Chlorate and Other Oxychlorine Contaminants Within the Dairy Supply Chain: Chlorate contamination in dairy...

Article *in* Comprehensive Reviews in Food Science and Food Safety · October 2018

DOI: 10.1111/1541-4337.12393

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Chlorate and Other Oxychlorine Contaminants Within the Dairy Supply Chain

William P. McCarthy, Tom F. O'Callaghan, Martin Danahar, David Gleeson, Christine O'Connor, Mark A. Fenelon, and John T. Tobin

Abstract: The presence of chlorate in milk and dairy products can arise from the use of chlorinated water and chlorinated detergents for cleaning and sanitation of process equipment at both farm and food processor level. Chlorate and other oxychlorine species have been associated with inhibition of iodine uptake in humans and the formation of methemoglobin, with infants and young children being a high-risk demographic. This comprehensive review of chlorate and chlorine derivatives in dairy, highlights areas of concern relative to the origin and/or introduction of chlorate within the dairy supply chain. This review also discusses the associated health concerns, regulations, and chemical behavior of chlorate and chlorine-derived by-products, and provides a summary of mechanisms for their detection and removal.

Keywords: chlorate, chlorine disinfection by-products, contaminants, dairy, food processing

Introduction

Chlorate (ClO_3^-) and other chlorine-derived residues have become a growing concern within the dairy, food, and beverage industries in recent years. Chlorine compounds (compounds containing chlorine in their structure) possess bactericidal and sanitizing properties and, therefore, are commonly used in farm, water treatment, and industrial food manufacturing processes for sanitation purposes. Chlorine, as a sanitizing agent, plays a crucial role in food production; however, the formation of chlorinated residues as by-products of their use has raised concerns with food regulatory bodies (EFSA, 2015).

Milk and other dairy products are highly nutritious and provide many of the key nutrients required for the growth and development of infants and children, and they are beneficial for the maintenance of health in adults. The sanitation of dairy processing equipment is of major importance across the dairy supply chain, in order to prevent outbreaks of foodborne illness (FAO/WHO, 2009). There is a wide range of disinfectants used in cleaning regimens throughout the dairy industry, with chlorine disinfectants employed widely across the production and processing operations of many different food groups (Gil, Marín, Andujar, & Allende, 2016).

Chlorate enters the supply chain almost exclusively as a disinfection by-product (DBP), either through contact of the product with chlorinated water or as a residue from cleaning processes present on equipment surfaces. For dairy products, the entry points for chlorate lie both at the primary producer (on-farm practices) and at the processor level, which are linked to both chlorinated water usage and/or sanitation practices. Water usage in all aspects of dairy production remains a critical entry point of chlorate into the supply chain, thus it is necessary to understand how sanitation of water itself influences this risk of cross-contamination into the dairy supply chain. Sanitation of water with chlorine gas (Cl_2), dioxide (ClO_2), or hypochlorite (ClO^-) remains common practice in many jurisdictions due to chlorine's bactericidal and oxidative properties.

Hypochlorous derivative disinfectants

Active chlorine (chlorine in a form that is readily available for chemical reaction with microorganisms [FAO/WHO, 2009] is typically introduced to disinfection processes in the form of gaseous chlorine or hypochlorite [OCl^-]). In both these forms, it acts as a strong oxidizing agent and often participates in side reactions at such a rate that little disinfection of the system is achieved until the chlorine demand of the system is overcome. Active chlorine, being a potent oxidizing species, reacts with a wide variety of compounds in solution. Most commonly those species are categorized as reducing agents, which include hydrogen sulfide (H_2S), manganese(II), iron(II), sulfite (SO_3^{2-}), bromide (Br^-), iodide (I^-), and nitrite (NO_2^-; Driedger, Rennecker, & Mariñas, 2000). When analyzing the formation of DBPs, the aforementioned compounds may act as a catalyst, resulting in the formation and persistence of chlorine DBPs in food matrices.

Chlorine gas (Cl_2) is the most utilized active chlorine species (ACS) in disinfection procedures in the United States (FAO/WHO, 2009). However, upon coming in contact with organic matter, chlorine has been shown to produce DBPs, which can pose a threat to human health (Richardson, 2012). Sodium

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doi: 10.1111/1541-4337.12393

hypochlorite (NaClO) sanitizers are effective against a wide range of microorganisms, including Gram-positive and Gram-negative bacteria, bacterial spores, and viruses (Bremer & Seale, 2009). Hypochlorite has the added benefit of being easily transported and stored when produced onsite, and it also acts as a residual disinfectant when used for sanitation purposes. For hypochlorite solutions, chlorate is the primary degradation by-product, an artifact which can be exacerbated by storage conditions (temperature/UV exposure) and duration, prior to use (Garcia-Villanova, Leite, Hierro, de Castro Alfageme, & Hernandez, 2010).

Analysis of oxychlorine levels in commercial bleach solutions found that chlorite concentration ranging from 135 to 310 μg/L and chlorate concentration ranging from 1.67 to 13.35 mg/L were common (Gordon, Adam, & Bubnis, 1995). Use of Hypochlorite solutions in water treatment has been attributed to significant chlorate and chlorite contamination in potable water. In studies conducted to measure chlorate contamination using liquid chlorine solutions (i.e., hypochlorite), chlorate was found to be present at notably high (g/L) levels. In contrast, in treatments using gaseous chlorine, there was no residual chlorate present, indicating that gaseous chlorine does not contribute to chlorate levels in treated water (Bolyard, Fair, & Hautman, 1992; Nieminski, Chaudhuri, & Lamoreaux, 1993). Chlorine gas has become less widely used in the water treatment process but still plays a major role with 63% of facilities still utilizing it (AWWA, 2008). In recent years, 30% of water treatment facilities in North America switched from chlorine gas to hypochlorite ion solutions (Routt et al., 2008). Furthermore, chlorine gas has been replaced in more than 80% of these treatment plants by bulk sodium hypochlorite solutions, and 17% of the sites switched to the use of sodium hypochlorite solutions generated *in situ*.

Chlorine dioxide

Chlorine dioxide exists almost completely as a monomeric free radical system. When stored at high concentrations, gaseous chlorine dioxide is potentially explosive, and attempts to store this gas at high pressure, either alone or as a mixture of other gases, have been unsuccessful. As a result chlorine dioxide, like ozone, must be manufactured at the site of use (PubChem).

Although chlorine dioxide is commonly used in the treatment of water, it has also found applications as an alternative to chlorine gas sanitation of processing equipment, as it does not have as vast a catalog of toxic DBPs, is active over a wider pH range, and is an effective bactericidal agent, making it a more favorable alternative to be used for food processing applications (Pereira et al., 2008).

Chlorine DPBs

The presence of chlorine DBPs in the diet has been linked to the consumption of contaminated water and food, where chlorine sanitation has been involved at some point across the supply chain. The contribution of tap water to the total intake of chlorate for a Japanese sample group was found to be as high as 47% to 77%, with this water being introduced into food during rehydration steps during food preparation (Asami, Yoshida, Kosaka, Ohno, & Matsui, 2013). In addition, certain food groups such as dairy have been identified as a significant contributor of chlorate in the diets of children between 2 and 10 years of age (EFSA, 2015; Murray, Egan, Kim, Beru, & Bolger, 2008; Schier et al., 2010).

