Application in Support of the Use of Cetylpyridinium chloride (CPC) as a Processing Aid for the Decontamination of Raw Poultry Products

APPLICANT: SAFE FOODS CORPORATION
NORTH LITTLE ROCK, ARKANSAS, U.S.A.
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NATURE OF BUSINESS: FOOD SAFETY COMPANY/ PROCESSING AID SUPPLIER

[redacted]

DATE SUBMITTED: NOVEMBER 13, 2020

SUBMITTED TO: FOOD STANDARDS AUSTRALIA NEW ZEALAND

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Annex A Referenced Journal Articles

a. Slavik, M.F., W.J. Kim, and J.T. Walker, 1995. Reduction of *Salmonella* and *Campylobacter* on chicken carcasses by changing scalding temperature. J. Food Prot. 58: 689-691.

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c. Li, Y., M.F. Slavik, J.T. Walker, and H. Xiong, 1997. Pre-chill spray of chicken carcasses to reduce *Salmonella typhimurium*. J. Food Sci. 62:605-607.

d. Beers, K. W., J. Rheingans, K. Chinault, P. Cook, B. Smith, and A. Waldroup, 2006. Microbial efficacy of commercial application of Cecure® CPC antimicrobial to ingesta-contaminated pre-chill broiler carcasses. Intern. J. Poultry Sci. 5(8):698-703.

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f. Waldroup, A.L., K.L. Beers, P.E. Cook, E.A. Dell, R. Odglen, R.A. Baker, C.W. Coleman, B.A. Smith, and B.W. Maingi, 2010. The effects of cetylpyridinium chloride (Cecure® CPC Antimicrobial) on *Campylobacter* Spp. on raw poultry: A review. Intern. J. Poultry Sci. 9(4):305-308.

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v. EFSA, 2018. Re-evaluation of propane-1,2-diol (E 1520) as a food additive.

Annex B Experimental Protocols (Proprietary Efficacy and Residue Studies), and Methodologies for determining CPC and Propylene Glycol Residues in Poultry

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b. MCA 060401 – Microbial efficacy
c. MCA 060407 – Microbial efficacy
d. MCA 060510 – Microbial efficacy
e. MCA 060607 – Microbial efficacy
f. MCA 060613 – Microbial efficacy
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l. MCA-R-1005132010 – Residue study
m. Annex 26: Summary of residue studies
n. Methodologies for determining CPC and PG residues in Cecure-treated poultry

Annex C Published Toxicology references (as presented in Annex C, and summarized in **Table 4**):

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r. Rodrigues, F., M. Lehmann, V.S. do Amaral, M.L. Reguly, and H.H.R. de Andrade, 2007. Genotoxicity of three mouthwash products, Cepacol®, Periogard® and Plax®, in the Drosophila wing-spot test. Environmental and Molecular Mutagenesis 48:644-649.

Annex D Proprietary Toxicology Reports on CPC (summary of studies provided in **Table 5**)

Annex E Cecure® Safety Assessments from Various Countries

a. U.S. Food and Drug Administration Federal Register 21 CFR 173, November 29, 2007

b. Canadian Food Inspection Agency Cecure® Approval Letter

c. Russian Ministry of Health Cecure® Certificate of Registration

d. EFSA 2012 Scientific Opinion on the evaluation of the safety and efficacy of Cecure®

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f. Testing with Campylobacter jejuni (ATCC 33560)

3.1. GENERAL REQUIREMENTS FOR APPLICATIONS

3.1.1. GENERAL REQUIREMENTS

B. Applicant Details

Applicant details are provided on the cover page of this application.

C. Purpose of the Application

The purpose of this application is to request the addition of Cetylpyridinium chloride (CPC) to the list of approved poultry carcass washing processing aids listed under Schedule 18 of the Australia New Zealand Food Standards Code. CPC is the active ingredient in the commercial product Cecure®, which is prepared in solution with propylene glycol and water. CPC is diluted to ≤ 1% using potable tap water for use as an antimicrobial treatment for raw poultry carcasses and poultry parts. The CPC solution is used to treat the inner and outer surfaces of raw poultry carcasses prior to entry into the chiller (immersion or air chiller). Optionally, the solution can be applied to post-chill (immersion or air-chilled), whole poultry carcasses or to poultry parts.

