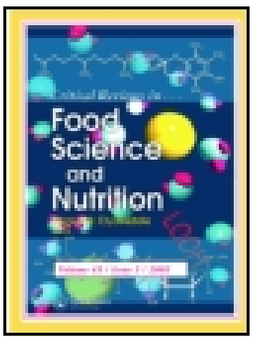

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REVIEW

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Antimicrobial resistance associated with the use of antimicrobial processing aids during poultry processing operations: cause for concern?

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ABSTRACT

Antimicrobial resistance has become a global issue and a threat to human and animal health. Contamination of poultry carcasses with meat-borne pathogens represents both an economic and a public health concern. The use of antimicrobial processing aids (APA) during poultry processing has contributed to an improvement in the microbiological quality of poultry carcasses. However, the extensive use of these decontaminants has raised concerns about their possible role in the co-selection of antibiotic-resistant bacteria. This topic is presented in the current review to provide an update on the information related to bacterial adaptation to APA used in poultry processing establishments, and to discuss the relationship between APA bacterial adaptation and the acquisition of a new resistance phenotype to therapeutic antimicrobials by bacteria. Common mechanisms such as active efflux and changes in membrane fluidity are the most documented mechanisms responsible for bacterial cross-resistance to APA and antimicrobials. Although most studies reported a bacterial resistance to antibiotics not reaching a clinical level, the under-exposure of bacteria to APA remains a concern in the poultry industry. Further research is needed to determine if APA used during poultry processing and therapeutic antimicrobials share common sites of action in bacteria and encounter similar mechanisms of resistance.

KEYWORDS

Antimicrobial; carcass decontaminant; cross-resistance; poultry

Introduction

Poultry meat production is one of the most important food industries worldwide, with its products offering affordable selling prices, high quality proteins, and a relatively low fat content (Magdelaine, Spiess, and Valceschini 2008). However, poultry meat is also recognized as a source of zoonotic pathogens (e.g., nontyphoidal *Salmonella*, *Campylobacter* spp.), representing the highest risk for public health among foods of animal origin. Human disease outbreaks attributed to poultry meat products costs about $2.4 billion annually in the United States (Lemonakis et al. 2017). In Canada, it has been estimated that, in 2016, 10% to 37% of the nontyphoidal *Salmonella* infection cases in humans were attributed to the consumption of contaminated poultry and poultry products (Butler, Pintar, and Thomas 2016). Managing the microbiological quality of poultry meat products remains the most important challenge for poultry processors (Chen et al. 2012). In this context, the Food Safety and Inspection Service (FSIS), an agency of the United States Department of Agriculture (USDA) announced, on July 2016, increasingly stringent guidelines for the control of *Salmonella* and *Campylobacter* on broiler carcasses, where the prevalence of *Salmonella*-positive carcasses must be less than 9.8%, and the prevalence of *Campylobacter* must be below 15.7% among the tested carcasses (FSIS 2016). In order to meet these requirements, various antimicrobial processing aids (APA) (also referred to as microbial control agents) used as carcass decontamination technological tools (or agents), have been approved for use during poultry processing in Canada, in the United States, in the European Union and in Australia. These compounds act as biocides and are primarily used during chilling to reduce the presence of foodborne pathogens and therefore to mitigate the microbiological risk for consumers. The broad spectrum of action of these compounds also helps increase the shelf life of products (Walsh et al. 2018). Chlorine, acidified sodium chlorite (ASC), cetylpyridinium chloride (CPC), chlorine dioxide, ozone, sodium hypochlorite (SHY), calcium hypochlorite, lactic acid and peroxyacetic acid (PA; also known as peracetic acid) represent the most commonly used APA in processed poultry in Canada (Kim et al. 2017). Many APA, such as chlorine, are used at various steps throughout the slaughter process, including during inside-outside bird washers, pre-chilling, chilling, and as a post-chill application (Wideman et al. 2016). The desired effect of APA is to reduce bacterial loads of *Salmonella*, *Campylobacter* and *Escherichia coli*, as well as of other pathogens, such as *Listeria monocytogenes* and *Clostridium*

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Table 1. Keywords used to retrieve the scientific articles related to the scope of the review.

Cluster	Keywords
Biocides	Biocide OR antibiotic* OR antimicrobial* OR antimicrobial agents OR disinfectant* OR antimicrobial processing aids OR decontaminant OR chemical decontaminants OR chemical treatments OR sanitizer OR biocide exposure OR quaternary ammonium compound OR QAC OR peroxyacetic acid OR biocide usage OR acidified sodium chlorite OR chlorine OR chlorine dioxide OR peracetic acid OR trisodium phosphate OR sodium hypochlorite OR chlorine-based compounds OR acid compounds OR organic acids OR under-dosing OR sub-inhibitory concentrations OR sub-lethal concentrations
Resistance or tolerance	Reduced susceptibility OR tolerance OR decreased susceptibility OR biocide tolerance OR biocide resistance OR adaptation OR cross-adaptation OR resistance OR cross-resistance OR co-resistance OR cross-protection OR resistance mechanisms OR microbial resistance mechanisms OR resistance bacteria OR multidrug resistance bacteria OR efficacy OR efflux pump OR disinfectant resistance genes OR gene expression OR genetic elements OR minimum inhibitory concentration
Poultry and poultry products	Poultry OR broiler OR chickens OR turkeys OR ducks OR geese OR chicken meat OR poultry carcasses OR chicken carcasses OR broiler carcasses OR poultry skin OR poultry product* OR ready-to-eat
Poultry processing operations and food safety	Poultry processing operations OR poultry processing plants OR slaughter OR poultry decontaminant OR production line OR surface contamination OR chilled water OR bacteria OR pathogen OR residential bacteria OR bacterial loads OR contaminants OR biofilm OR foodborne pathogens OR slaughterhouse OR sanitation OR spray washing OR aqueous chemical solution OR surveillance OR safety OR public health OR risk management

perfringens on poultry carcasses and products (Oyarzabal 2005). Various APA have been tested for their effectiveness in reducing *Campylobacter* and *Salmonella* on broiler chicken carcasses during processing (Wideman et al. 2016; Park, Harrison, and Berrang 2017). However, results on reducing the loads of these pathogens vary between studies and compounds, with the APA and the poultry meat type acting as influencing factors (Kemp, Aldrich, and Waldroup 2000; Oyarzabal 2005; Sarjit and Dykes 2015; Wideman et al. 2016). Also, for the specific case of *Salmonella*, the antimicrobial activity of some APA was shown to be serovar-dependent (Sarjit and Dykes 2015).

Despite the extensive use of chlorine and other decontaminants in poultry processing during the last three decades, several surveys have reported that up to 20% of the post-chill carcasses and up to 22% of the retail poultry meat products commercialized in the United States are contaminated with *Salmonella* (Paul, Sullivan, and Shah 2017).

The use of APA in poultry processing establishments could potentially impose a selective pressure contributing to the emergence of biocide-tolerant bacteria and may indirectly lead to the selection of antimicrobial resistant bacteria. Hence, the aim of the present work is to review the information available on the mode of action of APA, bacterial adaptation to APA used during poultry processing, and to discuss the relationship between APA bacterial adaptation and the concomitant development of resistance to clinically used antimicrobials. In addition, current data gaps and future perspectives regarding the assessment of bacterial sensitivity to APA are detailed and discussed.

The persistence of chemical residues of APA in the environment, as well as the impact of their by-products on public health and on the organoleptic quality of poultry carcasses and parts are not covered in the present review.

Materials and methods

Article searching

We conducted a narrative literature review to identify scientific articles related to the objectives of the present review as explained above. The literature from international online databases (CAB Abstracts, PubMed, and Global Health) was retrieved using a combination of keywords belonging to four clusters (Table 1). In fact, keywords were combined by adding the function "and" between each cluster in the search engines. This search was complemented by published reports from relevant international and national organizations and agencies. Only articles published in English OR in French over the period of January 2000 to April 2019 were considered in this review. All retrieved articles were saved in an EndNote file for further analysis.

Article selection and analysis

A total of 342 non-duplicate articles were found using the search terms listed above. Two screening steps were conducted to select articles that were within the scope of the present review (Figure 1). Indeed, the first screening focused on titles, keywords and abstracts. The second screening step was performed to determine the access to the full papers, either in French or English, and to confirm or invalidate their relevance to the scope of the review. After applying these inclusion and exclusion criteria, 103 citations were considered as potentially eligible for inclusion in this review (Figure 1).