Consumption of inorganic chlorine derivatives has been related to hematotoxic and nephrotoxic effects and inhibition of thyroid function. Such implications have encouraged some countries to establish enforceable regulations for chlorite and chlorate residues in foods (EFSA, 2015). In particular, concerns have been raised relative to foods consumed by infants due to their increased susceptibility to these toxic effects, particularly in the case of dairy which forms the base ingredient for the majority of infant milk formulas and is often the sole source of nutrients in the early stages of life (Sadeq et al., 2008). Subsequently, chlorate has been noted as one of the most critical unregulated emerging DBPs, which future research should focus on (EFSA, 2015). It is noted that adverse effects in humans are sparsely investigated and evidence of toxicity to date has been inconclusive (Aggazzotti et al., 2004; Contu et al., 2005; EFSA, 2015; Ouhoummane, Levallois, & Gingras, 2004). In general, over 600 volatile and nonvolatile DBPs have been identified to arise from cleaning processes, including the use of chlorine compounds (Krasner et al., 2006; Richardson, Plewa, Wagner, Schoeny, & Demarini, 2007). Chlorate formation from chlorine dioxide can also occur through photochemically initiated reactions (Gordon et al., 1995).

This article aims to provide a comprehensive review of existing literature on the use of chlorine gas and alternative chlorinated compounds across the dairy supply chain. The entry and fate of chlorine DBPs in dairy products, the analytical methods employed in chlorine DBP quantification, and their associated health impacts will be discussed below.

Analysis of Chlorate and Perchlorate

The analysis of liquid milk, milk powders, and other dairy samples presents a number of challenges. Dairy samples contain a number of components that can interfere with analysis, such as proteins, fat, and sugars. Consequently, most analytical methods include protein precipitation steps, which involve the addition of a water-miscible organic solvent and acid. Fat is a component that is present in whole milk, but at lower concentrations in skimmed milk, skimmed milk powders, and whey powder. Fat can simply be removed from milk or reconstituted samples by centrifugation, or more costly solid phase extraction steps can be included to eliminate fat. Schier et al. (2010) used cold ethanol to precipitate milk proteins in solution. Centrifugation removed the precipitated milk proteins and the supernatant was isolated and dried using N_2 evaporation. The pellet formed was dissolved in water and passed through a C_{18} column to purify the sample. The development of this procedure allowed milk samples to be analyzed without having milk proteins hindering analysis making it an easier matrix to work with.

Capillary electrophoresis (CE) and ion chromatography (IC) are the primary methods used by forensic scientists to identify multiple anions in a single analysis (Breadmore, Haddad, & Fritz, 2001; Soga & Imaizumi, 2001; Wildman, Jackson, Jones, & Alden, 1991). However, the detection of inorganic oxides in food and water has been focused primarily on IC analysis. Ion chromatography coupled in series with conductivity detection is generally the method of choice for the analysis of chlorates and perchlorates in water samples. Perchlorate seems to be the major analyte resolved by ion chromatography, as the selectivity of the separation system is better than other techniques, and sensitivity can be improved by increasing the amount of sample injected onto the column.

Accepted methods for the quantification of perchlorate are Environmental Protection Agency methods 314.0 and 314.1, based on ion chromatography with in-line column concentration/matrix elimination (Hautman & Munch, 1999) and ion chromatography with suppressed conductivity detection, respectively. These methods have stated a limit of detection (LOD) of 30 ng/kg. Furthermore, methods developed for IC quantification of chlorate as per EPA 300.1 have reported accurate detection to a LOD of 1.31 μg/kg (Hautman & Munch, 1997). The EPA methods have been developed for the testing of groundwater or other simple matrices, although the complexity of food increases the chance of inaccurate results and selectivity (Yu et al., 2006).

An ion chromatography-tandem mass spectrometry (IC-MS/MS) method has been developed by Martinelango et al. (2005) and was used in EPA method 332.0 for the detection of perchlorate in drinking water (Hedrick, Behymer, Slingsby, & Munch, 2005). IC-MS/MS has been demonstrated to have a LOD of between 5 and 25 ng/kg when utilized in the quantification of perchlorate in a variety of matrices such as water, urine, amniotic fluid, wine, and food (El Aribi, Le Blanc, Antonsen, & Sakuma, 2006; Krynitsky, Niemann, Williams, & Hopper, 2006). Later work surrounding perchlorate levels in milk products led to the development of new analytical methodologies for milk (Dyke, Kirk, Martinelango, & Dasgupta, 2006; Sanchez, Blount, Valentin-Blasini, Lesch, & Krieger, 2008) and infant formula (Schier et al., 2010).

Isotope dilution ion chromatography with tandem mass spectrometry (ID IC-MS/MS) utilizes an internal standard and analyzes via a signal ratio instead of using intensity to determine analyte concentration. This is achieved by the addition of known amounts of isotopically enriched substrate to the analyzed sample. It was developed and validated by Wang et al. (2009) for fruit and vegetables and later developed into a method for infant formula which quantified perchlorate with a LOD of 400 ng/kg for liquid infant formula and 950 μg/kg for powdered samples.

Ion chromatography coupled with ion-spray mass spectrometry works on the premise of being able to evaporate ions directly from a condensed phase into a gas phase. The sample is sprayed into an electric field whereby solvent evaporation causes ions to migrate to the liquid–gas interface. This method, developed by Charles and Pepin (1998), was capable of chlorate detection to a limit of quantification (LOQ) of 50 ng/kg making it an interesting technique for oxyhalide analysis.

The main drawback to these techniques is that ion chromatography is not commonly employed in food analysis labs, particularly those involved in the area of food safety which use mainly mass spectrometry-based detection. Indeed, the coupling of IC to MS presents challenges because the mobile phase additives, that is, nonvolatile buffers, are incompatible with these detectors.

Modern analytical developments have given rise to liquid chromatography with coupled mass spectral detection (LC-MS) (Barron & Paull, 2006; Charles & Pepin, 1998), but although these methods have been developed for detection in water, their application to complex biological matrices has been explored to a lesser degree (Beier et al., 2007). Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been developed as a multiresidue analytical method for polar pesticides (Anastassiades et al., 2016; Hepperle et al., 2005) and has been employed by EFSA for the testing of fruits and vegetables for pesticide residues at levels of μg/kg (EFSA, 2015). LC-MS/MS methodology has also been developed to analyze perchlorate residues in several animal matrices including dairy (Capuco et al., 2005; Dodds, Kennish, von Hippel, Bernhardt, & Hines, 2004; Kirk, Smith, Tian, Anderson, & Dasgupta, 2003). This method was analyzed on a matrix by matrix basis by Smith and Taylor (2011), who were capable of detection of chlorate at 500 μg/L for milk samples. There are some reports of mixed mode separation for the analysis of chlorates and perchlorate, some of which employ MS or MS/MS-based detection (Hepperle et al., 2005; Watanabe & Matsumoto, 2014).

Due to the anionic nature of oxychlorine residues, their detection in complicated matrices can be challenging, and several methodologies to minimize ionic interferences have been proposed (Anderson & Wu, 2002; Basheer, Obbard, & Lee, 2005; Cañas, Cheng, Tian, & Anderson, 2006). Microwave-assisted digestion (MAD) with solid-phase extraction (SPE) has been used to purify samples for instrumental analysis (Basheer et al., 2005); however, this can compromise sample recovery. Electromembrane extraction (EME) is a cheaper and simpler approach, and has been widely used for perchlorate extraction from biological matrices (Basheer, Lee, Pedersen-Bjergaard, Rasmussen, & Lee, 2010; Kiplagat, Doan, Kubáň, & Boček, 2011; Schmidt-Marzinkowski, See, & Hauser, 2013; Tan, Basheer, Ng, & Lee, 2012).