CPC is used to reduce, to the maximum extent practicable, foodborne pathogens such as Salmonella and Campylobacter that may be present on raw poultry.

D. Justification for the Application

CPC is a safe and efficacious antimicrobial agent that assists poultry processors in meeting pathogen and human illness reduction targets set by the USDA's Food Safety and Inspection Service (FSIS) in the U.S., and by regulatory agencies in other countries where it is has received regulatory approval. Cecure® product has been safely used in the U.S. and other countries without any safety incidences for over 15 years. It is currently installed and used in 49 poultry facilities in the U.S., Canada, several countries in Latin America, Israel, Saudi Arabia and the UAE.

Food safety is an important objective for all poultry processors, as well as the regulatory agencies. To consistently meet the regulatory objectives requiring reductions in foodborne pathogens such as *Salmonella* and *Campylobacter*, poultry processors typically seek a multi-hurdle approach in their use of antimicrobial interventions. The use of a multi-hurdle approach in poultry processing has been recognized by various agencies, such as the USDA's Food Safety and Inspection Services (FSIS), as the most effective means to control for *Salmonella* and *Campylobacter*. The addition of CPC to the list of interventions available for the Australian and New Zealand poultry processors would provide processors with an additional intervention that would meaningfully supplement the substances currently listed on Schedule 18-Processing aids because it represents a safe, widely used, type of antimicrobial group that is distinct from the chemical groups currently represented.

CPC is considered to be a stable compound due to its three carbon-nitrogen bonds. CPC is a quaternary ammonium compound (N atom with 4 attached groups) therefore the nitrogen atom possesses no unpaired electrons leaving no site for N-oxidation, a requirement for reactions with the nitrogen atom. There are no known impurities, by-products, contaminants or reaction products of concern in concentrated or diluted CPC. CPC is not an oxidant, or acidic in nature and will not alter the structure or function of proteins, lipids, or carbohydrates. In addition, CPC has a neutral pH and will not alter the sensory characteristics of the product being treated.

Based on the above facts concerning the stability of the CPC compound and the multi-year history of safe use in poultry processing plants, we believe that the following situations reflect the use of CPC in a poultry processing facility:

1. CPC solutions will not react with organic acids, sodium hypochlorite, ammonia, or chlorinated water.
2. CPC solutions will not produce odors when used with chlorinated water.
3. CPC solutions will not be negatively impacted by a high or low pH.
4. CPC solutions will not produce toxic or hazardous by-products in poultry fat during processing.

CPC is approved for the petitioned usage for raw poultry, and in some cases for treatment of other foods, in other countries including Argentina, Canada, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Israel, Jordan, Mexico, Panama, Peru, Russia, Saudi Arabia, South Africa, U.A.E., and Uruguay. CPC also received an EFSA opinion in 2012 for the requested use of Cecure® as a treatment for raw poultry. In the opinion, EFSA stated it had no concerns on the efficacy of CPC and Cecure® and no safety concerns for humans from the intended use.

D.1. Regulatory Impact Information

D.1.1. Cost and Benefits of the Application

The World Health Organization (WHO) estimates the annual cases of food borne illnesses due to consumption of unsafe food at 600 million, and related deaths at 420,000 worldwide.[1] The most common causes of foodborne illnesses and death have been identified as diarrheal agents such as norovirus, *Campylobacter spp*. and *Salmonella enterica*. Other major causes of death include *Salmonella typhimurium*, and hepatitis A virus and aflatoxins.

An article comparing foodborne disease outbreaks and transmission vehicles between Australia and New Zealand from data published in annual and quarterly reports by the Institute of Environmental Science and Research (ESR, New Zealand) and the health

network OzFoodNet (Australia) between 2007-2011 identified the major pathogens associated with outbreaks in Australia and New Zealand. The leading pathogens in Australia were identified as: *Salmonella typhimurium* (31%), norovirus (8%), *Salmonella spp*., and ciguatoxins (5% each), and in New Zealand as: norovirus (20%), campylobacter (10%) and Salmonella spp. (7%).[2] The outbreaks in Australia generally remained consistent at about 150 cases over the 5 years analyzed above, while in New Zealand, the outbreaks increased by 39.3% over the same time to approximately 120 cases in 2011.

