Aquaox LLC
17355, Hamlin Boulevard
Loxahatchee, FL 33470, USA
+1.800.790.7520
Info@aquaox.net

TO WHOM IT MAY CONCERN

Loxahatchee, January 6, 2023

I. Background

This is in response to your request for an opinion on the regulatory status of your intended use of up to 60 ppm hypochlorous acid produced in situ as an antimicrobial in food processing. The hypochlorous acid is generated *either* on-site using an Aquaox device using only water sodium chloride and electricity *or* supplied as Aquaox 275/525/1650 ppm hypochlorous acid bottled solution. In case of onsite generation, the system is remotely monitored by Aquaox, which permits the calibration of the system to the desired concentration of hypochlorous acid production, but at no greater than 60 ppm hypochlorous acid. In case of bottles solution, a dilution with municipal water will reduce hypochlorous acid content to less than 60ppm. The food contact substance is intended for use as an antimicrobial solution to reduce or eliminate pathogenic and non-pathogenic microorganisms that may be present on the food or in the process water or ice used during production. Use of the FCS helps prevent cross-contamination, ultimately providing for safer foods for consumers. The hypochlorous acid is intended to treat process water or ice which may contact a variety of foods including whole or cut meat and poultry, including carcasses parts trim and organs, processed and preformed meat and poultry products, whole or cut fish, fruits and vegetables and for the washing of shell eggs. Our opinion is limited to the applicability of provisions of the Federal Food, Drug and Cosmetic Act (the Act) and FDA's implementing regulations and we are not opining on other statutes or regulations.

II. Legal, Regulatory, and Scientific Background

To place our conclusions regarding the status of hypochlorous acid under FDA's program into the proper context, and so that this letter will present a complete analysis of this matter, we first describe the manner in which food processing substances like hypochlorous acid are regulated in the United States.

A. Definition of a Food Additive

Substances used in food processing or food-contact applications, are regulated under the Act

as "food additives" if they are reasonably expected to become components of food under their intended conditions of use and are not otherwise exempt from regulation. Section 201(s) of the Act defines a food additive as any substance the intended use of which results, or is reasonably expected to result, in its becoming a component of food, unless the substance is generally recognized as safe (GRAS) or is used in accordance with a sanction or approval issued by either the FDA or the United States Department of Agriculture (USDA) prior to the enactment of the Food Additives Amendment of 1958. Under Section 409 of the Act, a substance that falls within the statutory definition of a food additive must be the subject of an applicable food additive regulation or an effective food contact notification (FCN).[1] In the past, FDA has also issued exemptions from the need for a food additive regulation on a case-by-case basis under the "Threshold of Regulation" rule.[2] Food that contains an "unsafe" food additive (*i.e.*, one that is not being used in accordance with an applicable regulation, notification, or exemption) is deemed adulterated, *per se*, under Section 402(a)(2)(C) of the Act.

Consequently, a food processing chemical, or component thereof, that is reasonably expected to become a component of food must be one of the following: (a) the subject of an applicable food additive regulation, a Threshold of Regulation exemption letter, or an effective FCN, (b) the subject of a prior sanction or approval, or (c) deemed generally recognized as safe (GRAS) for the intended application. If a substance is not reasonably expected to become a component of food under the intended conditions of use, it is not a food additive as defined under Section 201(s), and may be used without any prior action by, or consultation with, FDA.

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[1] The Food and Drug Administration Modernization Act of 1997 amended the Federal Food, Drug, and Cosmetic Act to provide for the submission of notifications for food-contact substances in lieu of food additive petitions. Under this program, a manufacturer or supplier of a food-contact material may submit a notification to FDA regarding the identity and use of the new food-contact substance, along with information supporting the conclusion that the substance is safe for the intended use. If FDA does not object in writing to the notification within 120 days of receipt, the submitter may market the product. Unlike food additive regulations, the notifications may be relied upon only by the submitter and its customers. The final rule implementing FDA's food-contact notification program was published in the Federal Register on May 21, 2002; *see* 67 Fed. Reg. 35724.