Mechanisms Involved in the Formation of Inorganic Chlorine DBPs

Disinfection with chlorine agents is also associated with inorganic chlorine species, which are formed through oxidation reactions rather than being associated with reacting with organic matter in solution. Chlorine is able to form an extensive number of these oxidized inorganic DBPs due to its ability to undergo redox reactions, going from a negative one oxidation state to a plus-seven oxidation state (Al-Otoum, Al-Ghouti, Ahmed, Abu-Dieyeh, & Ali, 2016). These inorganic DBPs are more readily associated with the use of chlorine dioxide and hypochlorite solutions.

Chlorine dioxide does not undergo extensive hydrolysis in water. Neutral or acidic dilute aqueous solutions have been found to be quite stable if kept cool, well-sealed, and out of direct sunlight. Chlorine dioxide has an oxidation state of +4 which is in between those of chlorite (+3) and chlorate (+5). This makes it unique as no acid or ion of the same degree of oxidation is known. Chlorine dioxide can decompose to chlorite in the absence of oxidizable matter and in basic conditions; it dissolves in water, decomposing slowly to form chlorite and chlorate:

$$\mathbf{2ClO_2 + H_2O \rightarrow ClO_2{}^- + ClO_3{}^- + 2H^+}$$

The decomposition of chlorine dioxide leads to the formation of inorganic compounds, including chlorite, chlorate, and chloride ions; with chlorite accounting for 50% to 70% of the DBPs formed. Its use as an alternative disinfectant to chlorine gas has increased in Europe to meet the regulatory trihalomethane (THM) limits put in place for potable water (Gates, Ziglio, & Ozekin, 2009). Chlorine dioxide can be involved in a wide range of redox reactions, such as oxidation of iodide ion, sulfide ion, iron (II), and manganese (II). When chlorine dioxide reacts with aqueous contaminants it is often reduced to chlorite ions (Tratnyek & Hoigné, 1994). Major chlorine dioxide by-products of concern include chlorite and chlorate. Chlorine dioxide is a good electron acceptor and does not undergo substitution reactions in the presence of C–H or N–H structures (Hoigné & Bader, 1994). Chlorine dioxide reacts only by oxidative processes, as opposed to chlorine gas, which can undergo oxidation and electrophilic substitution reactions; it is this characteristic which accounts for the lack of organochlorine compound formation. The industrial synthesis of chlorine dioxide is generally performed using aqueous sodium chlorite and hypochlorite (Gordon & Rosenblatt, 1997).

$$\mathbf{2ClO_2{}^- + HOCl + H^+ \rightarrow 2ClO_2 + Cl^- + H_2O}$$

However, when this reaction is performed under an equimolar reaction between chlorite and hypochlorite the reaction produces chlorate ion.

$$\mathbf{ClO_2^- + HOCl \rightarrow ClO_3^- + Cl^- + H^+}$$

The above reaction is common in production environments which use increased chlorine concentrations shifting the reaction equilibrium to the right, increasing chlorite consumption. An alternative route to produce chlorine dioxide industrially is through the use of hydrochloric acid (HCl), which leads to a lower occurrence of chlorate formation.

$$\mathbf{5NaClO_2 + 4HCl \rightarrow 4ClO_2 + 5NaCl + 2H_2O}$$

Chlorine dioxide reacting with natural organic matter (NOM) may also lead to the formation of chlorite (Gordon & Rosenblatt, 1997).

$$\mathbf{ClO_2 + NOM \rightarrow Products + ClO_2^-}$$

Chlorite is formed from the reaction of two units of hypochlorite and is the rate-limiting step for chlorate formation. Gordon et al. (1995) carried out a study on the reaction kinetics of the decomposition of hypochlorite solutions. Chlorate is formed in concentrated hypochlorite solutions during their production and storage through the following reactions (Gordon & Rosenblatt, 1997).

$$\mathbf{OCl^- + OCl^- \rightarrow ClO_2^- + Cl^-}$$

$$\mathbf{OCl^- + ClO_2^- \rightarrow ClO_3^- + Cl^-}$$

It was found that when the hypochlorite ion concentration is increased by a factor of two then there is a concomitant four-fold increase in the rate of decomposition, making it a second-order reaction. Thus, it is recommended to dilute hypochlorite solutions by a factor of two, which reduces the concentration of hypochlorite ions, resulting in a decrease in the rate of decomposition. Storage conditions of concentrated hypochlorite solutions is a major concern, as the rate of degradation is proportional to the molarity of the solution (Gordon et al., 1995). It is recommended that sodium hypochlorite is stored in highly alkaline conditions at pH values greater than 12, this prevents rapid decomposition and ensures sufficient hypochlorite ion concentrations (Gordon et al., 1995).

Sodium hydroxide is added during the manufacture of sodium hypochlorite to ensure an alkaline environment, minimizing the decomposition of hypochlorite to its oxidized DBPs. Most clean-in-place (CIP) cleaning agents used on dairy farms (in Europe/USA) contain a combination of sodium hydroxide (15% to 20%) and sodium hypochlorite (3% to 9%) at pH 13 approximately (Gleeson & O'Brien, 2011).

Hypochlorous acid, the protonated form of hypochlorite, a prime species involved in the disinfection process, is a weak acid with a p*K*a of 7.5 at 25°C. Therefore, at a pH below 7.5 the hypochlorous acid is the dominant active species over the hypochlorite ion, which is the dominant form at a pH above 7.5. The rate of decomposition of active chlorine increases as the environment becomes more alkaline, and these reactions can theoretically produce breakdown by-products of chlorite and chlorate. The decomposition of hypochlorite (ClO^-) is promoted in alkaline solutions and is driven by the removal of the thermodynamic stability of the hypochlorite ions. These oxyhalides undergo further reactions to form a more thermodynamically stable oxyhalide species (1) and can react further to form the perchlorate species (2) as seen below (Aieta & Berg, 1986; Condie, 1986; Gordon & Tachiyashiki, 1991).

$$\mathbf{ClO^- + ClO_2^-. \rightarrow Cl^- + ClO_3^-} \quad (1)$$

$$\mathbf{ClO_3^- + ClO^- \rightarrow Cl^- + ClO_4^-} \quad (2)$$

The perchlorate ion is found in sodium hypochlorite solutions, and similar to the chlorate ion, perchlorate concentration increases over time (Pisarenko et al., 2010; Snyder, Stanford, Pisarenko, Gilbert & Asami, 2009; Stanford, Pisarenko, Snyder, & Gordon, 2011). The rate of perchlorate formation is a second-order reaction, dependent on hypochlorite and chlorate concentrations (Gordon & Tachiyashiki, 1991; Snyder et al., 2009).

$$\mathbf{OCl^- + ClO_3^- \rightarrow ClO_4^- + Cl^-}$$

$$\mathbf{d\left[ClO_4^-\right]/dt = k_{ClO-4}\left[OCl^-\right]\left[ClO_3^-\right]}$$

Hypochlorite has an alternative decomposition route outside of forming oxychlorine species which involves the breakdown of hypochlorite to oxygen and chloride. This can become significant when certain metal ions are present (Lister, 1956), at higher temperatures, increased acidic pH, and when exposed to UV radiation.

$$\mathbf{2ClO \rightarrow O_2 + Cl^-}$$

Hygiene Practices Leading to Contamination in Dairy Processing

The sanitation of processing equipment is of major importance across the dairy supply chain, mainly in order to prevent outbreaks of foodborne illnesses (FAO/WHO, 2009). In industrial food processes, effective sanitation is achieved by the implementation of a CIP program which embodies a systematic cleaning of the interior surfaces of pipelines, filters, and other equipment without the need to dismantle the equipment. The efficiency of cleaning and sanitation of product contact surfaces is influenced by multiple factors, including the nature of contamination, microtopography of surfaces within the processing unit, straightness of passageways, and compatibility of surface agents. Each factor must be taken into account to develop an effective CIP program. Typically, CIP systems incorporate various rinse-and-wash cycles with water, disinfectants, and acidic solutions to achieve an effective removal of contaminating organic and inorganic materials, thus maintaining the integrity of process equipment, as seen in Figure 1 (Bylund, 2003).