According to the OzFoodNet annual report in 2004, foodborne illnesses cost Australia more than $1.2 billion annually at the time.[3] The total cost of potentially foodborne infectious disease in New Zealand was estimated to be $88.8 million in 2000.[4] This cost remained the same in Australia in OzFoodNet's 2011 annual report[5], while in New Zealand, the total estimate costs related to foodborne illness rose to $161.9 million in 2009.[6] These costs include the costs of treatment and hospitalization, government costs for investigating and surveillance of outbreaks, business output loss, and residential private costs.[7]

The upward trend in foodborne illnesses and costs over the years has been a major cause for establishing food regulations and standards in various countries, including Australia and New Zealand, to aid in reducing foodborne illnesses around the world. One of the ways prevention of foodborne illnesses is accomplished is through interventions aimed at the food production industry, such as poultry and meat processing facilities, food services and consumers. This application aims to contribute to decreasing the cases of foodborne illnesses and deaths in Australia and New Zealand and around the world.

The expected costs of this application to the government are expected to be minimal due to the fact that a food standard and related enforcement activities already exist for processing

aids applied to processing water in poultry facilities. The cost of approval is expected to be limited to the costs associated with the review, notification and final publication of the approval.

D.1.2. Impact on International Trade

Most of the poultry produced in Australia and New Zealand is consumed domestically, although export markets exist for chicken, turkey and duck meat.[8] According to "The Poultry Site's 2018-19 outlook of the chicken market in Australia, "exports of chicken meat are expected to remain low, with majority of the consumption being domestic". Exports of chicken meat in Australia make up less than 5% of the chicken produced, and comprise mostly of low value cuts and offals.[9] Imports make up less than 1% of the chicken consumed in the country and are mostly from New Zealand.[10] Similarly in New Zealand, imports of poultry meat (duck and turkey meat) are relatively low compared to its local production numbers.[11] The country exports chicken to Australia and other countries in the region. Exports of New Zealand chicken brought earnings of $27 million in 2017. [12]

In spite of the relatively low poultry export and import figures from Australia and New Zealand, the proposed approval of Cecure® product is expected to make a significant impact in improving the safety of treated poultry exported from Australia and New Zealand to other countries in the region.

F. Assessment Procedure

Based on the fact that a standard already exists for the use of processing aids in wash water for various foods (category S18-7 of Schedule 18), and that Cecure® product would be a supplementary product to those already listed in category S18-7, we submit that the application for Cecure® would fall under Level 3 of the general assessment procedure. The

active ingredient, though not currently approved in Australia and New Zealand, is not a novel product as it has many applications outside the food industry, such as its long and safe use in oral hygiene products, as well as disinfectant products used in surface sanitation. The level of complexity for the assessment of microbiological, toxicology and dietary exposure data submitted is expected to be average.

G. Confidential Commercial Information

The following information and studies either commissioned by the Applicant or internally generated by the Applicant in support of the regulatory approval of Cecure® in the U.S. and other countries are considered proprietary in nature:

1. **Toxicity (feeding studies) summarized in Table 5 of Section 3.3.2 and provided in full in Annex D of this application.** The Company spent millions of dollars on the feeding studies and considers the study results proprietary. It would put the Company at a significant competitive disadvantage and be entirely unfair to provide its competitors with this extremely expensive information free of charge.

2. **Internally generated (unpublished) efficacy and residue studies provided in full in Annex B of this application.** The Company designed and conducted efficacy and residue studies and generated data using internal resources, including using years of experience and know-how. It would put the Company at a significant disadvantage to disclose the details of the internally developed studies and data to competitors free of charge.

3. **Methodologies developed for analysis of CPC and PG residues on Cecure-treated poultry, provided in full in Annex B of this application.** The

methodologies were developed using internal resources, including using years of experience and know-how. It would put the Company at a significant disadvantage to disclose the details of the internally developed protocols to competitors free of charge.