APA used during poultry processing; antimicrobial mechanisms of action and efficiency

The use of APA on poultry carcasses and parts

The use of APA during poultry processing in North America has been approved by Health Canada (HC) and by the U.S. Food and Drug Administration (FDA) (Kim et al. 2017). The approved list of APA is subject to continuous changes and revision, this revision being mostly based on import and export requirements. By 2015, HC had approved 14 APA for use during poultry processing, with a letter of no objection (LONO) and 4 APA with an interim letter of no objection (iLONO) (Tables 2 and 3) (Health Canada 2015). As of June 2019, HC updated the list of APA used on red meat and poultry meat for which HC has expressed No Objection (Table 4) (Health Canada 2019). Indeed, The LONO list contains all APA that have been evaluated and

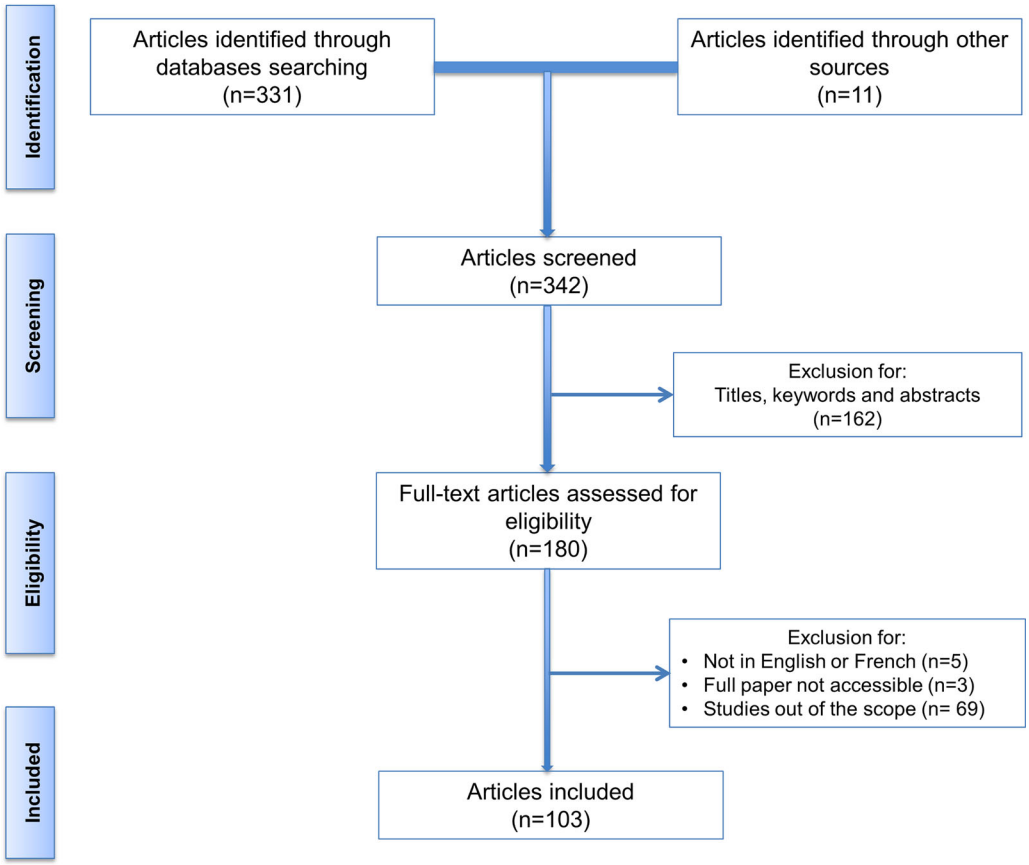

Figure 1. Flow diagram of the selection and exclusion criteria for the selection of publications related to the scope of this review.

approved by HC for specific uses on meat and poultry surfaces. However, if a corresponding request has not been received by HC, the compound is classed in the iLONO list and may be transferred to the LONO when HC completes a full assessment of that substance (Table 4). A survey conducted in 2017 by the Canadian Food Inspection Agency (CFIA) reported that 59% of the federally-registered poultry processing establishments were using chlorine-based products (e.g., chlorine, ASC, sodium or calcium hypochlorite, chlorine gas, chlorine dioxide, and electronically generated hypochlorous acid), 21% of these establishments were using CPC, whereas 20% were using peracetic acid as decontaminants during processing (Hardie et al. 2019). In Canada, chlorine dioxide can be applied either on whole or eviscerated poultry carcasses, as well as in the chiller water at a level that does not exceed 50 ppm. ASC can be used on the surface of poultry carcasses, on parts, organs and trims at up to 1,200 ppm in an aqueous solution of sodium chlorite acidified with citric acid (CA), phosphoric acid, hydrochloric acid, sodium acid sulfate, acetic acid or lactic acid (Health Canada 2015). Of note, organic acids are often added to the process water to lower the pH and increase the disinfection potency of chlorine. In the United States, the Poultry and Egg Association reported that chlorine was used in 72% of commercial poultry processing establishments as a decontaminant during water immersion-chilling of carcasses (Paul, Sullivan, and Shah 2017). The massive use of chlorine is mainly due to its low cost and its effectiveness in preventing cross-contamination in chilling water (Park, Harrison, and Berrang 2017). Chlorine forms several compounds in water such as hypochlorous acid (HOCl), chlorine gas (Cl_2) and hypochlorite ion (OCl^-), with their concentrations being dependent on the water pH (Gil et al. 2016). The antimicrobial activity of chlorine depends on the concentration of free residual chlorine (as HOCl) in the water that comes into contact with the microorganisms (Chaves et al. 2019).

Mechanisms of action of APA

The different modes of action of biocides belonging to the various chemical groups have been reviewed extensively elsewhere (Russell 2003a, 2003b; Morente et al. 2013; Park, Harrison, and Berrang 2017; Rodriguez-Lopez et al. 2018). Also, the efficacy of various spray and dip APA treatments, applied on chicken carcasses during primary processing, was examined in a systematic review and meta-analysis (Bucher et al. 2012). The current work provides a brief overview of the antimicrobial efficacy of APA commonly used in poultry processing establishments, with a focus on the most recent publications. The most documented antimicrobial activity of APA is linked to their strong oxidative potential on the bacterial cell wall, leading to a disruption of this membrane, and resulting in the leakage of cellular components and bacterial cell death (Estrela et al. 2002; Oyarzabal 2005). Although APA are recognized to act through multiple bacterial targets, their ultimate mechanism of action remains unknown (Wales and Davies 2015). The antimicrobial spectrum of APA activity is very different from one product to

Table 2. Antimicrobial processing aids approved in processed poultry in Canada with a Letter of No Objection (LONO) (2015) (Health Canada 2015).

Antimicrobial processing aids	Poultry parts to treat	Terms of use
Acidified sodium chlorite (ASC)	Poultry carcasses, poultry parts, organs and trim applied prior to immersion in a pre-chiller or chiller tank	Applied as spray or dip at levels between 500 and 1200 ppm of sodium chlorite prepared by acidifying the sodium chlorite solution with food-grade acid (e.g., citric acid, phosphoric acid or hydrochloric acid) to achieve a pH of 2.2 to 3.0, equivalent to 50 to 266 ppm chlorous acid formed when prepared in the same manner as above to achieve a pH of 2.5 to 2.9
Bacteriophage preparation (*Listeria monocytogenes* targeted)	Various poultry products	Applied on the surface of the product to achieve a level of 1×10^7 to $1 \times$ ddde10^9 phage per gram of product
Calcium hypochlorite	Poultry chiller water	Not to exceed 50 ppm calculated as free available chlorine (measured in the incoming potable water)
	On whole or eviscerated poultry carcasses prior to immersion in a pre-chiller or chiller tank	Not to exceed 50 ppm calculated as free available chlorine measured prior to application
Cetylpyridinium chloride (CPC) containing 1.5 times its (e.g., CPC) weight of propylene glycol	Raw poultry carcasses before or after air or immersion chilling	Not to exceed 1% aqueous solution of CPC and not to exceed 1.5% propylene glycol applied to raw poultry carcasses followed by a potable water rinse
Chlorine dioxide	On whole or eviscerated poultry carcasses prior to immersion in pre-chiller and chiller tanks	Applied as a spray at a level not to exceed 50 ppm chlorine dioxide, without subsequent potable water rinse
	Poultry chiller water	Not to exceed 50 ppm chlorine dioxide in pre-chiller or chiller tank water with no more than 3 ppm residual chlorine dioxide in the chiller overflow water
Chlorine gas	On whole or eviscerated poultry carcasses prior to immersion in a pre-chiller or chiller tank	Not to exceed 50 ppm calculated as free available chlorine measured prior to application
	Poultry chiller water	Not to exceed 50 ppm calculated as free available chlorine (measured in the incoming potable water)
DBDMH (1,3-dibromo-5,5-dimethylhydantoin)	(1) In water applied to poultry carcasses via an inside-outside bird washer; (2) in water used in poultry processing for poultry carcasses, parts and organs; and (3) in water supplied to ice machines to make ice intended for general use in poultry processing	In each application, at a level not to exceed that needed to provide the equivalent of up to 100 ppm available bromine (corresponding to a maximum level of 90 mg DBDMH/kg of water)
	In poultry carcass chiller water	At a level not to exceed that needed to provide the equivalent up to 100 ppm available bromine (corresponding to a maximum level of 90 mg DBDMH/kg of water). The resulting solution will be in direct contact with poultry carcasses submersed in water chiller for approximately 45 to 90 minutes
Electrolytically generated hypochlorous acid	On whole or eviscerated poultry carcasses prior to immersion in a pre-chiller or chiller tank	Not to exceed 50 ppm calculated as free available chlorine measured prior to application
	Poultry chiller water	Not to exceed 50 ppm calculated as free available chlorine (measured in the incoming potable water)
Lactic acid	Poultry carcasses	Up to 4.25% lactic acid solution followed by a rinse with potable water
Ozone	Chicken drumsticks	An aqueous solution of ozone, generated on-site, to be sprayed for up to 5 seconds
Peroxyacetic acid (PA), hydrogen peroxide, acetic acid, sulfuric acid (optional), and 1-hydroxy-ethylidene-1,1-diphosphonic acid (HEDP) (an aqueous mixture)	Poultry carcasses, parts, and organs	The level of use in water that yields a concentration no greater than 220 ppm PA, a concentration of hydrogen peroxide no greater than 110 ppm, and a concentration of HEDP no greater than 13 ppm
PA, peroxyoctanoic acid, hydrogen peroxide, acetic acid, octanoic acid and HEDP (an aqueous mixture)	Applied during poultry scalding, feathering, evisceration; pre-chiller washing of carcasses; in the chiller and on post-chill carcasses, parts and organs	The level of use in water that yields a concentration of total peroxy acids no greater than 220 ppm expressed as PA, a concentration of hydrogen peroxide no greater than 110 ppm, and a concentration of HEDP no greater than 13 ppm
PA, hydrogen peroxide, acetic acid, and HEDP (an aqueous mixture)	Process water to treat poultry carcasses, parts and organs	The level of PA will not exceed 220 ppm, hydrogen peroxide will not exceed 162 ppm and HEDP will not exceed 13 ppm
Sodium hypochlorite	On whole or eviscerated poultry carcasses prior to immersion in a pre-chiller or chiller tank	Not to exceed 50 ppm calculated as free available chlorine measured prior to application
	Poultry chiller water	Not to exceed 50 ppm calculated as free available chlorine (measured in the incoming potable water)