Milk and dairy products offer highly nutritious food for microorganisms to multiply, which can lead to product spoilage. The concentration and types of microbial contamination depend on the raw material quality, the conditions under which the products were produced, and the temperature and duration of their storage (Tamime, 2009a, b). Milk and dairy products have also been linked to foodborne illness. In the USA, milk was found to be the cause of 1.1% to 1.7% of foodborne disease outbreaks with a known vehicle in the period of 1998 to 2002, with over 90% of these being caused by bacteria in raw milk (Te Giffel, 2003).

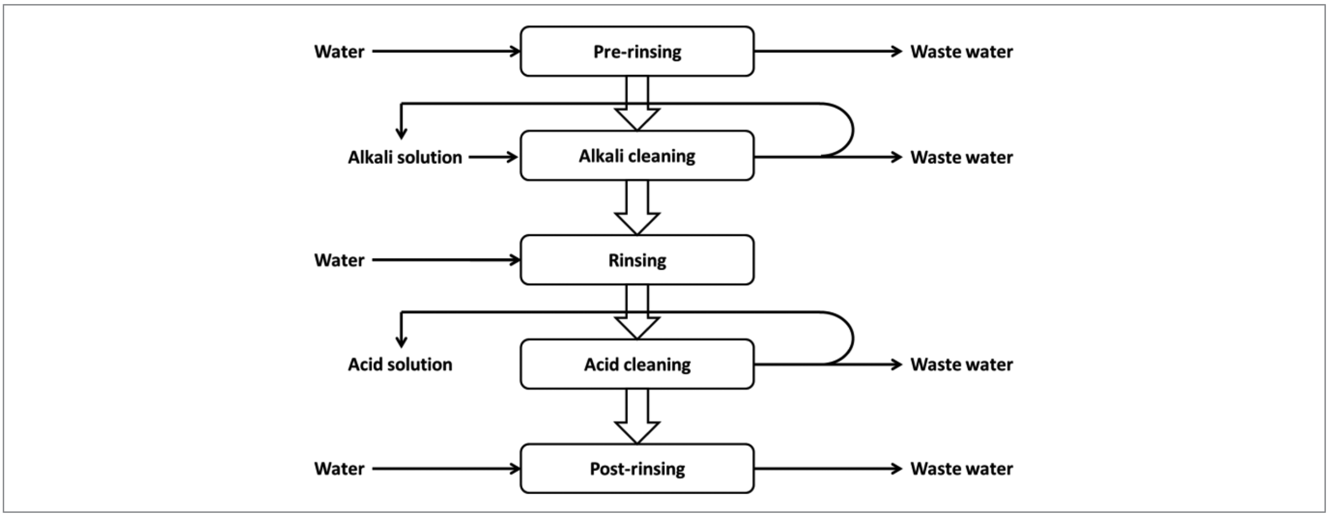

Figure 1–Conventional cleaning steps of the CIP process in dairy industries (Paul et al., 2014).

Due to the development of hygiene program, the quality of milk has increased significantly over time. In 1997, it was reported in Germany that raw milk had an average count of 5×10^5 colony forming units (cfu)/mL, whereas in 2002, an average count of 2×10^4 cfu/mL (Suhren & Reichmuth, 2003).

Cleaning of dairy equipment was once completely manual, using brushes and detergent solutions, and it involved dismantling the equipment to access every surface. This approach was labor-and-time-intensive and also often quite counterproductive since contamination can be reintroduced to the system by imperfectly cleaned equipment. These issues were solved by the introduction of CIP programs, which adapt automated cleaning systems in various parts of the processing plant to achieve the necessary cleaning and sanitation results. Cleaning procedures are carried out by strictly following a program that is carefully designed to attain the necessary degree of cleanliness before the product is introduced. Bylund (2003) reported that the cleaning cycle in dairy processing is composed of the following stages:

(1) Recovery of product residues through scraping, drainage, and expulsion with water or compressed air.
(2) Pre-rinsing with treated water to remove loose dirt.
(3) Cleaning with detergent.
(4) Rinsing with clean water.
(5) Sanitizing using heat or, optimally, chemical agents.

Most of the equipment used in the handling of milk and milk products is kept clean and disinfected by CIP systems, where product contact surfaces, normally of stainless steel construction, are cleaned daily (Tamime, 2008). In dairy plants, CIP is employed daily to ensure product quality, maintain optimal efficiency of processing equipment, and to efficiently stop bacterial contamination. Many studies have been conducted focused on modelling of CIP processes in dairy plants (Bremer, Fillery, & McQuillan, 2006; Changani, Belmar-Beiny, & Fryer, 1997; Kumari & Sarkar, 2014; Paul et al., 2014; Piepiórka-Stepuk & Diakun, 2014; Piepiórka-Stepuk, Diakun, & Mierzejewska, 2016). The cleaning philosophy employed in any CIP process can vary depending on the nature of the material being processed and its tendency for fouling of equipment-product contact surfaces. The identification of best practices for subsequent removal of fouling include cycling of detergents and sanitizers, and it has led to the development of optimized cleaning systems for dairy plants (Palabiyik, Yilmaz, Fryer, Robbins, & Toker, 2015; Suárez, Díez, García, & Riera, 2012; Tamime, 2008). Regulation (EC) No 853/2004 states that there are specific rules for hygiene of vessels, transport containers, and tanks, which must be cleaned at least once a day and disinfected before reuse (Regulation, 2004). However, the wide range of detergents and sanitizers employed across the dairy industry has led to a greater focus on the chemicals used in the cleaning process and, in particular, any subsequent DBPs associated with their use (Farn, 2006; McCaslin, 2013; Valls, Pujadas, Garcia-Vallve, & Mulero, 2011).

Chlorate can enter the food chain during food processing because of two actions:

(1) The disinfection of surfaces and food processing equipment.
(2) The use of chlorinated water throughout food processing/preparation.

Chlorine-based sanitizers (HOCl and ClO_2) are the most commonly used sanitizers in food processing and handling applications, and they have been approved by the U.S. Food and Drug Administration (FDA) for use as no-rinse sanitizers in food production. These are sanitizers that are used as rinses, sprayed onto surfaces, or circulated through equipment in CIP operations (Fischer, Schilter, Tritscher, & Stadler, 2011), including the final rinsing of dairy equipment at the farm and the processor level. Included in these are broad-spectrum germicides which act on microbial membranes, impede cell function through inhibition of enzymes involved in the glucose metabolism, are genotoxic, and can oxidize cellular protein (McDonnell & Russell, 1999). Contamination, with residues of detergents and sanitizers, can occur as a result of improper use of detergents and incorrectly conducting cleaning regimens at farm or dairy processor levels. Recently, cleaning protocols have been developed for dairy farm equipment without the requirement for sodium hypochlorite, reducing the risk of chlorine residues being introduced into the system (Gleeson & O'Brien, 2013). Possible routes of entry of disinfectants in dairy processes include their application for teat and skin disinfection, cleaning of milk storage tanks, and CIP treatment of milking equipment (Fischer et al., 2011).

The use of chlorinated water during food processing is the main cause for the occurrence of chlorate residues in food. This is especially apparent in food processing scenarios where the rinse water is retained, retreated, and reused. This recycling practice is common throughout food processing with treatments using active chlorine utilized to keep the microbial quality of the water at an acceptable level. The further chlorination of the rinse water can cause a concentration of chlorate residues, which leads to residual contamination within the food chain (EFSA, 2015; Kettlitz et al., 2016). In the case of the water industry, chlorate is considered to come from hypochlorite reagents (Garcia-Villanova et al., 2010).

