studies of Hou et al. (2019) detected up to a 5.6-fold increase in resistance to ceftazidime, chloramphenicol, and ampicillin in chlorine-tolerant *P. aeruginosa* treated with 4 mg/L sodium hypochlorite, where efflux pump activation was overexpressed [82]. Research by Vijayakumar et al. (2018) assessed the presence of BRGs and minimum inhibitory concentration (MIC) values in MDR strains of *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* having high occurrence of *cepA* genes [68]. The MIC is the minimum concentration of antimicrobial agent needed to inhibit the growth of the test microorganism. The studies of Chen et al. (2023) detected antibiotic and biocidal resistance in *Salmonella* and *E. coli* strains having the *intI1* gene, and/or *qacEΔ1-sul1* gene conferring resistance to disinfectants [83]. Tetracycline-resistant *E. coli* had increased resistance to chlorine at concentrations of 1 mg/L compared to non-resistant strains [84]. Studies identified pathogenic diarrheagenic *E. coli* strains, including enteroinvasive *E. coli*, enterotoxigenic *E. coli*, and enteropathogenic *E. coli* possessing significant MDR, which survived wastewater chlorination, had the ability to grow in the presence of 5 mg/L chlorine [76]. Similarly, antibiotic-resistant *E. coli* and *P. aeruginosa* achieved re-growth following chlorination at 1, 2, and 5 mg/L [62]. Chlorine treatment of *A. baumannii* caused expression of efflux pumps and ARGs conferring resistance to chloramphenicol, sulfonamides, and β -lactam antibiotics [66]. Studies also describe resistance to clinical antibiotics amoxicillin, penicillin, trimethoprim sulfamethoxazole, and

cephalothin in chlorine-resistant *S. aureus*, *Micrococcus*, and *Aeromonas* species isolated from treated water [85]. Research suggests that chlorine-resistant bacteria possess high levels of resistance to sulfamethoxazole and tetracycline antibiotics in particular, which may be due to domestic, industrial, agricultural, and clinical effluent contaminating surface waters with antibiotics and anthropogenic chemicals [76]. Chlorine-resistant bacteria can promote chlorine-resistant biofilm formation in water distribution systems, which are distinctly different than their non-resistant counterparts, where the presence of antibiotic residues enhances chlorine tolerance [86]. Studies also report a high presence of bacterial plasmids and mobile genetic elements such as insertion sequences in chlorinated water [69], which can be taken up by bacterial species, enabling AMR proliferation in water. Studies have shown that the chlorination of water increased the frequency of transformation and HGT of ARGs amongst bacterial species in chlorine-tolerant species, enhancing the ARG profile of bacteria [72]. Transformation is a natural process in bacteria where naked DNA is taken up and incorporated into the genome of bacteria or held as an extra-chromosomal replicon.

Importantly, chlorine DBPs are also associated with AMR in bacterial strains such as *P. aeruginosa* PAO1 and *Acinetobacter baylyi* due to selective pressure in the presence of DBPs [73]. DBPs associated with AMR include iodoacetic acid, bromoacetic acid, and dibromoacetic acid, which significantly increase the mutation rate in bacterial species conferring resistance mechanisms [69]. The genotoxic and mutagenic activity of DBPs in bacterial species results in genetic mutations of AMR-associated genes such as *cepA*, *gyrA*, and *proS* genes [70,78], thus conferring AMR on exposed species. For example, sub-toxic or sublethal concentrations of DBPs, namely chlorite and iodoacetic acid, are associated with gene mutations in *proS* (prolyl-tRNA synthetase) and *gyrA* (DNA gyrase) in *E. coli*, resulting in resistance to amoxicillin and ciprofloxacin [87]. Lv et al. (2014) reported the enhanced resistance to 10 antibiotics, including norfloxacin and polymyxin B, in *P. aeruginosa* associated with exposure to the mutagenic DBPs dibromoacetic acid, dichloroacetonitrile, and potassium bromate [88]. Importantly, higher levels of DBPs in water correlate with increased AMR [69]. Studies are warranted to determine such mutagenic potential of unregulated DBPs and DBP mixtures to fully establish their association with the emergence and proliferation of AMR. In Germany, the 2023 amendments to their Drinking Water Ordinance included extending monitoring of drinking water to include chlorite and HAAs, amongst other pollutants. Monitoring for additional DBPs having mutagenic potential is important to mitigate AMR emergence.