Table 3. Antimicrobial processing aids used in processed poultry in Canada with an interim Letter of No Objection (iLONO) (2015) (Health Canada 2015).

Antimicrobial processing aids	Poultry parts to treat	Terms of use
Peroxyacetic acid (PA), hydrogen peroxide, acetic acid, 1-hydroxy-ethylidene-1,1-diphosphonic acid (HEDP) (an aqueous mixture)	Whole, half or quarter poultry carcasses and poultry carcass parts and organs	Applied once by low-temperature immersion bath (less than 40 degrees F), at levels not exceeding 2000 ppm PA and 136 ppm HEDP, for 30 to 60 seconds
	Poultry carcass, parts and organs	Applied at up to 2000 ppm PA, 750 ppm hydrogen peroxide, and 136 ppm HEDP
	Processed and preformed red meat and poultry products	Applied in process water or ice for washing, rinsing, storing, or cooling at up to 230 ppm PA, 165 ppm hydrogen peroxide, and 14 ppm HEDP
Sulfuric acid and sodium sulfate (equivalent to sodium bisulfate)	Meat and poultry surfaces	Spray, wash, or dip, at levels not to exceed those needed to achieve a target pH range of 1.0 – 2.2 on the meat or poultry surface
Bacteriophage preparation (*Salmonella enterica* targeted)	Ready-to-eat (RTE) poultry products prior to slicing and on raw poultry prior to grinding or after grinding	Applied as a spray, at a level of approximately 1×10^6 to 1×10^7 plaque-forming units (PFU) per gram of food
Ozone (aqueous solution)	Raw, fresh meat and poultry	An aqueous solution of ozone, generated on-site, applied directly by spray at up to 2.5 ppm ozone, for up to 5 seconds

another, and there is significant variation in the response of different microorganisms to APA (Russell 2003b). For poultry meat decontamination, it was reported that CA and trisodium phosphate (TSP) were the most effective compounds to fight against Gram-positive bacteria, whereas ASC and TSP are the most effective decontaminants against Gram-negative bacteria (Capita et al. 2013). This variation could be explained mostly by the difference in the structure and chemical composition of the bacterial membranes, as well as by the cell wall peptidoglycan of the different bacterial strains. Indeed, TSP disrupts bacterial membranes as a result of its alkaline pH (∼pH 12) by removing a thin layer of lipids, which leads to the leakage of the intracellular content and, ultimately, to the bacterial cell death (Koolman et al. 2014). However, other authors reported that the principal mode of action of TSP is based on the physical removal of bacterial cells and not on an antimicrobial effect (Meredith et al. 2013). In a previous publication, Singh et al. demonstrated that TSP combined with a hot water dip and brushing was the most effective approach against naturally occurring bacteria on broiler chicken carcasses (Singh et al. 2017). When crossing the bacterial cell wall under their undissociated forms, organic acids will dissociate and release H + ions, resulting in a reduction of the bacterial internal pH, consequently activating an efflux pump system and eventually causing the bacterial cell death following an energy depletion (Mani-López, García, and López-Malo 2012; Koolman et al. 2014). It should be stressed here that the antimicrobial activity of a given acid is dependent on the temperature, pH, product concentration, contact time, nature of the surface treated, and of the amount and type of organic matter found in the chiller water in which the acid is dissolved (Bashor et al. 2004). It is unknown, however, how much organic matter can be tolerated, for example in the immersion-chilling tank, to maintain the optimum antimicrobial activity of APA (Paul, Sullivan, and Shah 2017). In the case of chlorine, free chlorine is the key substance responsible for the antimicrobial activity of this APA. However, organic matter can easily bind free chlorine and lead to a significant loss of its bactericidal activity (Oyarzabal 2005; Paul, Sullivan, and Shah 2017). It was reported that sodium dodecyl sulfate (0.5%) enhanced (29%–53%) the antimicrobial activity of chlorine against *Salmonella* on chicken skin (Zhang et al. 2019). On the other hand, several reports showed that some APAs such as chlorine, ASC and peracetic acid were unable to eliminate adherent *Campylobacter* on chicken skin; the oil present on the skin preventing the decontaminants from establishing contact with the surface (Yang, Li, and Johnson 2001; Chantarapanont, Berrang, and Frank 2004). However, Chen et al. reported that peracetic acid and CPC, which are used as post-chill decontaminants for poultry parts, were effective to significantly reduce *Salmonella* and *Campylobacter* populations, while maintaining the organoleptic quality of the meat product (Chen et al. 2014). This study has confirmed the results of Nagel et al. showing that peracetic acid, used in a post-chill immersion tank, was more effective than chlorine in reducing populations of *Salmonella* and *Campylobacter* on poultry carcasses (Nagel et al. 2013). Ramirez-Hernandez et al. reported that the treatment of chicken pieces with lactic acid (2.84% and 5.11%) and peracetic acid (200 and 400 ppm) was associated with a significant reduction in *Salmonella* present on these chicken parts (Ramirez-Hernandez, Brashears, and Sanchez-Plata 2018). Another study showed that peracetic acid (0.07% or 0.1%), and CPC (0.35% or 0.60%) used in the post-chill decontamination tank are effective treatments for reducing *Salmonella* and *Campylobacter* on chicken parts, including breasts, thighs, wings, and drumsticks (Zhang et al. 2018).

It is worth mentioning that the antimicrobial efficacy of APA is mainly expressed as the log reduction in bacterial numbers (Bloomfield 2002). This antimicrobial activity is usually evaluated using classical bacterial culture methods, followed by the enumeration of bacterial colonies and their identification with biochemical testing (Wideman et al. 2016; Lemonakis et al. 2017). Recently, high-throughput sequencing has become a method of particular interest as a novel tool to assess changes in bacterial communities after APA use during poultry processing (Kim et al. 2017; Handley et al. 2018).

Bacterial resistance to APA used in poultry processing establishments

Terminology

While the terminology "resistance" relating to therapeutic antibiotics is well understood, it is still a subject of

Table 4. Antimicrobial processing aids approved in processed poultry in Canada with a Letter of No Objection (LONO) (2019) (Health Canada 2019).