[2] *See* 21 C.F.R. § 170.39. The "Threshold of Regulation" rule (TOR)was issued prior to the creation of the food- contact notification system, when the only process for obtaining FDA authorization of a food-contact material was a food additive petition leading to an indirect food additive regulation. The TOR system provides for expedited review of food-contact substances which involve a dietary concentration not exceeding 0.5 part per billion, corresponding to a dietary exposure of not more than 1.5 micrograms/person/day. In the case of substances already authorized for direct addition to food, the threshold is set at a dietary exposure not exceeding 1% of the acceptable daily intake. The Threshold of Regulation clearance process is limited to substances which have not been shown to be carcinogens in humans or animals and for which there is not reason to suspect carcinogenicity based on chemical structure. There also is a limit on the allowed potency of carcinogenic impurities in the substance. Although the TOR process remains in effect and FDA exemption letters issued according to the process remain valid, along with FDA's indirect additive regulations, both the Threshold of Regulation and food additive petition procedures have been largely replaced by FCN submissions.

B. "Not Reasonably Expected to Migrate" Exemption

Under the Act, a company is entitled to determine independently whether the use of a substance for a particular food-contact application poses a food additive situation. As the food additive definition implies, a suitable regulatory status for a substance may be established based upon a determination that the substance is not reasonably expected to become a component of food, the so-called "no migration" exemption. FDA has never provided definitive criteria for determining when a substance may reasonably be expected to become a component of food.
Nevertheless, there are sources of guidance (such as the *Monsanto v. Kennedy* decision[3] and the "Ramsey Proposal"[4]) on which industry has come to rely over the years.

On the basis of the statutory language, the *Monsanto* decision and the principles of the "Ramsey Proposal," it is our opinion that, if properly conducted extraction studies simulating the intended conditions of use do not yield detectable migration of a tested substance at an appropriate analytical sensitivity, one may conclude that the substance is not reasonably expected to become a component of food and, thus, is not a food additive within the meaning of Section 201(s) of the Act. Alternatively, if "worst case" calculations, assuming 100% migration of a substance to food, or other appropriate calculations such as those employing widely accepted diffusion principles, demonstrate that the substance will not be detected at the appropriate sensitivity level, the same "no migration, no food additive" conclusion can be reached.

C. GRAS Exemption

If migration is detected, it nevertheless is possible to determine that the substance is not a food additive because the level of migration is minimal, and the substance can be considered GRAS for its intended use.

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[3] *Monsanto v. Kennedy*, 613 F.2d 947 (D.C. Cir. 1979). In this case, FDA argued that any contact of a substance with food may be expected to result in some transfer of the substance to the food, leading to the conclusion that FDA could require a food additive clearance for every food-contact material, even without evidence that it actually migrates to food. In rejecting FDA's argument, the United States Court of Appeals stated:

> Congress did not intend that the component requirement of "food additive" would be satisfied by . . . a mere finding of any contact whatever with food..... For the component element of the definition to be satisfied, Congress must have intended the Commissioner to determine with a fair degree of confidence that a substance migrates into food in more than insignificant amounts. *Id.* at 955.

[4] The "Ramsey Proposal," circulated by FDA in 1969, would have permitted the use, without the prior promulgation of an applicable food additive regulation, of substances that migrate to food in quantities no greater than 50 parts per billion (ppb). Named after its author, Dr. Lessel Ramsey, then Assistant Director of Regulatory Programs at FDA's Bureau of Science, this regulation would have applied to all substances except those known to pose some special toxicological concerns, *e.g.*, a heavy metal, a known carcinogen, or a substance that produces toxic reactions at levels of 40 parts per million (ppm) or less in the diet of man or animals. Although never formally adopted by FDA, the standards in the proposal were deemed scientifically acceptable at the time.

As indicated above, substances properly deemed GRAS are excluded from the definition of "food additive," and thus are exempt from the premarket clearance requirement that applies to food additives. Section 201(s) of the Act defines a GRAS substance as one that is:

> "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use."

FDA has published regulations describing eligibility requirements for GRAS substances at 21 C.F.R. § 170.30. General recognition of safety requires a "common knowledge" about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food. *See* 21 C.F.R. § 170.30(b). For substances not widely used in food prior to 1958, general recognition of safety based on "scientific procedures" requires the same quantity and quality of scientific evidence as required to obtain approval of a food additive regulation for the ingredient. General recognition of safety is ordinarily based on published studies, which may be corroborated by unpublished studies and other data and information. *See* 21 C.F.R. § 170.30(b).