Table 3. Presence of MDR and chlorine resistance in bacterial species, including ones listed on the WHO priority pathogen lists as updated in 2024 [77].

Pathogen	Antibiotic	Mechanism of Resistance
Twenty-two genera of bacteria, including <i>E. coli</i> *, <i>Pseudomonas</i> , <i>Burkholderia</i> ,	Tetracycline, sulfamethoxazole, ciprofloxacin, and amoxicillin [89].	Chemical stress, resistance genes, intrinsic traits, e.g., spore forming [89].
<i>Salmonella</i> Enteritidis, and <i>S. Typhimurium</i> **.	Ceftiofur, tetracycline, ciprofloxacin, and florfenicol.	Eflux pump over-expression [90].
<i>Acinetobacter baumannii</i> *, <i>Pseudomonas aeruginosa</i> ** [66].	Chloramphenicol, sulfonamides, and β -lactam antibiotics.	Expression of efflux pumps and activation of ARGs [66], biofilms in <i>P. aeruginosa</i> [86].
<i>P. aeruginosa</i> **.	Ceftazidime, chloramphenicol, and ampicillin.	Chlorine tolerance and overexpression of the MexEF-OprN efflux pump [82].

Table 3. Cont.

Pathogen	Antibiotic	Mechanism of Resistance
<i>E. coli</i> , <i>S. Aberdeen</i> , <i>P. aeruginosa</i> and <i>Enterococcus faecalis</i> [72].	Ampicillin, kanamycin, and tetracycline.	Transfer of RP4 plasmid from chlorine-treated cells to chlorine-injured or tolerant bacteria [72].
<i>P. aeruginosa</i>	Aminoglycosides carbapenems resistance	<i>intI1</i> gene, chlorine tolerance [78] <i>bla</i> _{OXA-58} and <i>bla</i> _{OXA-78} [78].
<i>K. pneumoniae</i>	carbapenems resistance	disinfectant resistance genes <i>qacEΔ1</i> and <i>cepA</i> present in MDR species [70].
<i>A. baumannii</i> , <i>P. aeruginosa</i> and <i>K. pneumoniae</i>	Cephalosporins	<i>CepA</i> gene biocidal resistance [68].
<i>A. baumannii</i>	Chloramphenicol, sulfonamides, and β-lactam antibiotics.	Chlorine increases the expression of efflux pumps and activates ARGs [66].
<i>E. coli</i>	Amoxicillin and ciprofloxacin	DBP induced gene mutations in <i>proS</i> (prolyl-tRNA synthetase) and <i>gyrA</i> (DNA gyrase) [87].

* WHO critical priority pathogens, ** WHO high priority pathogens.