Antimicrobial processing aids	Poultry parts to treat	Terms of use	Status compared to the assessment conducted by HC in 2015
Acidified sodium chlorite (ASC)	Surface of poultry meat carcasses, parts, organs and trim	Up to 1200 ppm in an aqueous solution of sodium chlorite acidified with citric acid, phosphoric acid, hydrochloric acid, sodium acid sulfate, acetic acid or lactic acid	Slight changes in some specific conditions related to the use of this APA
Bacteriophage mixture (*Listeria monocytogenes* targeted)	Surface of ready-to-eat (RTE) red meat and poultry meat products	At a concentration of 10^7 to 10^9 plaque-forming units (pfu) in an aqueous solution per gram of meat product	Slight changes on the characteristic of the product: "mixture" instead of "preparation"
Calcium hypochlorite	Surface of poultry meat carcasses	Up to 50 ppm calculated as free available chlorine in an aqueous solution	Changes in some specific conditions related to the use of this APA
Cetylpyridinium chloride (CPC) containing 1.5 times its (e.g., CPC) weight of propylene glycol	Surface of skin on poultry meat carcasses	Up to 1% CPC and up to 1.5% propylene glycol in an aqueous solution; followed by a potable water rinse of the carcass if it is to be air chilled after treatment; followed by a potable water rinse of the carcass if the treatment is to be applied after chilling (whether air or immersion chilled) NOTE: The aqueous solution is used in a system	Changes in some specific conditions related to use of this APA
Chlorine dioxide	Surface of poultry meat carcasses and parts	(a) Up to 50 ppm chlorine dioxide in an aqueous solution (b) Up to 3 ppm residual chlorine dioxide in the chiller overflow water	Slight changes in some specific conditions related to the use of this APA
Chlorine gas	Surface of poultry meat carcasses	Up to 50 ppm calculated as free available chlorine in chiller water and/or in an aqueous solution applied prior to immersion in a pre-chiller or chiller tank	Slight changes in some specific conditions related to the use of this APA
1,3-dibromo-5,5-dimethylhydantoin (DBDMH)	Surface of poultry meat carcasses, parts and organs	Up to 100 ppm calculated as available bromine in an aqueous solution or ice	Changes in several specific conditions related to the use of this APA
Ethyl lauroyl arginate, hydrogen peroxide, lauryl glucoside, citric acid and ascorbic acid	Surface of poultry meat carcasses, parts, trim and organs	Up to 300 ppm ethyl lauroyl arginate and 300 ppm hydrogen peroxide in an aqueous solution	New approved APA except hydrogen peroxide and citric acid
Ethyl lauroyl arginate, hydrogen peroxide, polysorbate 20, citric acid and ascorbic acid	Surface of poultry meat carcasses, parts, trim and organs	Up to 200 ppm ethyl lauroyl arginate and 200 ppm hydrogen peroxide in an aqueous solution	New approved APA except citric acid
Hypochlorous acid, electrolytically generated	Surface of poultry meat carcasses	Up to 50 ppm calculated as free available chlorine in chiller water and/or in an aqueous solution applied prior to immersion in a pre-chiller or chiller tank	Changes in some specific conditions related to the use of this APA
Lactic acid	Surface of poultry meat carcasses, parts, trim and organs	Up to 5% in an aqueous solution	Changes in some specific conditions related to the use of this APA
Ozone	Surface of hot dogs (frankfurters) and chicken drumsticks	Up to 3 ppm in an aqueous solution; contact time not to exceed 5 seconds	Changes in some specific conditions related to the use of this APA
Peroxyacetic acid (PA), hydrogen peroxide, acetic acid, sulfuric acid (optional), and 1-hydroxy-ethylidene-1,1-diphosphonic acid (HEDP) (an aqueous mixture)	Surface of poultry meat carcasses, parts, trim, and organs	(a) Up to 2000 ppm PA, up to 2750 ppm hydrogen peroxide and up to 83 ppm of HEDP in an aqueous solution or ice (b) Up to 2000 ppm PA, up to 1333 ppm hydrogen peroxide and up to 136 ppm of HEDP in an aqueous solution or ice	Changes in some specific conditions related to the use of this APA
	Surface of processed and pre-formed red meat and poultry meat products	Up to 220 ppm PA, up to 85 ppm hydrogen peroxide and up to 11 ppm HEDP in an aqueous solution or ice	
PA, peroxyoctanoic acid, hydrogen peroxide, acetic acid, octanoic acid and 1-hydroxyethylidene-1,1-diphosphonic acid (HEDP) (an aqueous mixture)	Surface of poultry meat carcasses, parts and organs	Up to 220 ppm PA, up to 110 ppm hydrogen peroxide and up to 13 ppm HEDP in an aqueous solution	Changes in some specific conditions related to the use of this APA
PA, hydrogen peroxide, acetic acid, 1-hydroxy-ethylidene-1,1-diphosphonic acid (HEDP), sulfuric acid, dipicolinic acid (an aqueous mixture)	Surface of poultry meat carcasses, parts, trim and organs	(a) Up to 2000 ppm PA, up to 787.4 ppm hydrogen peroxide, up to 87.5 ppm HEDP and up to 1.25 ppm dipicolinic acid in an aqueous solution (b) Up to 2000 ppm PA, up to 435 ppm hydrogen peroxide, up to 104 ppm HEDP and up to 0.87 ppm dipicolinic acid in an aqueous solution	Changes in some specific conditions related to the use of this APA
Sodium hypochlorite	Surface of poultry meat carcasses	Up to 50 ppm calculated as free available chlorine in chiller water and/or in an aqueous solution applied prior to immersion in a pre-chiller or chiller tank	Changes in some specific conditions related to the use of this APA

(*continued*)

Table 4. Continued

Sulfuric acid, copper sulfate and ammonium sulfate (an aqueous solution)	Surface of poultry carcasses	At levels that achieve a pH range of 1.2 to 3.0 for scalder application; at levels that achieve a pH range of 1.0 to 3.0 for dip and spray application; and at levels that achieve a pH range of 4.0 to 7.0 for dip application where chlorine is also used	New approved APAs except sulfuric acid
Bacteriophage mixture (*Salmonella* spp. targeted)	Surface of poultry meat carcasses and parts	At a concentration of 10^8 plaque-forming units (pfu) in an aqueous solution per gram of poultry meat carcass or part	Changes in some specific conditions related to the use of this APA (was with iLONO in 2015)
Citric acid	Surface of fully cooked red meat and poultry meat products enclosed in permeable casing	Up to 3% in an aqueous solution, applied by spray, prior to removal of the casing	Changes in some specific conditions related to the use of this APA
Ozone	Surface of poultry meat carcasses, parts, trim and organs	Up to 10 ppm in an aqueous solution	Changes in some specific conditions related to the use of this APA
Ozone (gaseous)	Surface of poultry meat carcasses during air-dry chilling	Up to 10 ppm	New approved APA
	Surface of poultry meat parts and deboned poultry meat	Up to 20 ppm	
Sulfuric acid and sodium sulfate (equivalent to sodium bisulphate)	Surface of red meat or poultry meat carcasses, parts, trim and organs	In an aqueous solution; levels to achieve a target pH range of 1.0 to 2.2 when used on the red meat or poultry meat surface	New approved APA except sulfuric acid

HC, Health Canada.

debate when used to describe microbial resistance to APA, as well as other biocides (antiseptics, disinfectants, and preservatives) (Russell 2003a; Wales and Davies 2015). Antibiotic clinical resistance is observed when phenotypic testing of a microorganism/antibiotic combination gives a result greater than the clinical breakpoint (Humphries, Abbott, and Hindler 2019). However, microbial resistance to antimicrobials is defined by the presence of an acquired or a mutational resistance mechanisms to the antimicrobial in question in comparison with the susceptible "wild-type" strain (Wales and Davies 2015). On the other hand, APA have multiple cell targets, and neither the defined resistance mechanisms nor the breakpoints are currently available for these compounds. Therefore, it has been proposed to describe "resistance" to APA by using a different terminology such as "reduced susceptibility," "insusceptibility," "tolerance," and "tolerant" (Bloomfield 2002; Russell 2003a; Wales and Davies 2015).

Cross-resistance occurs when an antimicrobial or a biocide selects for the expression of genes conferring a resistance phenotype that is common to both the antimicrobial and the biocide products, and that involves the same mechanisms. Cross-resistance can arise when the antimicrobial resistance mechanism used by bacteria is nonspecific in terms of the substrate, such as a multidrug efflux pump which can also give rise to biocides tolerance, or *vice versa* (Yu et al. 2017).

Co-resistance occurs when the genes conferring the resistance phenotype to therapeutic antibiotics and biocides are located together on the same mobile genetic element (plasmids, transposons, integrons) (Chapman 2003; Capita and Alonso-Calleja 2013; Yu et al. 2017). Indeed, it is well known that these bacterial genetic determinants are highly transferable, which suggests that biocide resistance and antibiotic resistance-encoding genes harbored on the same mobile genetic element are readily transferred together to other bacteria (Yu et al. 2017). The end result is the same for both cross-resistance and co-resistance; the microorganism develops resistance against both antibiotic and biocides. Moreover, cross-resistance and co-resistance are both considered as co-selection mechanisms involved in the dissemination of multiple antimicrobial resistant bacteria (Donaghy et al. 2019; Imran, Das, and Naik 2019).

Mechanisms of bacterial tolerance to APA

As APA act through multiple target sites on microbial cells, the emergence of acquired reduced susceptibility or insusceptibility to biocides is unlikely to be caused by the modification of a target site or by the bypass of a metabolic process (EFSA 2008). However, there is limited understanding on the development of bacterial tolerance to APA (Table 5). Some of the modifications that can occur in a tolerant bacterial cell following exposure to APA include the up-regulation of genes involved in the heat shock response, redox reactions, cell replication and universal stress response (Pleitner et al. 2014), as well as in an up-regulation of the efflux pump activity (able to pump out a wide range of compounds) or on the structural alterations of the bacterial cell wall (reduction in porins and changes on the structure of lipopolysaccharides [LPS] and other lipids) (Alonso-Hernando, Capita et al. 2009b; SCENIHR 2009; Condell et al. 2012).