The presence of substances at extremely low levels in the diet may be considered generally recognized as safe in specific instances. Supporting this conclusion, a panel of renowned independent experts convened by the Canadian Center for Toxicology (CCT) concluded that substances present in the diet at concentrations of 1.0 ppb or below can be considered safe even if no toxicity testing has been performed on the specific chemical, provided that there is no reason to believe that the substance demonstrates unusual toxicological properties.[5] For substances with some toxicity data that indicate a lack of genotoxic potential, a higher level may be determined safe based upon classical toxicological principles as outlined in various regulatory guidelines. Based on the principles discussed in the Canadian report, it is reasonable for a company to take the position that low levels of nontoxic substances may be considered GRAS in certain applications.

FDA's "Threshold of Regulation" rule provides additional support for the proposition that substances can be considered safe on the basis of low dietary exposure. See 60 Fed. Reg. 36582 (July 17, 1995). In this rule, the Agency chose 0.5 ppb as the level for the regulatory threshold after conducting an extensive review of the toxicology literature, and concluded that the presence of a substance in the daily diet at or below this level is so negligible as to present no public health concerns.[5] The full report and all of the individual papers written as part of the study were published in the August, 1990 issue of *Regulatory Toxicology and Pharmacology. See* Munro, "Safety Assessment Procedures for Indirect Food Additives: An Overview," 12 *Regulatory Toxicology and Pharmacology* 2 (August, 1990).

While the Threshold of Regulation rule is intended as a mechanism for FDA to consider the suitability of food additives present in the diet at *de minimis* levels, it also provides guidance for the private sector's evaluation of food-contact materials, since this policy represents at least a tacit acknowledgment that the presence of a substance in the diet at these low levels is GRAS.

More recently, I with two other scientists at FDA's Center for Food Safety and Applied Nutrition published a paper providing a scientific basis for an expanded threshold scheme. *See* M.A. Cheeseman *et al.*, A Tiered Approach to Threshold of Regulation, 37 *Food and Chemical Toxicology* 387 (1999). We examined data on 709 carcinogens listed in the Carcinogenic Potency Database (CPDB) compiled by Gold *et al.*[6] and found that the chemical structure of an untested substance can be a strong indicator of whether it is likely to be a carcinogen.[7] Further, results of short-term toxicity data and genotoxicity tests, *i.e.*, Ames assays and LD_{50} tests, can be strong indicators of carcinogenic potency.

As a result of these findings, we concluded that the dietary threshold could be expanded to as high as 15 ppb for certain substances, depending on the structure of the substance and available toxicity data. Specifically, the authors recommended the following tiered threshold scheme:

1. A dietary threshold of 4-5 ppb for (a) those substances lacking structural alerts related to potent carcinogens or toxins, without the need for an Ames mutagenicity assay (examples of such alerting structures include the chemical classes identified in footnote 9 below); and (b) those substances with structural alerts other than *N*-nitroso and benzidine-like compounds testing negative in the Ames assay.

2. A dietary threshold of 10-15 ppb for those substances testing negative in the Ames test and having an LD_{50}[8] above 1000 mg/kg.

In addition, two groups of internationally recognized expert scientists (Kroes et al. 2000 and Kroes et al. 2004)[9] published papers evaluating the utility of the Threshold of Toxicological Concern (TTC) in the risk assessment of chemical exposures generally.

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[6] *See* L.S. Gold and E. Zeiger (Eds) (1997), *Handbook of Carcinogenic Potency and Genotoxicity Databases*, CRC Press, Boca Raton, FL.

[7] More specifically, we authors found that most carcinogens can be grouped into one of the following seven classes of substances: *N*-nitroso compounds, strained heteronuclear rings, alpha-nitro-furans, polycyclic amines, hydrazines/triazenes/ azides/azoxy compounds, organophosphorous compounds and heavy metal-containing compounds.

[8] The LD_{50} is defined as the dose that induces death in 50% of dosed animals.

[9] Kroes, R., Galli, C., Munro, I., Schilter, B., Tran, L.-A., Walker, R. & Würtzen, G. (2000). Threshold of Toxicological Concern for Chemical Substances Present in the Diet: A Practical Tool for Assessing the Need for Toxicity Testing, Food and Chemical Toxicology 38, Nos. 2-3, 255-312.