Disinfection of processing water is an essential activity necessary in the reduction of cross-contamination during the wash cycle, and, furthermore, inadequate disinfection can lead to this rinse water becoming a major source of contamination (Gil, Selma, López-Gálvez, & Allende, 2009). There is currently limited information available on chlorate contamination in dairy processes, but a large body of work has been performed on other food groups of plant origin (Kaufmann-Horlacher, Ströher-Kolberg, Wildgrube, & Cerchia, 2014).

Health Impact of Oxychlorine Species

The addition of oxidants as part of a CIP process generates a variety of DBPs, which have been linked to numerous health effects (Clark, Goodrich, & Deininger, 1986). The toxicology of chlorate and other chlorine DBPs has become an area of growing interest, due to the wide distribution of these micropollutants in food and water used for public consumption worldwide with established health-based guidance values summarized in Table 1 (Asami et al., 2013; EFSA, 2014, 2015; Erdemgil, Gözet, Can, Ünsal, & Özpınar, 2016; Kettlitz et al., 2016).

Oxidative stress

The interconversion between chlorite, chlorate, and chloride occurs in the gut and has been found to cause oxidative stress within the body (Bathina et al., 2013). The body has many antioxidant mechanisms to protect its cells from this process, mainly the glutathione (GSH) redox cycle. However, when the oxidative stress is too high it can overcome this defense mechanism and cause substantial injury to the cells, proteins, lipids, and amino acids (Bathina et al., 2013; EFSA, 2015). The blood is especially sensitive to this oxidative stress, whereby hemoglobin can be oxidized to methemoglobin. Thus, cell membranes may be subjected to oxidative crosslinking of spectrin and lipid peroxidation leading to intravascular hemolysis (Bathina et al., 2013; Couri, Abdel-Rahman, & Bull, 1982; EFSA, 2015).

Methemoglobin is formed when the iron center of deoxyhemoglobin is oxidized from its ferrous (Fe^{2+}) to its ferric (Fe^{3+}) state, as depicted in Figure 2 (Murray, Granner, Mayes, & Rodwell, 2000), impairing its ability to act as an oxygen transport vehicle through alteration of its ability to bind reversibly with oxygen (Brunato, Garziera, & Briguglio, 2003). This alteration induces tissue hypoxia and metabolic acidosis (García-Saura & Serrano, 2013). Furthermore, methemoglobin initiates the inflammatory cascade mechanism by stimulating the release of interleukin-6, interleukin-8, and E-selectin, which cause the release of cytokines and adhesion molecules, thereby intensifying the inflammatory response (Umbreit, 2007; Wagener et al., 2001). It can lead to acute kidney injury and renal failure in cases of chronic exposure, the exact mechanism of which has not yet been clearly established (EFSA, 2015).

Infants are much more sensitive than adults to this intracellular methemoglobin induction. This is related to a relative difference in methemoglobin reductase in red blood cells in neonates as the fetal red blood cells are much more sensitive to reducing agents and because the fetus has a greater oxygen demand. A large percentage of the hemoglobin in infants is this fetal hemoglobin which is more readily oxidized to methemoglobin than adult hemoglobin (Mensinga, Speijers, & Meulenbelt, 2003; Sadeq et al., 2008). Furthermore, this is of growing concern as at the 95th percentile the established tolerable daily intake (TDI) for chlorate was exceeded in all surveys of "infants" and "toddlers' in a 2014 study, meaning higher exposure levels in these demographics (EFSA, 2015).

Fetal development

A study carried out in Northern Italy by Righi et al. (2012) on chlorine DBPs and their associated health effects found the presence of elevated chlorite and chlorate levels ($>700\ \mu g/L$) in the drinking water of 3.4% of women during their first trimester. This gave a significant increase in risk factors for urinary tract defects, cleft palate, spina bifida, and abdominal wall defects in the mothers exposed to high levels of chlorate and chlorite during their pregnancy. The mechanism of these inorganic DBPs has not been thoroughly investigated in humans and no clear explanation has been established to date (Coleman, 2011).

Thyroid hormone synthesis inhibition

A definite trend is evident regarding chlorate and its oxidized form perchlorate (ClO_4^-), concerning the competitive inhibition of the natrium iodide symporter (NIS), found in the thyroid and other tissues to transport iodide across a high concentration gradient. The primary function of the thyroid is the production of thyroid hormones, triiodothyronine (T_3) (regulates growth and cellular metabolism) and thyroxine (T_4; converted to T_3 in the peripheral tissue). The NIS plays a key role in the production pathway of these hormones, via the translocation of iodide into the follicular cells, which forms thyroglobulin downstream. Thyroglobulin undergoes cleavage to release T_3 and T_4 regulated by the pituitary (Dohan et al., 2003; Eskandari et al., 1997).

Although the mechanism of thyroid hormone depression is well established, the potency of perchlorate and chlorate in causing such effects in humans remains a matter of debate within the scientific community. Chlorate is chemically similar to perchlorate, a well-known thyroid gland toxicant, and chemical oxidant. Investigations carried out into the potency of chlorate found that perchlorate was a much more potent inhibitor than chlorate due to it having a higher affinity of uptake by the NIS (Di Bernardo, Iosco, & Rhoden, 2011; Van Sande et al., 2003). Perchlorate competitively inhibits iodide uptake by the NIS due to similarities in ionic radius and charge (Van Sande et al., 2003), with similar observations noted for comparably sized ions such as thiocyanate (Wolff & Walrey, 1963).

Although the inhibition of thyroid hormones is not an issue for the majority of the population, due to reserves of stored thyroid hormones that can negate the inhibition of the NIS, infants do not have these stores of thyroid hormones (Dowling, Martz, Leonard, & Zoeller, 2000; Savin, Cvejic, Nedic, & Radosavljevic, 2003; van den Hove, Beckers, Devlieger, de Zegher, & De Nayer, 1999). This means that they depend on the daily production of these to meet their hormonal requirements. Therefore, any inhibition of the thyroid gland will result in a reduction in serum T_4, with acute exposure leading to measurable neurological and cognitive deficits (Negro, Soldin, Obregon, & Stagnaro-Green, 2011; Van Vliet, 1999; Zimmermann, 2009).

It has been noted that inhibition of the thyroid gland is of growing concern due to studies which indicate that an increased

Table 1–Key oxychlorine BDPs their EU classification and their associated biological effect with established health-based guidance (TDI, ADI, and ARfD) and regulatory MRL values.

Compound	Biological effect	Classification	TDI	ADI	ARfD	MRL
			μg/kg b.w. per day	μg/kg b.w. per day	μg/kg b.w.	μg/kg
Chlorite	Oxidative stress/fetal development	Pesticide[a]	30[a]	0 to 30[a]	N/A	10[a]
Chlorate	Oxidative stress/fetal development/thyroid gland inhibition	Pesticide[a]	3[a]	0 to 10[a]	36[a]	10[a]
Perchlorate	Thyroid gland inhibition	Contaminant[b]	0.3[b]	N/A	ND[b]	ALARA[cb]

[a] EFSA (2015).
[b] EFSA (2014).
[c] As low as reasonably achievable.