Overexpression of efflux pumps

Studies and knowledge on the role of efflux pumps in the bacterial tolerance to APA is limited compared to their well-known role in antibiotic resistant bacteria, especially in those that are multidrug resistant (MDR). In *Salmonella*, at least nine drug efflux gene systems were identified of which three (AcrAB, AcrEF and MdsABC) are known to transport, out of the cell, various biocides used in the poultry processing industry (Møretrø et al. 2012). Similar efflux pumps in *E. coli* include AcrAB-TolC, AcrEF-TolC, and EmrE were reported (Levy 2002; Fernandez Marquez et al. 2017). For *Enterobacteriaceae*, it has been reported that increasing the expression of the AcrAB-TolC efflux system is the major

Table 5. Studies conducted to verify bacterial tolerance to some APA used in poultry and cross-resistance to therapeutic antimicrobials.

APA	Targeted Microorganisms	Reduced susceptibility to the tested APA	Reduced susceptibility to therapeutic antimicrobials	Proposed mechanism of APA's tolerance	References
HOCl	*Salmonella*	+ *Salmonella* grew in the presence of 28 mg/L of HOCl	Not evaluated	Catalase production, decreased activity of membrane-bound dehydrogenases, and decreased DNA damage	Mokgatla, Gouws, and Brözel (2002)
Hydrogen peroxide	*Salmonella*, *E. coli*, *Enterococcus faecalis*, *Enterococcus faecium.*	No	Not evaluated	NA	Aarestrup and Hasman (2004)
Sulfuric acid and sodium sulfate	*Campylobacter*, *Salmonella*, microbial communities	Not evaluated	Not evaluated	NA	Ae Kim et al. (2017)
SHY	*E. coli* ATCC 12806 (EIEC)	+ After exposure to increasing sub-inhibitory concentrations of SHY	Not evaluated	Efflux pumps and changes in cell surface hydrophobicity	Alonso-Calleja et al. (2015)
SHY and BAC	*Campylobacter jejuni*	No	No link between resistance to disinfectants and antibiotics	NA	Avrain et al. (2003)
SHY	*E. coli*	+ After exposure to increasing sub-inhibitory concentrations of SHY	Aminoglycosides, cephalosporins, and quinolones	Modifications of *E. coli* outer membrane	Capita et al. (2014)
TSP, ASC, CA, or PA	*Listeria monocytogenes* or *Salmonella enterica*	+ (ASC and PA) after exposure to increasing sub-inhibitory concentrations of these APA	Not evaluated	Changes in membrane fluidity of isolates after exposure to acid decontaminants (CA and PAs)	Alonso-Hernando, Alonso-Calleja, and Capita (2010)
BAC, CHA, and other disinfectant components	*Salmonella enterica*	+ (BAC)	Gentamicin, Kanamycin, Sulfamethoxazole, Streptomycin, and Tetracycline (no link between resistance to biocides and these antimicrobials)	NA	Beier et al. (2011)
BAC	*E. coli*	+ After exposure to increasing sub-inhibitory concentrations of BAC	No link between resistance to BAC and ciprofloxacin	NA	Maertens et al. (2019)
ClO_2	*Campylobacter*, *E. coli*, and *Salmonella*	Not evaluated	No difference on the antimicrobial resistance profile between isolates covered from ClO_2-treated or control carcasses	NA	Berrang et al. (2011)
BAC, TSP, and SHY	Methicillin-resistant *Staphylococcus aureus* (MRSA 48a)	+ (SHY) after exposure to increasing sub-inhibitory concentrations of SHY	Not evaluated	An increase in values for cell surface hydrophobicity, as well as morphological and ultrastructural changes and an enhancement of biofilm formation	Buzón-Durán et al. (2017)
CPC, ACH, and PA	*Salmonella* Heidelberg	Not evaluated	Several antimicrobials resistance genes were upregulated, especially after ACH exposure	NA	Cadena et al. (2019)
ASC, TSP, and CA	*Salmonella enterica*	+ (ASC)	Positive relationship was reported between ASC and the number of antibiotics to which strains were resistant	NA	Capita (2007)
TSP, ASC, ascorbic acid, or CA	*E. coli*	Not evaluated	Ampicillin-sulbactam, amoxicillin-clavulanic acid, cephotaxime, trimethoprim-sulphamethoxazole, tetracycline, ciprofloxacin, nitrofurantoin	NA	Capita et al. (2013)
BAC, TSP, and SHY	*Salmonella* Typhimurium	+ (BAC and SHY) After exposure to increasing sub-inhibitory concentrations of BAC or SHY	Adaptation to SHY significantly increased the ability of strains to form biofilms	NA	Capita et al. (2017)
TSP, SNI, and SHY	*E. coli* (ATCC 12806)	+ (SNI and SHY) After exposure to sub-lethal concentrations of SHY or SNI	Previous adaptation to SNI or SHY enhanced the formation of biofilms	Increase in cell surface hydrophobicity. Changes in the surfaces of adapted cells, which were more undulating and rougher than those of parent cells	Capita et al. (2014)
Triclosan, CHX, hydrogen peroxide, and BAC	*Salmonella enterica*	+ After exposure to sub-lethal concentrations	amikacin, ampicillin, cephalosporins, cefoxitin, chloramphenicol, ciprofloxacin, kanamycin, nalidixic acid, piperacillin, and tetracycline	Overexpress of efflux pumps	Condell et al. (2012)
BAC, CT, HDP, TC, hexachlorophene, and P3-oxonia	*Salmonella* spp. or *S. enterica*	+ Significant positive correlations between CT and BAC regarding bacterial tolerance	Most isolates were resistant to ampicillin. BC, CT, and HDP showed moderate or strong positive correlations with cefotaxime, ceftazidime, ciprofloxacin and netilmicin	95.2% of tolerant isolates were positive for *acrB* of the AcrB/TolC efflux pump system	Fernandez Marquez et al. (2017)
TC, BAC, CHA, CPC, and TSP	*Campylobacter coli*, *Campylobacter jejuni*	+ TC and BAC	No correlation between biocide and antibiotic resistance	NA	Mavri, Kurincic, and Mozina (2012)
BAC and glutaraldehyde	*E. coli*, *Salmonella*	+ Both active Components: after exposure to increasing sub-inhibitory concentrations	Ampicillin, tetracycline, ciprofloxacin, chloramphenicol, trimethoprim/sulphamethoxazole, and gentamicin	Generic efflux pumps	Nhung et al. (2015)

(*continued*)

Table 5. Continued

Chlorine	*Salmonella enterica* serovar Heidelberg	+ After exposure to increasing sub-inhibitory concentrations of chlorine	Fluoroquinolones, quinolones, aminoglycosides, penicillin and Tetracycline	Morphological change to the rugose morphotype Forming strong biofilms	Obe et al. (2018)
Chlorine	*Salmonella* Typhimurium	No	Expression of an antibiotic resistance phenotype does not confer cross-protection in *Salmonella* to chlorine	NA	Oscar, Tasmin, and Parveen (2013)
SHY	*Arcobacter butzleri*	+	Not evaluated	NA	Rasmussen et al. (2013)
CTAB, BAC, CPC, and CHX	*E. coli*	+ CTAB, BAC, CHX	Not evaluated	Genes mediate resistance to QACs and a broad spectrum of other cationic compounds (e.g., *ydgE*, *ydgF*, *qacF* and *qacEΔ1* genes)	Sun et al. (2019)
Formic acid and didecyldimethyl-ammoniumchloride	*E. coli*, enterococci	No	Chloramphenicol, florfenicol, piperacillin, sulphamethoxazole + trimethoprim) in *E. coli* Aminoglycoside in enterococci	NA	Wieland et al. (2017)
TSP, ASC, or SHY	Multi-drug resistant *Salmonella enterica* strains	+ After exposure to increasing sub-inhibitory concentrations of these APA	Aminoglycosides and cephalosporins	NA	Molina-González et al. (2014)
TSP, ASC, CA, and PA	*Listeria monocytogenes* or *Salmonella enterica* strains	+ (TSP and ASC) after exposure to increasing sub-inhibitory concentrations of these APA	Not evaluated	NA	Alonso-Hernando, Capita et al. (2009a)
TSP, ASC, CA, ClO_2, and PA	*Listeria monocytogenes* or *Salmonella enterica* strains	+ After exposure to increasing sub-inhibitory concentrations of these APA	Streptomycin, Chloramphenicol, Neomycin, rifampicin, nalidixic acid, erythromycin	Changes in the cell envelope, multi-drug efflux pumps, over-expression of multi-gene components or operons, and the alteration of the target site	Alonso-Hernando, Capita et al. (2009b)

ACH, acidified calcium hypochlorite; APA, antimicrobial processing aids; +, reduced susceptibility to the tested APA; ASC, acidified sodium chlorite; BAC, benzalkonium chloride; CA, citric acid; CHA, chlorhexidine diacetate; CHX, chlorhexidine; ClO2, Chlorine dioxide; CPC, cetylpyridinium chloride; CT, cetrimide; CTAB, cetyltrimethylammonium bromide; EIEC, entero-invasive *Escherichia coli*; HDP, hexadecylpyridinium chloride; HOCl, hydrochlorous acid; NA, not available; PA, peroxyacetic acid; SHY, sodium hypochlorite; SNI, sodium nitrite; TC, triclosan; TSP, trisodium phosphate.