A member of the second expert group and the Cheeseman et al. 1999 paper was cited significantly in the Kroes et al. 2004 paper on the application of TTC to chemical risk assessment. The Kroes et al. papers explore the scientific basis for establishing thresholds of toxicological concern for chemicals falling into defined structural classes. Based on structure activity analysis, the TTC indicates several safe thresholds of chemical exposure: 0.15 µg/p-d, 1.5 µg/p-d , 18 µg/p-d, 90 mcg/person/day, 540µg/p-d, and 1800 µg/p-d , depending upon the structural alerts or lack thereof for the chemical and the level and content of available toxicity data on the substance. It is important to note that the TTC as laid out in the Kroes et al. papers has been applied by FDA to safety assessments involving pharmaceutical products and color additives and is under active consideration for use in the assessment of medical devices. In addition, the TTC approach has been adopted by European regulators for pharmaceuticals (EMEA) and is under consideration for numerous types of risk assessments performed by the European Food Safety Authority (EFSA) including assessments for uses of substances similar to your use of TGP 6877 and 6877-45. Finally, Munro et al. revised previous analysis of the lowest TTC based on exclusion of organophosphate compounds and determined that a Class III TTC of 180µg/p-d was appropriate.[10]

Most importantly, the TTC levels follow closely threshold levels applied by FDA in its review of food-contact substances and food ingredients. For example, the lowest two threshold levels above correspond to consumer exposures where FDA typically relies on structure activity analysis alone and does not ordinarily recommend toxicity data be developed for mutagenic (0.15 µg/p-d threshold) and non-mutagenic (1.5 µg/p-d threshold) compounds respectively.
Moreover, the 180 µg and 540 µg/p-d levels above correspond closely to those levels at which FDA generally begins to recommend differing levels of animal testing based on levels of concern. Thus, we believe that application of the TTC approach closely models FDA's review processes to assess the significance of migration from food-contact materials.[11]

While the threshold scheme discussed in the Cheeseman, *et al.* paper and the decision tree laid out in Kroes et al. 2004 do not yet represent the formal promulgation of new threshold criteria by the FDA for food contact substances, they do provide further guidance for the private sector's evaluation of food-contact materials by informing the interpretation of the significance of migration from food contact materials as indicated in *Monsanto v. Kennedy*. Moreover, they collectively provide a suitable basis for taking self-determined GRAS positions for dietary exposures at levels significantly higher than 0.5 ppb, for substances that qualify under the analysis set forth in the papers.

Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schalatter, J., van Schothorst, F., Vos, J.G. & Würtzen, G. (2004). Structure-based Thresholds of Toxicological Concern (TTC): Guidance for application to substances present at low levels in the diet, Food and Chemical Toxicology 42, Issue 1, 65-83.

[10] Munro, I.C., Renwick, A.G. & Danielewska-Nikiel, B. (2008). The Threshold of Toxicological Concern (TTC) in risk assessment, Toxicology Letters, 180, 151-156.

[11] The discussion in this paragraph of FDA's use of certain exposure thresholds to adjust toxicity testing requirements is based on knowledge of current agency practice, which the Agency has not yet published as a rule or in a guidance document.

We note that the scientific articles discussed above have been published in peer reviewed scientific journals. The analysis underlying the Threshold of Regulation rule was also published in the Federal Register. Therefore, these authorities meet the regulatory requirement for GRAS status that the scientific safety consensus is demonstrated in published sources. *See* 21 C.F.R. § 170.30 (b).

III. GRAS Assessment of Hypochlorous acid as an Antimicrobial in Processing of Meat and Poultry Products, Fish, Fruits and Vegetables and Shell Eggs