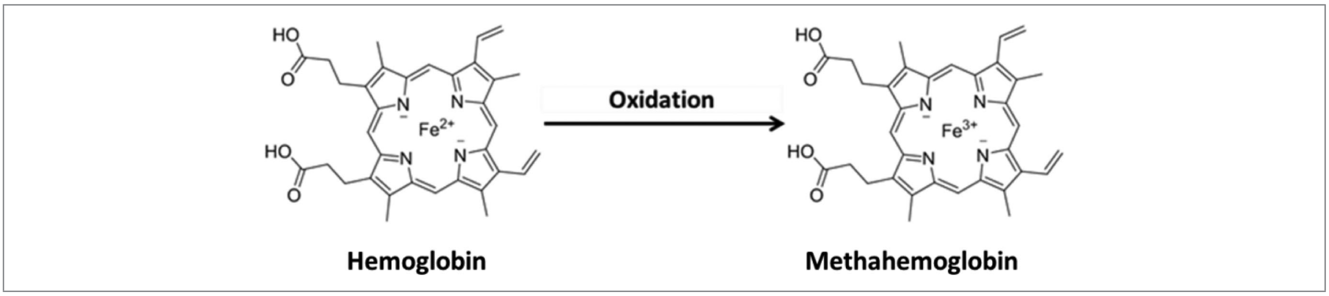

Figure 2–Oxidation of hemoglobins iron center from the ferric to the ferrous oxidation state leading to methemoglobin formation.

percentage of people are consuming a lower level of iodine in their diets than in past decades (Pearce, Andersson, & Zimmermann, 2013). Most iodine intake in the United States occurs as a result of the intake of iodized table salt, established as a health mandate to tackle the growing number of iodine deficiency diseases which had been leading to increasing problems surrounding thyroid function and thus fetal and childhood development (Markel, 1987). This has come back into scientific interest lately due to health policies linked to salt intake. A number of scientific bodies and professional health organizations, including the World Health Organization (WHO), the American Heart Association, the American Medical Association, and the American Public Health Association, have been supporting a reduction of dietary salt intake to combat the rising levels of hypertension, a leading risk factor for premature death (Campbell et al., 2012).

International efforts to correct Iodine deficiency through the universal salt iodization are considered a major health triumph (Campbell et al., 2012). However, in the USA this process is not mandatory and has led to the decline of iodine intake from 320 μg/day in the 1970s to circa 150 μg/day recently (Caldwell, Jones, & Hollowell, 2005; Hollowell et al., 1998). However, it is also important to note that the FDA mandates that infant formula contain iodine concentrations of 100 to 233 μg/L to prevent iodine deficiency. Iodine supplementation is also given to pregnant and lactating women, as the American Thyroid Association recommends that iodine supplementation is included in all prenatal vitamin supplements (Becker et al., 2006). Notably, it has been successful to add iodine to drinking water supplies to alleviate iodine deficiency in communities in Malaysia, Italy, and the Central African Republic (Foo, Zainab, Nafikudin, & Letchuman, 1996; Squatrito et al., 1986; Yazipo et al., 1995).

The presence of chlorine DBPs in potable water and food consumed by the "at risk" iodine-deficient groups increases the risks of the aforementioned health effects through both acute and chronic exposure models. Perchlorate is produced by a natural atmospheric process (Dasgupta et al., 2005) and has been measured in groundwater (Snyder, Vanderford, & Rexing, 2005), with this water then subsequently used for treatment, consumption, and irrigation schemes. Perchlorate has been found in milk and other dairy products, presumably due to the NIS during milk formation, allowing it to pass through the blood-milk barrier, after consumption of contaminated water and feed (Murray et al., 2008). Studies have indicated that perchlorate in human breast milk has been found to be five times higher than that of cow milk (Kirk et al., 2005), possibly linked to evidence that up to 80% of perchlorate consumed by the cow is metabolized, providing the animal with a degree of resistance to perchlorate (Capuco et al., 2005). Baier-Anderson et al. (2006) Estimated human exposure of this DBP from water, cow, and human milk and provided a further insight into the dietary contribution of each group.

Oxychlorine Regulation

A maximum residue limit (MRL) is the maximum concentration of a pesticide recommended by the Codex Alimentarius Commission, which is legally allowed to be in food commodities and animal feeds. Such limits are critically important, as these regulations protect the consumer from adverse health effects associated with the consumption of these residues. There have been very few investigations relating to dairy foods carried out focusing on these residues; and although cleaning is thought to be a major entry route, there are limited literature data on the potential impact of other manufacturing processes within the supply chain at this time.

A study carried out in 2013 by the German food control authority Chemisches und Veterinäruntersuchungsamt (CVUA) Stuttgart investigated chlorate contamination levels in produce on the German market. They found chlorate levels above regulatory limits (>10 μg/kg) in 24.5% of samples taken, with a median chlorate level across all samples of 22 μg/kg (EFSA, 2015). The report from this investigation speculated different sources of this chlorate contamination, including the use of chlorinated water, which subsequently led to a number of products being withdrawn from the market due to chlorate levels above the default MRL of 10 μg/kg (EFSA, 2015; No, 2005). These findings caused much debate surrounding the entry of this inorganic compound into the food supply chain and cleaning practices in the food industry (EFSA, 2015). It should be noted that this WHO guideline for chlorate in potable drinking water is 700 μg/L, much higher than the regulated levels set for food products. Therefore, the use of water in the preparation of food is a major source of chlorate entry into numerous food products (CVUA, 2014). This can have a substantial impact on chlorate levels in dairy products that must be rehydrated before consumption, namely infant milk formula and nutritional protein powders (Kettlitz et al., 2016).

To date, no extensive reports have been conducted on the occurrence of chlorates in foods of animal origin. In a 2015 study, 166 samples in the category of "milk and dairy products" were assessed by EFSA, accounting for 2% of all the samples examined in their report and it was found that daily consumption of bovine milk had a calculated exposure of 56 μg per kilogram body weight per day, highlighting dairy and water as potential high-exposure commodities (EFSA, 2015). Furthermore, there have been no *in vivo* studies carried out with humans to assess the inhibition of iodine uptake by chlorate. However, as mentioned previously, similar modes of action between chlorate and perchlorate have allowed the establishment of a TDI using data collected by Greer, Goodman, Pleus, and Greer (2002) as a pivotal study for a dose-response assessment. The Panel on Contaminants in the Food Chain (CONTAM) established a TDI of 0.3 μg/kg/day to humans using a benchmark dose confidence limit (BMDL_{50}) established for thyroid iodine uptake inhibition by perchlorate and factoring in an uncertainty factor to the reference point (EFSA, 2014). From here it was possible to calculate a TDI for chlorate by applying an extrapolation factor to account for the difference in potency between chemical species. Using an extrapolation factor of 10, a TDI for chlorate was calculated to be 3 μg/kg/day (2015), which is over three times lower than the acceptable daily intake (ADI) established previously (FAO/WHO, 2007, 2009).

Risk–benefit assessment

The use of chlorine-based treatments throughout the entire CIP cycle (chlorine sanitizers and treated water) may lead to an accumulation of oxychlorine residues in the final dairy product. Dairy processing and manufacture of ingredients requires high standards in microbial safety, especially for at-risk populations such as infants and toddlers. It is therefore important to consider the relationship between achieving the necessary level of sanitation, and the potential for contamination of the product with these oxychlorine residues. A risk–benefit assessment must be completed to fully understand this relationship, evaluate its risks and benefits, and assess the associated risks with improper cleaning regimes for potential product contamination and health effects (FAO/WHO, 2009).

The potential for bacteriological contamination of milk starts at farm level and is related to multiple factors employed during on-farm production practices. The approach and extent of control of these factors vary from farm to farm at the discretion of the farmer, therefore, the quantities of cleaning detergents used and adherence to a specified cleaning protocol can vary. Each factor potentially contributing to residual contamination at farm level, before industrial processing has commenced (Elmoslemany & Keefe, 2008; Gleeson & O'Brien, 2013). There are currently no extensive studies carried out examining chlorate contamination versus bacterial safety in dairy at this level, such a task would be challenging to carry out given the wide variation of on-farm practices.