mechanism involved in reducing bacterial susceptibility to antibiotics and biocides (Slipski, Zhanel, and Bay 2018). The over-expression of these efflux pumps may be the consequence of mutations in their regulatory genes, as well as the effect of various stressors, such as low pH, osmotic changes and chemical compounds (Møretrø et al. 2012). The acquisition of mobile genetic elements carrying disinfectant resistance genes such as *qacEΔ1*, *qacF*, *qacE*, *qacG* and *sugE(p)* can confer efflux-mediated resistance to quaternary ammonium compounds (QACs) in Gram-negative bacteria (Long et al. 2016). In fact, Sun et al. reported that *E. coli* isolates, from retail chicken meat, carrying *qacF* gene have a higher cetyltrimethylammonium bromide (CTAB) resistance, while isolates carrying *qacEΔ1* showed higher resistance to benzalkonium chloride (BAC) (Sun et al. 2019). Moreover, the expression of the nonspecific efflux pump encoding gene *lde* by *L. monocytogenes* strains isolated from pork processing plants was influenced by the quality of the cleaning and disinfection procedures and by the concentration of biocides used (Conficoni et al. 2016). Similarly, in *Salmonella enterica* serovar Typhimurium, the expression and cross-regulation of the transcription factors MarA and SoxS that act as homologous regulators in the bacterial adaptive response was increased after exposure to SHY (NaOCl) (Collao et al. 2012). These regulators belong to the AraC family of proteins and respond to many stimuli, including pH variations, antibiotics, oxidative stressors and biocides (Duval and Lister 2013). On the other hand, it was reported that the adaptation of *E. coli* ATCC 12806 strain to APA such as SHY was accompanied by a reduction in its growth rate, even in the absence of this compound in the culture medium, suggesting that such adaptation imposes a fitness cost on the bacterium (Alonso-Calleja et al. 2015). Therefore, the mechanism of adaptation, mostly mediated by the expression of efflux pumps effective against a broad range of substrates, appears to be demanding in terms of bacterial energy resources utilization and seems to reduce the competitiveness of biocide-tolerant isolates (Gilbert and McBain 2003; Alonso-Calleja et al. 2015; Wales and Davies 2015).

Interestingly, increasing evidence from many recent studies suggests that bacterial efflux pumps could also play an important role in biofilm formation, which represents an important mechanism of bacterial resistance to biocides in the food industry. Efflux pumps, including AcrAB-TolC in *E. coli*, MexAB-OprM in *Pseudomonas aeruginosa*, AdeFGH in *Acinetobacter baumannii* and AcrD in *Salmonella enterica*, seem to play a crucial role in biofilm formation (Alav, Sutton, and Rahman 2018).

Biofilms formation

Biofilms are surface-associated communities of bacteria that are embedded in a hydrated matrix of extracellular polymeric substances and organized in a three-dimensional structure (Dubois-Brissonnet, Trotier, and Briandet 2016; Hathroubi et al. 2018). This complex structure provides protection to the microorganism from altered pH, nutrient shortage, host's immune cells, mechanical and shear forces,

as well as from antibiotic and biocide action (Sharma, Misba, and Khan 2019). It has been reported that the exposure of *Salmonella*, *E. coli*, methicillin-resistant *Staphylococcus aureus* (MRSA) or *L. monocytogenes* to sub-minimum inhibitory concentrations (MICs) of some food-grade biocides enhances biofilm formation (Capita et al. 2014; Buzón-Durán et al. 2017; Capita et al. 2017; Rodriguez-Melcon et al. 2019). Indeed, in a methicillin-resistant *Staphylococcus aureus* strain of food origin (MRSA 48a), the presence of sub-MICs of SHY enhanced the biofilm formation ability in the bacteria that had undergone previous adaptation to this compound (Buzón-Durán et al. 2017). In *Salmonella*, sub-MICs of SHY were not only unable to prevent the formation of biofilm, but also enhanced the biofilm-forming ability of this microorganism (Capita et al. 2017). These findings suggest that the use of APA at inappropriate doses in the food industry may increase the ability of bacteria to produce biofilms, contributing to increase the risk of contamination of foodstuffs. The enhancement of biofilm formation in the presence of low doses of biocides such as SHY could be related to alterations in the cellular morphology and ultrastructural composition (e.g., change in cell surface hydrophobicity), to the increased expression of specific genes (e.g., genes involved in quorum sensing), or to an increased production of extracellular polymeric substances (EPS) in the biofilm matrix (Capita et al. 2014; Rodriguez-Melcon et al. 2019). Cells tolerant to SHY were associated with several bacterial surface changes such as a more undulating and rougher surface than the one observed for the parent cells. Those changes were also associated with the formation of blebs on the outer membrane of the bacterial cell envelope (Capita et al. 2014).

Changes in the bacterial outer membrane

For some pathogens, alterations to the bacterial membrane fluidity were associated with microorganism adaptation to some poultry chemical decontaminants, as well as to environmental stressors (e.g., variations in temperature, pressure, pH, etc.) (Alonso-Hernando, Alonso-Calleja, and Capita 2010). In *L. monocytogenes* and *Salmonella enterica*, exposure to sub-inhibitory concentrations of acid decontaminants (CA or peroxy acids) has been associated with higher anisotropy values (lower membrane fluidity) when compared with unexposed cells of the same species, also indicating an increase in cell membrane rigidity of the exposed bacteria (Alonso-Hernando, Alonso-Calleja, and Capita 2010). However, no change in the membrane fluidity of these strains was observed following their exposure to TSP or to ASC decontaminants. This finding may be related to the mechanisms of action of acid decontaminants, limiting the proton flux through the exposed bacterial cell wall. Recently, Cadena et al. reported that the exposure of a *Salmonella* Heidelberg strain, isolated from a commercial broiler processing plant, to various carcass decontaminants such as CPC, acidified calcium hypochlorite, and PA, was correlated with the up-regulation of 90 genes that were either related to virulence, pathogenicity, or resistance (Cadena et al. 2019). When exposing a *Salmonella* Heidelberg strain to increasing sub-lethal concentrations of chlorine, Obe et al. reported that the tolerance of the pathogen to this APA remained stable, even in the absence of chlorine exposure (Obe et al. 2018). More than that, this chlorine-adapted *Salmonella* Heidelberg strain grew in the presence of high chlorine concentrations, even above the concentration approved by the USDA for sanitation purposes (200 ppm). In this study, *Salmonella* Heidelberg changed its morphology from the smooth to the rugose variant after 4 days of exposure to chlorine and showed the ability to form stronger biofilms than those the strain was able to form before exposition to this APA. Additionally, *Salmonella* isolates surviving a chlorine treatment were characterized by significant longer division times (Chaves et al. 2019). On the other hand, Capita et al. reported that the *E. coli* ATCC 12806 strain, an entero-invasive *E. coli* (EIEC) strain, exhibited an acquired tolerance to SHY when it was exposed to increasing sub-inhibitory concentrations of this APA (Capita et al. 2014). Furthermore, the reduced sensitivity to SHY persisted up to seven generations in SHY-free medium, indicating that adaptive resistance of *E. coli* ATCC 12806 strain to SHY was stable (Alonso-Calleja et al. 2015), and these findings corroborated with the results of Capita et al. who reported that an adaptive *Salmonella* isolate, tolerant to BAC and SHY, was stable after 10 repeated sub-culturing in nonselective broth without these biocides (Capita et al. 2017).

Thereby, bacterial exposition to sub-inhibitory concentrations of APA could facilitate bacterial morphology changes, biofilm formation and the up-regulation of various genes involved in many cellular processes which all lead to the selection of more resistant bacterial variants.

Bacterial acid stress adaptation

Bacterial acid stress adaptation is a food industry concern as it allows bacterial cells to protect themselves against environmental stressors encountered during processing such as high temperatures or various chemicals, which negatively impact the quality of the decontamination procedures of chicken carcasses in processing establishments. With regards to acids, it has been reported that prior exposure to acidic poultry decontaminants (CA or peroxy acids) can increase the survival of *L. monocytogenes* to a severe acid stress (Alonso-Hernando, Alonso-Callej and Capita 2009). This bacterial acid tolerance can be explained by the glutamate decarboxylase (GAD) acid resistance system activity or by the buffering capacity of the cytoplasm, of proton pumps and of general stress proteins such as the proteins encoded by the GroESL operon that are overexpressed during an acid stress (Azcarate-Peril et al. 2004; Alonso-Hernando, Alonso-Calleja and Capita 2009). A study showed that the survival of *L. monocytogenes* isolates to a sub-lethal chlorine dioxide exposure was associated with the expression of several general stress response regulatory networks such as the alternative sigma factor (σ^B) and the transcriptional regulator (CtsR) (Pleitner et al. 2014). Furthermore, it has been reported that TSP adapted *E. coli* O157:H7 strain can also adapt to high acidity conditions by increasing the expression

of the alternative sigma factor *RpoS* and this molecular expression leads to the expression of a general stress resistance phenotype by the bacteria (Yuk and Marshall 2006).