4. **Studies on bacterial resistance to antimicrobials, provided in Annex F of this application.** The bacterial resistance studies were commissioned by the applicant, who spent significant time and expense on the studies. It would put the Company at a significant competitive disadvantage and be entirely unfair to provide its competitors with this extremely expensive information free of charge.

H. Other Confidential Information

The applicant does not wish to treat other non-confidential commercial information submitted as confidential.

I. Exclusive Capturable Commercial Benefit (ECCB)

The application for the use of CPC as a processing aid in Australia and New Zealand is not expected to confer an exclusive capturable commercial benefit to the applicant.

J. International and Other National Standards

J.1. International Standards

The relevant Codex guidelines to this application are the Codex Guidelines on Substances used as Processing Aids, CAC/GL 75-2010.

J.2. Other National Standards or Regulations

Other national standards or regulations relevant to this application include:

- The U.S. Food and Drug Administration Code of Federal Regulations (CFR) Title 21, Part 173 describing secondary direct food additives permitted in food for human consumption;

- The Canadian Food and Drug Regulations;
- Regulation (EC) No 853/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin;
- The Russian Federation's Sanitary Rules and Regulations (SanPin) for hygienic requirements for safety and nutrition value of foodstuff.
- Jordanian Standard Specification No. 204 of 1997 on Fresh Chilled and Frozen Chicken allowing the addition of sterilizing agents to the water used to wash slaughtered poultry.

Approval of Cecure® in other countries (listed in Table 2 of Section B.2) relied heavily on the current U.S. FDA and U.S.D.A. Food Safety Inspection Services' regulations and approvals allowing the use of Cecure® as a processing aid for poultry products.

K. Statutory Declaration

SAFE FOODS™
KNOWLEDGE | SERVICE | SOLUTIONS

STATUTORY DECLARATION

I, Beatrice Maingi, Senior Manager, Regulatory Affairs at Safe Foods Corporation, 1501 E. 8th Street, North Little Rock, AR 72114, make the following declaration under the *Statutory Declarations Act 1959*:

1. the information provided in this application fully sets out the matters required
2. the information provided in this application is true to the best of my knowledge and belief
3. no information has been withheld that might prejudice this application, to the best of my knowledge and belief

I understand that a person who intentionally makes a false statement in a statutory declaration is guilty of an offence under section 11 of the *Statutory Declarations Act 1959*, and I believe that the statements in this declaration are true in every particular.

Declared at Safe Foods Corporation, 1501 E. 8th Street, North Little Rock, AR 72114 on the 3rd day of August 2020.

Before me,

Todd Coleman, Ph.D.

Director, Research and Development
Safe Foods Corporation,
1501 E. 8th Street,
North Little Rock, AR 72114, U.S.A.

3.3. GUIDELINES FOR APPLICATIONS FOR SUBSTANCES ADDED TO FOOD

3.3.2. PROCESSING AIDS

A. TECHNICAL INFORMATION

A.1. Information on the type of processing aid

Cecure® solution is a food processing aid that is supplied as a solution of the active ingredient, Cetylpyridinium chloride (CPC), in propylene glycol and water. CPC is classified as a quaternary ammonium compound, consisting of a pyridine ring and a long hydrophobic carbon chain (see the molecular structure in section A.2 below), with a net positive charge on the nitrogen atom. CPC is pH-neutral at the use concentration. Cecure® is diluted to ≤ 1% CPC concentration using potable tap water for use as an antimicrobial treatment for raw poultry carcasses and poultry parts. We submit that, as a food processing aid, Cecure® solution would fall into category S18-7 Permitted bleaching, washing and peeling agents of Schedule 18.

Cecure® may be used to reduce a broad spectrum of microorganisms that may be present in food, including the following: *Salmonella, Campylobacter, Listeria, Staphylococcus aureus, E. coli* (including O157:H7), and total coliforms. Below is a review of relevant scientific publications on the efficacy of CPC for treating raw poultry.

A.1.1. **"Pre-Chill Spray of Chicken Carcasses to Reduce *Salmonella typhimurium*,"** Li *et al*., 1997 (See **Annex A**).