A. Intake Estimates

In the absence of specific residue data for the commodities of interest, we have relied upon publicly available residue information to estimate probable consumer intake for your intended use. We have not relied on the residual levels provided on the electrolyzed water itself because certain of these products may form upon reaction with organic matter in the processing water (such as the trihalomethanes (THMs). The European Food Safety Authority (EFSA) Scientific Committee on Veterinary Measures Relating to Public Health (SCVPH) has reviewed the safety of various antimicrobials in the treatment of poultry carcasses.[12] This opinion did not review hypochlorous acid specifically, it evaluated chlorine dioxide. The opinion reported that residues on poultry carcasses, after decontamination with chlorine dioxide for 1 hour, were 0.13 mg chlorite and 0.06 mg chlorate per kg carcass.[13] Although this discussion does not specify the starting concentration, based on the discussion of the chlorine dioxide identity, we expect the starting concentration to be 50 mg/L (50 ppm).[14] A review by Food Standards Australia New Zealand (FSANZ) of acidified sodium chloride also discusses residue data for chlorite and chlorate on poultry, meat, produce, processed and preformed meat, and fish.[15] The residue data submitted to FSANZ demonstrated residues for both chlorite and chlorate below the limit of detection (range <0.1 to 0.54 ppm for chlorite and <0.1 to <0.3 ppm for chlorate) in these foods, except that in fish and seafood no chlorate residues were detectable at 24 hours post-treatment. [16] With regard to chloride, FSANZ concluded that "the added impact of these treatment-derived chloride ions on the typical background levels of sodium chloride found in all foods is not measurable or detectable with current test sensitivities."[17]

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[12] EFSA SCVPH, *Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to Treatment of poultry carcasses with chlorine dioxide, acidified sodium chlorite, trisodium phosphate and peroxyacids*, Question Nº EFSA Q-2005-002, The EFSA Journal (2005), 297. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/297.pdf.

[13] Ibid., at p. 14.

[14] Ibid., at p. 6.

[15] Food Standards Australia New Zealand, Final Assessment Report Application A476 Acidified Sodium Chlorite as a Processing Aid (8 October 2003), included with this Attachment.

The at-use concentration is not specifically mentioned, but based on the intended use of the ASC, it appears that a range of 50- 150 ppm ASC was used for poultry carcasses while 500-1200 ppm ASC was used on all other foods. A post-treatment water rinse was used only for the fruits and vegetables. In addition, a JECFA review of ASC noted that levels of residue on foods is time-dependent and that in most cases residue level decline quickly after processing; for example, chlorite levels of 0.54 ppm detected on poultry carcasses immediately after a 1 hour immersion in 150 ppm ASC were reduced to 0.021 ppm within the first hour following treatment and were not detectable thereafter (<0.016 ppm), while chlorite residues on fish and seafood were detected only immediately following treatment, but not following a 24-hour holding period (LOD 0.1 mg/liter).[18]

In light of the relative agreement between these data and considering the typical manufacturing process where there will be considerable time between processing and consumption, we will rely upon the JECFA data, using the values provided after a specific dwelling/holding time and adjusted for the lower use level of the FCS (for example, if the JECFA testing used 1200 ppm, then the residual result is lowered 20-fold (1200 ppm ÷ 60 ppm = 20). Thus, the residual values used are the following:

Food	**Chlorite (mg/L)**	**Chlorate (mg/L)**	**Source**
Chicken	<0.005	<0.005	Chicken breast 15-30 second immersion at 1200 ppm followed by 1-8 hour dwell time with no rinse.
Meat, Processed and Preformed	<0.011	<0.011	Highest value from testing immediate post treatment; 5-10 second spray of 1200 ppm solution, 30 second drip, 1-2 second rinse or air dry.
Seafood	<0.0005	<0.0005	30 second immersion at 1200 ppm, 30 second drip, with or without rinse 24-48 hour dwell time.
Produce	0.12 (0.84)	<.0005	30 second dip at 1200 ppm, water wash and airdry for 24 hours. Lettuce value (0.23 mg/L) used for chlorate. Analysis also run with value for no water rinse/

[16] Ibid., at p. 16.

[17] Ibid., at p. 17.

[18] Madduri, V. Rao, Acidified Sodium Chlorite Chemical and Technical Assessment, Prepared for the 68th JECFA (2007), http://www.fao.org/fileadmin/templates/agns/pdf/jecfa/cta/68/Acidified_Sodium_Chlorite.pdf.

For trihalomethanes, there is good information available on residues in food, as well as their potential presence on food after cooking. As summarized in Najjar (2009), residues in chicken fat after immersion for 20 minutes in a 50 ppm solution of chlorinated water resulted in 46 ppb of chloroform, while a chilling step analysis demonstrated <5 ppb levels of chloroform in skin and fat.[19] Cooking significantly reduces the presence of halocarbons, which have a low boiling point and evaporate under heat.[20] The JECFA study similarly found no detectable levels of oxidized or chlorinated lipids in chicken wings immersed for 5 minutes in 2525 mg/liter ASC solution, LOD of 0.05 mg/l. A published study on fresh-cut lettuce demonstrated total trihalomethane levels on lettuce after 1 hour of washing with chlorine, continuously added to maintain a residual chlorine concentration in the water of 1 mg/liter (total cumulative chlorine dose of 235.8-609.0 mg/liter, depending on the chemical oxygen demand), of 27.8-124.5 µg/liter.[21] No trihalomethanes were found on the fresh-cut lettuce after rinsing.