Cross-resistance and co-resistance to therapeutic antibiotics following bacterial exposure to APA

Contextualization

It was suggested that cross-resistance to clinically used antibiotics could occur, in some cases, following bacterial exposure and adaptation to a biocide. Generally, reduced susceptibility emerges after an improper use (concentration, contact time, suboptimal temperature or pH, mode of application (spraying or dipping), unintended dilution, inadequate quality of water as diluent, etc.), or storage of biocides, resulting in a decrease in the effective biocide concentration (Sheridan et al. 2012). This co-selection mechanism can be explained as follows: (1) when the biocide and the antibiotic act on the same cellular target or (e.g., by enhancing DNA repair by activating the SOS response in bacteria), (2) when the biocide and the antibiotic use the same transport mechanism, (3) when the biocide and the antibiotic can be accommodated by the same resistance mechanism, and (4) when an antibiotic also selects for a gene encoding resistance to a biocide through the recruitment of a mobile genetic element (Capita and Alonso-Calleja 2013; Gadea et al. 2016).

Many reports showed that sub-inhibitory concentrations of quaternary ammonium compound (QAC) can select for bacteria resistant to medically-important antibiotics such as ampicillin, cefotaxime, ceftazidime, and ciprofloxacin (Soumet et al. 2016; Nasr et al. 2018). However, limited data are available on the co-resistance between APA, other than QACs, used in poultry processing operations and therapeutic antimicrobials (Table 5).

Salmonella spp

A MDR *Salmonella enterica* strain showed a significant reduction in its susceptibility to many antibiotics, mainly of the aminoglycosides family, after having been exposed to increasing sub-inhibitory concentrations of SHY (Molina-González et al. 2014). Likewise, several *L. monocytogenes* and *Salmonella enterica* strains that were exposed to increasing sub-inhibitory concentrations of four poultry decontaminants (TSP, ASC, CA, and PA), showed a reduced susceptibility, as well as a cross-adaptation to these chemical compounds (Alonso-Hernando, Capita et al. 2009a). It is worth mentioning in this study that the final MICs of TSP, CA, and PA for the adapted bacterial strains were still much lower than the concentrations used in practical applications in poultry processing establishments (Alonso-Hernando, Capita et al. 2009a). However, the MIC of ASC for these adapted strains was higher than the lowest authorized concentrations (0.05 and 0.15 mg/mL) in poultry processing waters (Alonso-Hernando, Capita et al. 2009a).

Increases in resistance to various antibiotics (e.g., streptomycin; neomycin; rifampicin, erythromycin and nalidixic acid) were observed in *Salmonella enterica* strains after repeated exposures to increasing sub-inhibitory concentrations of ASC (Alonso-Hernando, Capita et al. 2009a). It is noteworthy that the antibiotic resistance patterns of these strains were compared before and after exposure to this poultry decontaminant. The decrease in *Salmonella enterica* strain susceptibility (observed for both ASC and those antibiotics despite their different mechanisms of action) suggest a nonspecific mechanism for resistance (e.g., increased impermeability due to an adaptation of the outer membrane) (Alonso-Hernando, Capita et al. 2009b). A chlorine-adapted *Salmonella* Heidelberg strain showed a slight reduction in its sensitivity to fluoroquinolones, aminoglycosides, penicillin, and tetracycline (Obe et al. 2018). Furthermore, Fernández Márquez et al. reported a strong positive correlation between antibiotic resistance and biocide tolerance in *Salmonella* strains isolated from eggshells (Fernandez Marquez et al. 2017). This observation was explained by the expression of the *acrB* gene encoding the AcrB/TolC efflux pump system in all of the isolates tested. These *Salmonella* strains shown to be resistant to antibiotics and tolerant to biocides, later showed an increase in their tolerance to essential oils such as carvacrol and thymol (Marquez et al. 2018).

However, other studies could not establish a direct relationship between bacterial exposure to biocides and increased resistance to antibiotics (Lear et al. 2002; Gradel et al. 2005; Mavri, Kurincic, and Mozina 2012; Humayoun et al. 2018). In addition, Condell et al. reported no increase in the tolerance to biocides of any *Salmonella* strains tested after several rounds of in vitro exposure to increasing concentrations of food-grade biocides, as used in the food industry (e.g., triclosan, chlorhexidine, hydrogen peroxide, and BAC) (Condell et al. 2012). However, when these *Salmonella* isolates were exposed to sub-inhibitory concentrations of the same biocides, bacterial isolates demonstrated an increased tolerance to each active biocide compound, as well as an increased tolerance to multiple therapeutic antimicrobials (Condell et al. 2012). On the other hand, Oscar et al. reported that *Salmonella* Typhimurium strains resistant to tetracycline, ampicillin, amoxicillin, cefoxitin, ceftiofur and sulfisoxazole were not more tolerant to chlorine (30 ppm, pH 6) in chilled water at 4 °C than susceptible strains. It was therefore concluded that the expression of an antibiotic resistance phenotype in *Salmonella* Typhimurium is not always associated with cross-protection against chlorine inactivation in chilling water. This study was conducted in vitro conditions using simulated process water containing SHY, acetic acid, peptone (e.g., organic material) and sterilized water (Oscar, Tasmin, and Parveen 2013).

The variable results observed in the scientific literature regarding this topic highlight the need to standardize the methodologies used to measure and monitor both biocide resistance and cross-adaptation between APA and clinically used antimicrobials (FAO 2018).

Listeria monocytogenes

Several studies have shown a possible link between the adaptation of *L. monocytogenes* to environmental stresses,

including acids, occurring in the food chain and antibiotic resistance (Komora et al. 2017). In fact, it has been shown that *L. monocytogenes* strains resistant to ciprofloxacin, nitrofurantoin and erythromycin were significantly less susceptible to acid (lactic acid 1% vol/vol) and osmotic stresses (37% wt/vol NaCl) when compared to antibiotic-susceptible strains (Komora et al. 2017). This observation was shown to be associated with the capacity of the *mdrL* bacterial efflux pumps to extrude different compounds out of the bacterial cell wall. In addition, *L. monocytogenes* strains resistant to one or more antibiotics exhibited significantly higher survival rates after a High Hydrostatic Pressure (HHP) treatment at 400 MPa (Bruschi et al. 2017). It has also been reported that tolerant bacteria to QACs exhibited other phenotypic alterations such as a thermo-tolerance and a resistance to gastrointestinal tract (GIT) stress factors (Gadea et al. 2017). Moreover, a co-selection has been described between ciprofloxacin resistance in *L. monocytogenes* strains and increased tolerance to BAC (Kovacevic et al. 2013). More recently, a new efflux pump, *emrE*, conferring tolerance to BAC has been described in *L. monocytogenes* isolates involved in the deadliest listeriosis outbreak in Canada in 2008 (Kovacevic et al. 2016).

Pseudomonas aeruginosa and Escherichia coli

It was demonstrated that the exposure of *Pseudomonas aeruginosa* isolates to increasing concentrations of BAC selected for mutations in the *pmrB* (polymyxin resistance) gene, as well as for some physiological adaptations contributed to a higher tolerance to polymyxin B and to other antibiotics (e.g., ciprofloxacin, chloramphenicol, and rifampin) (Kim et al. 2018). Moreover, an overexpression (6- to 40-fold) of the *mexCD-oprJ* multidrug efflux pump-encoding genes under BAC-supplemented conditions was reported in these *P. aeruginosa* isolates (Kim et al. 2018). The overnight exposure of antibiotic-susceptible *Pseudomonas* isolates to sub-inhibitory concentrations of SHY resulted in a statistically significant increase in colistin, ceftazidime, amikacin, meropenem, gentamicin, piperacillin-tazobactam, and ciprofloxacin MICs for these isolates, probably by selecting genetic determinants for resistance to non-antibiotic agents that are linked to antibiotic resistance genes (Nasr et al. 2018).

A co-existence of extended-spectrum β-lactamases (ESBLs)-encoding genes and/or plasmid-mediated quinolone resistance genes with QACs genes was reported in *E. coli* strains isolated from ready-to-eat (RTE) meat products (Li et al. 2017). Moreover, results from tolerance studies showed that the adaptation of the ATCC 12806 *E. coli* strain to sodium nitrite (SNI) increased its tolerance to SHY and *vice versa* (Alonso-Calleja et al. 2015). Previous adaptation of this strain to SHY was associated with an increasing capacity of biofilm formation, as well as with a significant reduction in its susceptibility to some previously effective antibiotics such as spectinomycin, nalidixic acid and ampicillin-sulbactam (Capita et al. 2014).

The potential co-resistance between therapeutic antibiotics and APA highlights the need to apply an overall approach providing better guidance for the use of both therapeutic antibiotics at the farm level and APA in meat processing establishments in order to avoid the development of bacterial resistance due to co-selection (Rhouma et al. 2016; Rhouma and Letellier 2017). In this context, it was pointed out that the use of APAs should be as part of an overall hazard analysis critical control point (HACCP) plan to enhance the microbiological safety and extended the shelf life of poultry meat products (González-Fandos and Herrera 2013).