In this early study, pre-chill broilers were inoculated with *Salmonella typhimurium* and sprayed in a test chamber with 0.1% CPC at 207, 345 or 827 kPa pressure for either 30 or 90 seconds of exposure time. Spraying with 0.1% CPC for 90 seconds at 827 kPa pressure resulted in a 1.6 $\log_{10}$ reduction in Salmonella. It should be noted that in commercial practice

a CPC concentration of > 0.1% is typically utilized, resulting in significantly greater reductions in all organisms, including Salmonella, as will be noted in the studies below.

A.1.2. "Microbial Efficacy of Commercial Application of Cecure® CPC Antimicrobial to Ingesta-Contaminated Pre-Chill Broiler Carcasses," Beers *et al*., 2006 (See **Annex A**).

A 12-week study was conducted under commercial processing conditions in three USDA/FSIS-inspected commercial poultry processing facilities in the U.S. In this study Cecure® was utilized as a pre-chill spray to treat raw poultry that were visibly contaminated with ingesta material. Briefly, pre-chill broilers were sprayed with 0.5% to 0.7% Cecure® in a recycling scenario for 2 to 3 seconds prior to chilling. All carcasses were microbiologically sampled prior to immersion chilling. The Cecure® treatment significantly reduced APC by at least 2.5 logs, E. coli by at least 1.6 logs, total coliform by at least 1.2 logs, and Campylobacter by at least 0.8 logs. Salmonella incidence was reduced from a high of 33% to less than 10% in one plant, and to less than 3% in the other two plants.

A.1.3. "Efficacy of Antimicrobials Against *Campylobacter jejuni* on Chicken Breast Skin," Arritt et al., 2002 **(See Annex A).**

This laboratory study evaluated the effects of 0.1% and 0.5% CPC, among other decontaminant treatments, on *Campylobacter jejuni* on chicken skin samples. When the organism was inoculated onto the skin surface before treatment, reductions of 1.4 and 2.9 $\log_{10}$ CFU/mL were achieved with 0.1% and 0.5% CPC, respectively. When *Campylobacter jejuni* was inoculated onto the chicken skin after the skin had been treated with 0.5% CPC, a 4.7 $\log_{10}$ reduction was noted. The authors noted that "Cetylpyridinium chloride (0.5%) was an effective decontaminant agent for inactivating, reversing attachment, and inhibiting attachment of *Campylobacter jejuni* to chicken skin."

A.1.4. "The Effects of Cetylpyridinium Chloride (Cecure® CPC Antimicrobial) on Campylobacter Spp. on Raw Poultry: A Review," Waldroup *et al*., 2010 (See **Annex A**).

This review article is based on numerous published studies and many of the Applicant's laboratory and commercial in-plant studies demonstrating the efficacy of Cecure® against Campylobacter on commercial broilers. The article states that at a concentration between 0.1% and 0.5%, the use of Cecure® will result in at least a 1 to 2.5 log10 reduction in Campylobacter levels on pre-chill broilers, with incidence rates being reduced from 80% to 90% to no greater than 7% to 9%. It should be noted that in all studies, the 0.4% and 0.5% Cecure® treatments resulted in significantly greater reductions than did the 0.1% or 0.25% Cecure® treatments, as would be expected.

Additional studies were conducted by the applicant to investigate the antimicrobial effect of Cecure® on raw poultry in support of application for the use of Cecure® in the EU. These studies were conducted using either a prototype or commercially available treatment equipment installed in commercial USDA/FSIS-inspected poultry slaughter facilities, and showed significant reductions in *Salmonella*, *Campylobacter*, APC, coliforms, *E. coli*, and *Enterobacteriacea*. These proprietary studies are provided in **Annex B**.

A.2. Information on the identity of the processing aid

The processing aid is an aqueous solution containing cetylpyridinium chloride ("CPC") as the active ingredient, and food-grade propylene glycol ("PG"). The mixture is commercially sold under the trade name Cecure®.

A.2.1. Chemical Identity

Cetylpyridinium chloride:

IUPAC name: 1-hexadecyl pyridinium chloride.

Common names: Ceepryn chloride, Cepacol chloride, Cetamium, Dobendan, Pristacin, and Pyrisept.