During industrial processing, milk is pasteurized, which reduces the level of vegetative pathogens and ensures food safety (Negro et al., 2011; Rysstad & Kolstad, 2006). To date, however, there have been no detailed studies into industrial processing practices contribution to chlorate contamination of dairy streams, however, FAO/WHO (2009) have completed risk–benefit assessments for a number of products during industrial processing. They found that for a number of detergents (hypochlorite, chlorine dioxide, and so on) and their associated residues (THMs, chlorite, chlorate), no health concerns were reported across all studies on different food commodities and food contact surfaces while showing beneficial decreases in pathogenic species (FAO/WHO, 2009).

A market survey conducted by CVUA (2014) found that chlorate levels were an issue on the German commercial market in food products. They found that 24.5% of samples analyzed were above the permitted MRL for chlorate contamination. This would not be an issue for the majority of the population whose intake of these foods would not surpass the TDI for chlorate. It was noted, however, that the levels of chlorate contamination found could be an issue for high consumers of chlorate containing foods in younger age categories with an iodine deficiency or those with a genetic predisposition to hypothyroidism. It was noted that chronic exposure exceeding the TDI at the 95th percentile such highly consumed commodities, namely water and liquid milk, are a major source of chlorate in their diets due to the key role these play in early nutrition (EFSA, 2015).

It is clear that the beneficial aspects of chlorine sanitizers in the food processing environment increase consumer safety from food-borne illness by contributing to microbial safe products. There is a lack of information on the impact of food processing practices on residual chlorate contamination at present, with it being unclear of the impact of efforts to reduce these residues on microbiological safety (EFSA, 2015). There is, therefore, a need for a deeper understanding of this issue to be established before a conclusive risk-benefit assessment can be completed.

Established Methods of Removal and Reduction of Oxychlorine Species

The removal and reduction of chlorate have not been successfully performed in a dairy matrix, but is common practice in simpler solutions like groundwater. This lacks the complex fat, protein, and sugar systems present in milk, and these are the factors that must be overcome before any of these methods can be applied to dairy samples.

Oxychlorine removal

In complex food processes, which rely heavily on multistep CIP procedures to ensure proper sanitation of equipment, there is always the risk of contamination of the subsequent food product with DBPs. However, there is the possibility of developing and implementing removal or reduction techniques to eliminate the DBPs in solution from liquid products, such as dairy, to ensure that products adhere to the highest food safety standards.

Physical removal techniques do not destroy oxychlorine species and, thus, create a subsequent need for disposal of both the oxychlorine compounds and other waste streams produced as part of the process. In addition, these techniques often suffer from a lack of selectivity, as, along with oxychlorine, they may also remove large quantities of dissolved salts that may be desirable within the product matrix.

Membrane separation selectively fractionates materials via pores and/or gaps in the molecular arrangement of a continuous structure. Membrane separations are classified by pore size and by the separation driving force. Membrane processes such as nanofiltration and reverse osmosis are effective at oxychlorine removal from water, being demonstrated to remove over 80% of the perchlorate in solution without transforming it chemically. However, membrane use in removal of oxychlorine species has not yet been investigated in a dairy matrix. Membrane fouling and treatment costs associated with these methods are major technical difficulties faced by membrane separation techniques (Wang, Shah, & Huang, 2013).

Among the methods of perchlorate removal techniques in water treatment, ion exchange is noted as the most widely used method of perchlorate removal (Gu, Brown, & Chiang, 2007). With this technique, perchlorate is swapped with an anion, commonly chloride. The solution flows through a resin containing high concentrations of the bound ion. The relative difference in the concentration of each ion in the resin promotes ion swapping and the release of the exchange ion into solution while the target ions remain associated with the resin. Eventually, the resin reaches an equilibrium concentration, where it is saturated with ions, and then the resin requires regeneration. In water treatment, ion-exchange resins are the most sensible method for removing perchlorate at levels <50 μg/kg (Darracq, Baron, & Joyeux, 2014). However, ion exchange is not found to be economically viable due to the high cost associated with it and the disposal of brine solutions (Ye, You, Yao, & Su, 2012). There can also be a reduction of resin adsorption capacity of perchlorate when other anions coexist in solution (Bardiya & Bae, 2011; Venkatesan & Batista, 2011).

Adsorption is the adhesion of molecules of gas, liquid, or solids in solution to a surface. Molecules or atoms which are adsorbed (adsorbate) create a thin film on the adsorbent. The most common sorbers used in oxychlorine removal are granular activated carbon (GAC; Chen, Cannon, & Rangel-Mendez, 2005; Na, Cannon, & Hagerup, 2002; Parette & Cannon, 2005). GACs efficient adsorption of perchlorate has allowed it to be the catalyst support for surface-mediated hydrogenation-reduction of perchlorate (Hurley & Shapley, 2007; Mahmudov, Shu, Rykov, Chen, & Huang, 2008), and is applied as a water-treatment technology in some dairy installations.

Various methods have been utilized for the removal of organic DBPs, such as chloroform, from water including reverse osmosis, ion exchange, coagulation, coprecipitation, catalytic-reduction, herbal filtration, electrodialysis, and adsorption (Bolto, Dixon, Eldridge, & King, 2002). However, removal of DBPs and their precursors is poor by coagulation using organic polymers. Therefore, alternative techniques were investigated, and it was found that adsorption processes were effective in their removal, leading to the use of granular activated carbon and powdered activated carbon for removal of organic chlorine DBPs (Gopal, Tripathy, Bersillon, & Dubey, 2007).

Oxychlorine reduction

Electrochemical reduction of oxychlorine species has become an area of growing interest because it is practical, has a low environmental impact, and does not use toxic solvents (Xue et al., 2016). As such, there have been numerous studies carried out surrounding the reduction of perchlorate by electrochemical means (Láng, Inzelt, Vrabecz, & Horányi, 2005; Rusanova, Polášková, Muzikař, & Fawcett, 2006; Theis, Zander, Li, Sene, & Anderson, 2002). Using electrodialytically assisted catalytic reduction (EDACR), a process has been successfully developed and has been demonstrated to have an 88% perchlorate purge when catalyzed by titanium (IV). Overall, EDACR involves a multistep reduction system including perchlorate transfer, accumulation, and reduction, followed by reduction of chloride mediated by reductive hydrogen species generated at the cathode (Wang & Huang, 2008).

Yao et al. (2017) successfully demonstrated a Pd/Pt-N-doped activated carbon fiber (Pd/Pt-NACF), which integrated adsorption and electrocatalytic degradation of perchlorate by effectively electro-reducing it to chloride by hydro-deoxygenation reactions, as seen below:

$$\mathbf{2Pd/Pt-H^{*}+ClO_4{}^{-}\rightarrow 2Pd/Pt+ClO_3{}^{-}+H_2O}$$

$$\mathbf{2Pd/Pt-H^{*}+ClO_3{}^{-}\rightarrow 2Pd/Pt+ClO_2{}^{-}+H_2O}$$

$$\mathbf{4Pd/Pt-H^{*}+ClO_2{}^{-}\rightarrow 4Pd/Pt+Cl^{-}+2H_2O}$$

The conversion of perchlorate to chlorate is thermodynamically favored, as chlorate has a lower internal energy than perchlorate. Nonetheless, the reaction rate is controlled by the kinetic barrier of the high activation energy of the transition state (Urbansky, 1998), which is lowered using catalysis. It was noted that there were no chlorate or chlorite species detected in the reaction system. This implies that the kinetic stability of chlorate and chlorite are much less than that of perchlorate and they would be completely reduced to chloride once formed (Chaplin et al., 2012).