Consequently, we will evaluate the dietary exposure to THMs for fruits and vegetables only, assuming no post-treatment water rinse. Research has shown that there are several factors affecting the formation potential of trihalomethanes: residence time, temperature, pH, disinfectant type and concentration, and total organic carbon concentration.[22] As these variables increase, so do the levels of THM.[23] In produce washing, the residence time and temperature are expected to be low, while the pH is neutral. Based on the lettuce study, we will use a residual level of THM on the lettuce of 60 ppb.

For shell eggs, we expect there to be virtually no exposure, as the solution will drain from the exterior after washing, will not penetrate the eggshell, and would be unlikely to become part of the food upon processing. In any case, any intake due to the use on shell eggs will be insignificant compared to the intakes form other uses.

The dietary exposure is calculated using the Environmental Protection Agency's Dietary Exposure Evaluation Model -Food Commodity Intake Database (DEEM-FCID)/Calendex, which incorporates food consumption data from the National Health and Nutrition Examination Survey/"What We Eat in America" (NHANES/WWEIA) dietary survey. The version used incorporates NHANES/WWEIA data from 2005-2010. EPA uses the model to estimate dietary intake of any component of food or water including toxicants, pesticides, and natural constituents to perform acute and chronic dietary exposure assessments.[24] The results from this software are reported in mg/kg bw/day, we have converted these values to a dietary concentration using FDA's default values that a person weighs 60 kg and consumes 3 kg food per day.

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[19] Najjar, M.B. and J. Meng, Risk Assessment of Disinfection Byproducts in Poultry Chilled in Chlorinated Water (August 26, 2009), http://www.nationalchickencouncil.org/wp-content/uploads/2012/02/U-of-Md-Chlorine¬Study.pdf, p. 13.

[20] Ibid., at p. 13.

[21] Van Haute, S., I. Sampers, K. Holvoet, M. Uyttendaele, *Physicochemical Quality and Chemical Safety of Chlorine as a Reconditioning Agent and Wash Water Disinfectant for Fresh-Cut Lettuce Washing*, Applied and Environmental Microbiology 79:9 (May 2013), 2850-2861, at 2856.

[22] Farron, E.A., *Reducing Trihalomethane Concentrations by Using Chloramines as a Disinfectant* (April 2003) (unpublished M.S. thesis, Worcester Polytechnic Institute), https://www.wpi.edu/Pubs/ETD/Available/etd-0429195058/unrestricted/Farren.pdf.

[24] More information available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/deem- fcidcalendex-software-installer

Migrant	DC(µg/kg)	EDI(µg/p/d)	EDI (Body Weight)(µg/kg/d)
Chlorite-Produce Rinse	2.2	6.6	0.11
Chlorite-No Produce Rinse	130	390	6.5
Chlorate	0.42	1.26	0.021
THM-No Produce Rinse	9.3	27.9	0.465

We reviewed FDA's online CEDI database and located listings for sodium chlorite and sodium chlorate, although both listings indicate a cumulative EDI and DC of 0.

B. Review of Toxicology Data

Under the intended conditions of use, there is no anticipated exposure to the FCS itself, as it is expected to break down. The potential exposures are to its breakdown products, chlorite and chlorate, as well as trihalomethanes (THM). Although there may be exposure to sodium and chloride ions, the potential exposure is expected to be a minuscule fraction of the daily dietary intake of sodium chloride, which is GRAS. Thus, there is no safety concern from the potential exposure to sodium and chloride ions.