Alternative Disinfection Modalities for the Dairy Industry

Replacing chlorine as a disinfectant for CIP in dairy is problematic due to the naturally inhibitory matrix of milk. While increasing the chlorine concentration currently used is not realistic, as it will lead to non-compliance with set MRLs. Alternative disinfection modalities for water disinfection include the use of peracetic acid (PAA), hydrogen peroxide (H₂O₂), ozone, and UV, each having its own advantages and disadvantages (Table 4) [91–95]. PAA, H₂O₂, and ozone are oxidizing agents causing cell death via disruption of cell protein synthesis and intracellular functions, and lysis of cell membranes. Meade et al. demonstrated the efficacy of peracetic acid against *E. coli*, *Pseudomonas* spp., and foodborne bacteria, spores, and yeast species [74]. Importantly, studies have also demonstrated the potential of PAA to degrade micropollutants, including pharmaceuticals and potentially EOMPs, due to its high oxidation potential [96]. Research by Zhang et al. (2017) determined that PAA oxidized 7 beta-lactam antibiotics in clean water, with degradation impacted by pH [96]. PAA was also found to be highly effective against bacterial biofilms of species isolated from dairy production facilities, including *Pseudomonas* and *Listeria* [97]. PAA is pH sensitive, however, with reduced activity above pH 8 and optimal activity below pH 7. PAA is corrosive to the eyes and mucous membranes of the respiratory tract, and skin at 5 ppm, resulting in irritation to the upper respiratory tract with short-term exposure (3 min) [98]. The studies of Twomey et al. (2023) demonstrated satisfactory microbial death using PAA as a CIP agent replacing chlorine in dairy processing [99]. H₂O₂ is also a greener disinfectant with potent broad-spectrum activity against AMR species, which does not generate DBPs [94]. The application of H₂O₂ is impacted by its instability when exposed to light, difficulty with transportation, storage, handling, and rapid decay rate [100]. Ozone as a water disinfectant represents the same risks as chlorination in terms of DBP formation with organic and inorganic byproducts, including aldehydes, ketones, and bromate [92]. The application of UV irradiation and chlorination as a combined water disinfectant is gaining momentum as an effective broad-spectrum antimicrobial protocol [59]. The impact of this UV combined approach on DBP formation is not fully established, however, as hydroxyl radical species and reactive chlorine species in the presence of bromide lead to the formation of brominated DBPs, which are more toxic than chlorinated DBPs [60]. Furthermore, UV irradiation of water and wastewater has limited penetration properties and

no residual disinfectant action post-treatment [61], with microbial species also possessing innate DNA repair mechanisms. Post UV treatment exposure to near-UV and visible light (300–500 nm) induces light repair in bacterial species with nucleotide or base excision repair pathways or dark repair also present [62]. Such mechanisms are effective against AMR species, but their efficacy in removing ARGs is unknown. Studies focusing on the removal of ABR genes assessed the combination of UV exposure followed by chlorination (UV-Cl₂) and demonstrated resistance gene removal or damage, which may be attributed to the radicals generated [59]. Research by Phattarapattamawong et al. (2021) determined that UV-Cl₂ enhanced *tetM* and *blaTem* (conferring resistance to β-lactams antibiotics) removal by 0.98–3.20 log and 1.28–3.36 log, respectively [91]. The studies of Destiani et al. (2019) determined that UV disinfection followed by chlorination had increased ability to remove ARGs *tet(A)*, *bla-TEM1*, *sul1*, *mph(A)* when compared to standalone disinfection where re-growth of pathogens also occurred at 5 mg/L and UV disinfection of up to 10 mJ/cm² [62]. Importantly, UV disinfection has been shown to promote MDR to sulfadiazine, vancomycin, rifampicin, tetracycline, and chloramphenicol in bacterial species [62]. Importantly, such alternative methods of disinfection are greatly impacted by the compositional matrix of milk, which will hinder their application in dairy facilities. For example, UV exposure can negatively impact the nutritional quality of the milk as UV radiation may result in protein, amino acid, and enzyme denaturation with OH[−] and H⁺ radicals potentially impacting fatty acid and other food components [101]. Chlorine-free CIP of milking equipment has demonstrated efficacy in a research environment [95]. However, its efficacy at the farm level needs to be established where adherence to strict cleaning and disinfection protocols, e.g., number of washes, high water temperatures, may not be implemented [95].

Table 4. Potential alternative water disinfection methods.