Biologically mediated (per)chlorate reduction has been observed in a diverse range of environments and has been associated with the presence of dissimilatory (per)chlorate-reducing bacteria (DPRB), of which many strains have been isolated and identified in recent years (Bruce, Achenbach, & Coates, 1999; Coates et al., 1999; Kim & Logan, 2001; Logan et al., 2001; Michaelidou, Achenbach, & Coates, 2000; Rikken, Kroon, & Van Ginkel, 1996; Wallace, Ward, Breen, & Attaway, 1996). The metabolic capability and ubiquity of these microorganisms have caused interest to grow in the natural reduction of oxychlorine species (Coates et al., 1999). DPRBs are capable of oxychlorine reduction and produce harmless chloride ions and, thus, have been identified as a potential method of remediating oxychlorine contamination (Coates & Achenbach, 2004). However, this method of perchlorate reduction from consumables is not viewed favorably by the public as microorganisms are involved in the treatment process (Vijaya Nadaraja, Gangadharan Puthiya Veetil, Vidyadharan, & Bhaskaran, 2013).

The DRPBs have been phylogenetically limited to Proteobacteria (Coates & Achenbach, 2004). It is possible that this ability may have evolved from a common ancestor within the Proteobacteria and was lost in multiple genera, but other theories suggest that this is a recent evolution and was transferred horizontally. This latter theory is supported by the lack of phylogenetic synteny between the 16s rRNA genes and the chlorite dismutase (cld; an essential gene in the per(chlorate) reduction pathway (Coates et al., 1999; Logan et al., 2001; Wallace et al., 1996) in the same organisms (Bender, Rice, Fugate, Coates, & Achenbach, 2004).

The reaction pathway for perchlorate reduction to chloride involves chlorate and chlorite as intermediates, and has been proposed to be:

$$\mathbf{ClO_4{}^{-}\rightarrow ClO_3{}^{-}\rightarrow ClO_2{}^{-}\rightarrow Cl^{-}+O_2}$$

This reduction pathway involves the enzymes (per)chlorate reductase to reduce the +5 and +7 forms to chlorite (Kengen, Rikken, Hagen, Van Ginkel, & Stams, 1999), which is disproportionate to chloride and oxygen using chlorite dismutase (Rikken et al., 1996; Van Ginkel, Rikken, Kroon, & Kengen, 1996).

This eco-friendly method of oxychlorine removal, however, has low kinetics and is sensitive to temperature and pH, and its effectiveness in low concentration solutions needs to be focused upon if its application in large-scale processes is to be explored (Kumarathilaka, Oze, Indraratne, & Vithanage, 2016). However, this method can be incorporated into the regeneration of resins as demonstrated by Song et al. (2017), who generated an amine cross-linked magnetic biopolymer resin (AM bio-resin), and after adsorption, they utilized microbial treatment to reduce the now concentrated sample of perchlorate on the resin. This step both regenerated the resin while it eliminated perchlorate as chloride and oxygen.

An emerging technology in water and wastewater treatment is the use of a membrane biofilm reactor (MBfR), which utilizes a pressurized membrane supplying a biofilm on the membrane's exterior with the gaseous substrate (Martin & Nerenberg, 2012). Hydrogen-based MBfR has been used to remove a wide range of inorganic oxidized contaminants. It has been demonstrated that a wide range of chemicals, including chlorine DBPs; perchlorate, chlorate, chlorite, and dichloromethane, could be effectively reduced by a hydrogenotrophic biofilm using an electron acceptor like nitrate or oxygen (Chen, Liu, Peng, & Ni, 2017; Chung, Rittmann, Wright, & Bowman, 2007; Nerenberg & Rittmann, 2004; Nerenberg, Rittmann, & Najm, 2002).

A methane-based MBfR has also been shown to be applicable in perchlorate reduction and could be advantageous as methane is inexpensive, and in wastewater treatment it can provide a solution for energy recovery as methane is respired by anaerobic digestion of bio-solids (Liu, Zhang, & Ni, 2015; Sun et al., 2017; Wei, Zhou, Wang, Sun, & Wang, 2017). This approach also has the potential to reduce greenhouse gas emissions that are produced during wastewater treatment (Silva-Teira, Sánchez, Buntner, Rodríguez-Hernández, & Garrido, 2017; Sun, Pikaar, Sharma, Keller, & Yuan, 2015).

Conclusion

This review investigated the current literature surrounding chlorates and other chlorine DBPs and their importance to the food and, in particular, dairy industries. Chlorate and other chlorine DBPs are a growing concern in modern-day food production with the establishment of stringent regulations, which may affect production practices throughout the entire dairy production chain.

The toxicological implications driving these regulations have been the focus of many research groups in recent years, with chlorate in particular highlighted as an emerging residue of concern by EFSA. However, very little research has been carried out on this emerging residue in milk and dairy products and therefore it is crucial that future research addresses this deficiency, particularly as dairy products are often a major source of nutrition for some of the most vulnerable consumers within the population. It is vital that the factors affecting oxychlorine contamination within the dairy supply chain are identified and a comprehensive risk-benefit assessment is completed for CIP procedure development within the dairy supply chain.

It is recognized that the use of chlorine-based treatment throughout the CIP process through the use of chlorinated water and active chlorine detergents is not ideal considering the large catalog of associated DBPs. These drawbacks can be overcome however by a better understanding of the reactions leading to their degradation and the steps needed to minimize their introduction into the dairy processing chain starting at the farm level. This is of particular concern with the risks of microbial contamination versus the risks associated with dietary DBP consumption which are controlled by CIP practices and its inputs. To ensure the safety of dairy products closer monitoring of detergents and processing water must be conducted during industrial production to minimize DBP contamination and hence increase consumer safety.

Acknowledgment

William P. McCarthy is the recipient of a Teagasc Walsh Fellowship award.

Authors' Contributions

W.P. McCarthy researched prior studies and compiled the manuscript with the assistance of T.F. O'Callaghan and J.T. Tobin. M. Danahar, D. Gleeson, C. O'Connor, and M.A Fenelon reviewed and contributed to the correction and final preparation of the manuscript.

Glossary of abbreviations

ACS	Active chlorine species
ADI	Acceptable daily intake
ALARA	As low as reasonably achievable
AM bio-resin	Amine cross-linked magnetic biopolymer resin
ARfD	Acute reference dose
CE	Capillary electrophoresis
cfu	Colony forming units
CIP	Clean-in-place
cld	Chlorite dismutase
DBP	Disinfection by-product
DPRB	Dissimilatory (per)chlorate-reducing bacteria
EDACR	Electrodialytically assisted catalytic reduction
EME	Electromembrane extraction
GAC	Granular activated carbon
IC	Ion chromatography
IC-MS/MS	Ion chromatography-tandem mass spectrometry
ID IC-MS/MS	Isotope dilution ion chromatography-tandem mass spectrometry
LC-MS	Liquid chromatography with coupled mass spectral detection
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LOD	Limit of detection
LOQ	Limit of quantification
MAD	Microwave-assisted digestion
MBfR	Membrane biofilm reactor
MRL	Maximum residue level
MS	Mass spectrometry
MS/MS	Tandem mass spectrometry
N/A	Not applicable
ND	Not Determined
NIS	Natrium iodide symporter
NOM	Natural organic matter
Pd/Pt-NACF	Pd/Pt-N-doped activated carbon fiber
T3	Triiodothyronine
T4	Thyroxine
TDI	Tolerable daily intake
THM	Trihalomethane

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