Current data gaps and future perspectives

A number of scientific reports has been published on the safety and toxicological features of some APA. However, data on the occurrence of bacterial acquired reduced susceptibility to these chemical compounds, as well as on the cross-resistance with therapeutic antibiotics are scarce (Alonso-Hernando, Alonso-Calleja and Capita 2009).

APA: assessment of the antibacterial effects and the bacterial tolerance

The purpose of APA in practical conditions is to kill bacteria, but to the best of our knowledge there is no study that has evaluated the minimum bactericidal concentration (MBC) which demonstrates the lowest level of antimicrobial agent that results in microbial death. Therefore, the establishment of MICs often have limited relevance as a measure of the effect of disinfectants in poultry processing operations, since it only evaluates the bacteriostatic effect and not the bactericidal action of these products (Møretrø et al. 2012). Furthermore, the MICs tests conducted to assess bacterial susceptibility to biocides were carried out using Mueller Hinton broth, which contains organic matter and might cause inactivation of the tested chemical compound. In addition, the MIC could be also influenced by compound evaporation as observed for ASC (Alonso-Hernando, Capita et al. 2009a). Of note, direct comparisons of the antibacterial activity, as well as the tolerance assessment of APA between studies are difficult to make because of the variation between experimental conditions and of the absence of breakpoint MICs for APA tolerance. It may become imperative to establish standardized simple microbiological tests to monitor the bacterial susceptibility to commonly used APA in poultry processing establishments. Furthermore, for organic acids, it would be relevant to document if their ineffectiveness is due to a loss of bacterial susceptibility as a result of an increase of the environmental pH, or to bacterial resistance (Lues and Theron 2012).

It is also important to bear in mind that most studies conducted in vitro with the aim of assessing bacterial tolerance to APA used only one serotype of a bacterial species, without evaluating the impact of the presence of organic matter on the antibacterial activity of the tested APA. However, it was reported that both the serotype and the levels of contamination by organic matter significantly influence bacterial survival and these variables should be

included in the assessment of both APA effectiveness and bacterial tolerance (Paul, Sullivan, and Shah 2017).

Moreover, most studies examining bacterial tolerance to APA were conducted using a single chemical compound. Future studies should involve different combinations of chemicals in order to determine the impact of such combinations on bacterial tolerance, as well as to identify the most efficient and cost-effective treatments for poultry carcasses.

Another concern raised is with regards to the stability of the adaptive ability of bacteria to APA in the absence of biocide selection pressure (e.g., in biocide-free medium). Alonso-Calleja et al. reported that the adaptive properties of *E. coli* to TSP were lost after seven days of passage of these bacteria in a TSP-free medium (Alonso-Calleja et al. 2015). However, the same experiment showed that bacteria tolerant to SHY were still present after up to seven generations in the absence of this compound in the culture medium (Alonso-Calleja et al. 2015). Further studies are needed to assess the stability of tolerant bacteria to APA in practical conditions, particularly if the stable adaptation is associated with a bacterial chromosomal mutation.

To the best of our knowledge, only one experimental study showed evidence of fitness costs in an APA (SHY) tolerant *E. coli* strain. In fact, these bacteria can compete with other bacterial strains, and consequently their competitive fitness determines their survival (Alonso-Calleja et al. 2015). This experimental finding should be verified in future studies using other chemical decontaminants and other bacteria or bacterial strains. An association between exposure to sub-lethal concentrations of APA and biofilm formation in bacterial strains previously adapted to these compounds has been reported. However, the exact mechanism or mechanisms responsible for biocide-enhanced biofilm-forming capacity are not well characterized. Thereby, additional studies are needed to elucidate the morphological, biochemical, and molecular changes in bacterial biofilms induced by biocides. Although much information on the control of planktonic bacteria through the use of various APA has been published, data on the control of biofilms in poultry processing establishments are limited. Indeed, there is no consensus on how to measure the sensitivity of biofilm to APA. Therefore, poultry processing establishments considering using new disinfectants or finding new tolerant APA bacterial strains should consider testing both the MIC and the minimum biofilm eliminating concentration in order to ensure the effectiveness of the disinfectant (Chylkova et al. 2017).

Cross-resistance development

There have been various laboratory-based experiments reporting a possible link between the use of sub-inhibitory concentrations of APA, especially with regard to chlorinated compounds, and the development of bacterial antibiotic resistance (Alonso-Hernando, Capita et al. 2009b). The exposure of bacteria to sub-lethal concentrations of APA could occur at multiple steps during the poultry processing process, especially when the dosage of the product is not adjusted to the intended purpose or when the product is applied before the carcasses have been properly cleaned. Indeed, with the selective pressure exerted by some APA used in poultry processing establishments, it seems possible to assume that those compounds could contribute to the expression and dissemination of antibiotic resistance mechanisms (Capita and Alonso-Calleja 2013). This hypothesis should be confirmed through further research to determine if APA and clinical antimicrobials may share target sites in bacteria and have common mechanisms of action.

On the other hand, it should be emphasized here that following bacterial exposure to sub-lethal concentrations of some APA, the levels of bacterial resistance to clinically used antimicrobials, in most laboratory-based experiments studies, were not high enough to indicate that they constitute a public health threat (Alonso-Hernando, Capita et al. 2009b). Therefore, additional studies should be performed to determine if the application of APA directly on poultry carcasses and parts is associated or not with an increase in bacterial resistance to antibiotics and if this resistance has any clinical significance.

Some studies reported that the impact of biocide exposure on reduced susceptibility to antibiotics was dependent on the bacterial strain and the antibiotic tested (Alonso-Hernando, Capita et al. 2009a). Changes in the susceptibility pattern to antibiotics after exposure to biocides could be strain-specific rather than species- or genus-specific (Molina-González et al. 2014). The inter- and intra-species differences in the bacterial susceptibility to poultry APA could influence the survival of strains on decontaminated carcasses. This emphasizes the importance of using the appropriate concentrations of these compounds to inactivate all pathogens of public health concern in commercial conditions (Alonso-Hernando, Capita et al. 2009a).

The scientific literature reports no evidence showing that bacterial adaptation to APA in poultry processing operations is responsible for the residual bacterial contamination found on the processed carcasses. According to a recent report of the Food and Agriculture Organization of the United Nations (FAO), research into the likelihood of emergence of acquired reduced bacterial susceptibility to biocides used in the food industry should be encouraged (FAO 2018).

As the use of biocides by the poultry processing industry could potentially contribute to the global antibiotic resistance problem and as more studies are needed to better define the link between biocide use and antibiotic resistance in bacteria of public health significance, the industry should already consider the development of new intervention strategies to reduce the use of chemical decontaminants. These could include the biocontrol methods tested against bacterial biofilms in slaughterhouses (Gray et al. 2018), hot water, steam decontamination and carcass cabinets spraying slightly acidic electrolyzed water (James et al. 2007; Wang et al. 2018).

Conclusions

Extensive use of APA at sub-lethal concentrations in poultry processing operations may lead to the selection of antibiotic-resistant bacteria and may represent a public health concern. Several studies, derived mostly from laboratory-based experiments, have reported that bacterial exposure to sub-lethal

concentrations of APA was associated with acquired tolerance to APA, as well as to an increase in their resistance to various therapeutic antibiotics. Indeed, repeated exposure of bacteria to sub-inhibitory concentrations of APA in poultry processing operations could occur as a consequence of improper use or inappropriate storage. Active efflux and changes in the bacterial membrane fluidity are the most documented mechanisms responsible for bacterial cross-tolerance to APA and antibiotics. The judicious and rational use of APA in poultry processing operations is crucial to reduce the risk of selecting antimicrobial-resistant bacteria. Studies describing the changes at both the bacterial genomic and proteomic levels contributing to APA tolerance and providing a greater understanding of bacterial cross-resistance between APA and antibiotics are warranted.

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Author contributions

M.R. designed the study, collected and analyzed the data, and drafted the manuscript. P.R.B., M.L.G., and S.B. designed the study and revised the manuscript.

Abbreviations

AMR	antimicrobial resistance
APA	antimicrobial processing aids
ASC	acidified sodium chlorite
CA	citric acid
CFIA	Canadian Food Inspection Agency
EFSA	European Food Safety Authority
EIEC	enteroinvasive *E. coli*
ESBLs	extended-spectrum β-lactamases
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
GAD	glutamate decarboxylase
HACCP	hazard analysis critical control point
HC	Health Canada
HHP	high hydrostatic pressure
LPS	lipopolysaccharides
MRSA	methicillin-resistant *Staphylococcus aureus*
MBC	minimum bactericidal concentration
MBEC	minimum biofilm eliminating concentration
MDR	multidrug resistant
MIC	minimum inhibitory concentration
PA	peroxyacetic acid
QACs	quaternary ammonium compounds
RTE	ready-to-eat
SHY	sodium hypochlorite
SNI	sodium nitrite
TSP	trisodium phosphate
USDA	US Department of Agriculture
WGS	whole-genome sequencing

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