Alternative Method	Mode of Action	Advantages	Disadvantages
Ultraviolet light	Causes damage to microbial genetic material, e.g., mutations, thymine-thymine dimers.	No disinfection byproducts identified, cost-effective, eco-friendly, EPA approved, no organoleptic changes to the water, can be used in combination approaches [62], inactivates AMR species.	No residual disinfectant remains; DNA repair mechanisms present in microbes are inhibited by OM, including milk components. Promotes MDR to sulfadiazine, vancomycin, rifampicin, tetracycline, and chloramphenicol [62], relies on electricity, limited penetration properties [61], UV rays are harmful to humans [101]
Ozone (O ₃) treatment	Ozone oxidizes organic material in the microbial membranes, leading to cell lysis.	Broad spectrum activity, effective over a wide range of pH, rapid disinfection needing shorter contact time, no quenching requirement.	Expensive, O ₃ has a short half-life, no residual disinfection activity, toxic gas, DBPs formed, including bromate, ketone, aldehydes, nitrosamines [92].

Table 4. Cont.

Alternative Method	Mode of Action	Advantages	Disadvantages
Peracetic acid (CH ₃ CO ₃ H)	Direct oxidation/destruction of the cell wall with leakage of cellular constituents due to free radicals' hydrogen peroxy (HO ₂) and hydroxyl (OH).	Potent bactericidal action, active over pH range < 7, temperatures, and inactivates MDR species, eco-friendly [74], no persistent toxic or mutagenic residuals or byproducts, no quenching requirement [93], inhalation exposure limits degradation of pollutants [96].	No residual disinfection action, microbial re-growth, high cost and production limits, affected by total suspended solids [93], lower efficacy against waterborne viruses and parasites <i>Cryptosporidium</i> [93], causes respiratory tract irritation [98].
Hydrogen peroxide (H ₂ O ₂)	Oxidizing action via the generation of reactive oxygen species (ROS).	Broad-spectrum activity, eco-friendly, non-carcinogenic, inactivates AMR species [94].	Not stable, affected by light and heat exposure, limited efficacy against microbial spores, expensive, and impacted by OM [94].

4. Conclusions

Chlorine reacts with organic matter in water to produce ca. 800 disinfection byproducts. Epidemiological studies have demonstrated the correlation between exposure to chlorinated water via ingestion and inhalation with bladder, colon, and rectal cancer, among other health hazards. Many of the chlorine DBPs are potential human mutagens and carcinogens and are associated with developmental and reproductive issues, including infertility. The presence of chlorine residuals and DBPs in dairy food is also of concern, as dairy production relies heavily on chlorine to ensure effective disinfection of food production equipment and facilities. For example, the dairy industry has a high-water consumption with ca. 5000 L of water used to make 1 kg of cheese, with CIP processes relying on chlorinated water supplies. Additionally, research increasingly highlights the relationship between biocide resistance, AMR, and environmental pollution with ARGs. There is an urgent need to develop alternative disinfection modalities for water disinfection and food production facilities. Considerations on alternative disinfectants must include the risk associated with BRG release due to the bactericidal action of biocides. Lysing cells may release ARGs into the treated water, allowing for HGTs amongst species or vertically proliferating AMR environmentally. More clinical research is needed to support and confirm the current epidemiology data, where correlation with DBP exposure and adverse health outcomes has been established. Toxicology risk assessment investigating varied parameters, including exposure routes, pharmacokinetics, target organ toxicity, and the synergistic effects of multiple DBPs and mechanistic cellular toxicity, is required. Investigative studies on the impact of confounding variables on toxicity data are also warranted, including individual exposure rates, alcohol consumption, smoking, and polymorphisms in essential metabolic enzymes, i.e., CYP2E1. Alternative disinfection methods, including UV radiation, come with their own limitations, where a combined UV-Cl₂ approach appears effective at ARG removal. Alarming, it appears that the chlorination of water, which so successfully prevented infectious disease for decades, may inadvertently be associated with morbidity, mortality, and declining fertility rates globally.

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