We expect the above-listed exposure levels to be largely, if not completely, substitutional for other chlorine-based antimicrobials already on the market for use in the same applications as sought in this case. The US Environmental Protection Agency (EPA) has established a standard under the National Primary Drinking Water Regulations (NPDWR) for chlorine disinfection byproducts, which addresses chlorite and THM.[25] EPA has established a Maximum Contaminant Level Goal (MCLG), the level of a contaminant in drinking water below which there is no known or expected risk to health, for chlorite of 0.8 mg/L (0.8 ppm), and a maximum contaminant level (MCL) of 1.0 mg/L (1 ppm). The dietary concentration of the FCS from the intended uses is well below the level permitted in drinking water. Furthermore, EPA has established an oral reference dose for chlorite, due to the potential for neurodevelopmental effects, of 0.03 mg/kg/day.[26] The potential exposure is well below the RfD. On these bases, we submit that there is no safety concern from the presence of chlorite on food from the intended uses of the FCS, even when no produce rinse is utilized.

Chlorate is another known breakdown product of chlorine-based antimicrobials and disinfectants.[27] EPA has not established a standard for the presence of chlorate in drinking water, but rather evaluates chlorate as part of its evaluation of chlorine dioxide and chlorite. Given that the safety of chlorate is considered as part of the safety of chlorite and chlorine dioxide, considering that the potential exposure is largely expected to be substitutional for existing chlorine antimicrobials, and considering the very low level of dietary exposure calculated above (0.42 ppb/0.000021 mg/kg bw/day) and the wide margin of safety between this dietary exposure and the RfD for chlorite (~1500), we submit there is no safety concern from the presence of chlorate.

[25] https://www.epa.gov/ground-water-and-drinking-water/table-regulated-drinking-water-contaminants
[26] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0648_summary.pdf
[27] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0648tr.pdf ("Chlorine dioxide is fairly unstable and rapidly dissociates, predominantly into chlorite and chloride, and to a lesser extent, chlorate," p. 2).

We expect the residual levels of THM to be largely, if not completely, substitutional for other chlorine-based antimicrobials already on the market for use in the same applications as sought in this case. EPA has established a drinking water standard maximum contaminant level (MCL) of 0.08 mg/L (80 ppb). As conservatively calculated in the exposure assessment, the dietary exposure to THM, even when a produce rinse is not used, is a conservatively calculated 0.000465 mg/kg bw/day. EPA has established oral reference doses for several THM, the most stringent of which is for chloroform, at 0.01 mg/kg/day.[28] The potential exposure is well below the RfD. On these bases, we conclude that there is no safety concern from the presence of THM on food from the intended uses of the FCS, even when no produce rinse is utilized.

Hypochlorous acid has also been stated as a safe and suitable ingredient for use in the production of meat, poultry, and egg products according to the U.S. Department of Agriculture Food Safety and Inspection Service's Directive 7120.1, Safe and Suitable Ingredients Used in the Production of Meat, Poultry and Egg Products. FDA has also approved the use of hypochlorous acid at concentrations up to 60 ppm on fresh cut fruits and vegetables as documented by FCNs 692, 1176, 1470, and 1606.

C. Conclusion

Based on all the data reviewed, including all relevant publicly available data, we have no hesitation stating that Aquaox's intended use of hypochlorous acid produced in situ by electrolysis of sodium chloride at a level of up to 60 ppm as an antimicrobial to treat process water or ice which may contact a variety of foods including whole or cut meat and poultry, including carcasses parts trim and organs, processed and reformed meat and poultry products, whole or cut fish, fruits and vegetables and for the washing of shell eggs is GRAS.

IV. Parameters of the Opinion

The opinion is limited to the Federal Food, Drug, and Cosmetic Act and the regulations issued and administered by FDA to implement the Act, and we are not opining on any other laws or regulations.

The opinion is an opinion only and does not constitute a guarantee or warranty of the matters discussed herein.

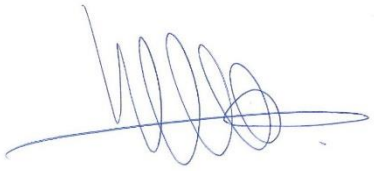
The opinion is made as of the date hereof and we assume no obligation to revise, supplement, or update it in the event of a change in the law or facts concerning the product or for any other reason.

[28] https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=25

This letter assumes that the information which you have provided to us, as described above, is complete and accurate. We have not independently verified the accuracy of that information, and we have not made any other factual investigation of any kind apart from the literature searches mentioned above. The opinion also assumes that the product will be used in accordance with the information which you have provided.

We trust that this letter is fully responsive to your request for our opinion. If you have any questions, or if we may be of further assistance, please to not hesitate to contact us.

Sincerely,



Michel van Schaik,
CEO / President Aquaox LLC