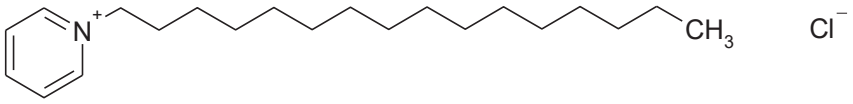
Synonyms: 1-palmitylpyridinium chloride, C16-alkylpyridinium chloride, Acetoquat CPC, Aktivex, Ammonyx CPC, Cepacol, Ceprim, Cetafilm, Halest, Ipanol, Medilave, Mercocet, Merothol, and Pionin B.

Chemical Abstract Service (CAS) Registry Number: 123-03-5.

EC Number: 204-593-9.

REACH Number: None

The structural formula for CPC is depicted below:



The molecular formula of CPC is $C_{21}H_{38}NCl$; the molecular weight is 340 g/mol. CPC is typically present in water in the monohydrate form. The monohydrate has the molecular formula $C_{21}H_{38}NCl{:}H_2O$ and has a formula weight of 358 g/mol. The calculated elemental content is C: 70.45%, H: 11.26%, Cl: 9.90%, O: 4.47%, and N: 3.91%.

Propylene glycol:

IUPAC name: Propane-1,2-diol.

Synonyms: α-propylene glycol, 1,2-propanediol, 1,2-Dihydroxypropane, methyl ethyl glycol (“MEG”), methylethylene glycol, PG, Sirlene.

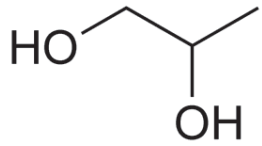
CAS Registry Number: 57-55-6.

EC Number: 200-338-0.

E Number: E 1520 (EU food additive under Directive Nº 95/2/EC)

REACH Number: None found

The structural formula for PG is depicted below:



The molecular formula of PG is $C_3H_8O_2$; the molecular weight is 76.09 g/mol.

Studies on Antimicrobial Resistance to CPC

Cetylpyridinium Chloride (CPC) is a quaternary ammonium salt with well-known antimicrobial properties. The most common use of CPC is in dental hygiene products such as toothpaste, mouth wash, and lozenges.

Safe Foods commissioned antimicrobial resistance testing of CPC with CREM Co Labs of Mississauga, Ontario, Canada. The studies were to evaluate the development of resistance in six pathogenic microorganisms, namely: *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, and *Campylobacter jejuni,* following the use of CPC. The principles of the resistance tests entailed: i) establishing the baseline susceptibility profiles of the target pathogen to CPC as well as a panel of antibiotics, ii) exposing the pathogens to CPC under use conditions that simulate as closely as possible typical field conditions, iii) measuring any changes in pathogen susceptibility profiles after exposure to CPC and development of

possible cross-resistance to selected antibiotics, and iv) in case any significant changes in the susceptibility profiles are observed, determine if the change is transient or stable.

CPC susceptibility in the target pathogens was based on measuring the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) using established and well-recognized standardized protocols.

The overall findings of the six individual studies showed no evidence for development of pathogen resistance to CPC, nor was there any reduced susceptibility to the antibiotics tested. The full report for Salmonella typhimurium is included in **Annex F**. The full reports for the other five pathogens are available upon request.

A.3. Information on the Chemical and Physical Properties.

Cecure® may be characterized in terms of the following physical and chemical properties:

Table 1. Physical and Chemical Properties of Cecure®

Appearance/Physical form	**Clear Liquid, homogeneous solution**
Color	Colorless to light yellow
Odor	Mild Organic
Liquid Density	0.98 g/ml at 25°C
pH (1% aqueous solution)	6 - 8 (1% in DI water)
Solubility*	freely soluble in water, alcohol and chloroform but insoluble in ether

*CPC does not dissolve in food products including poultry, which is the intended food of contact for this application.

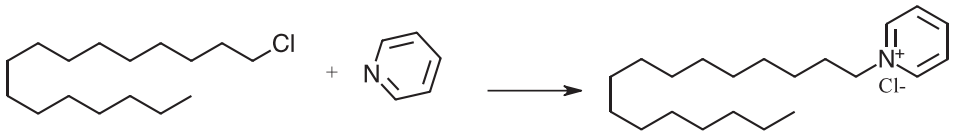
Cecure® is supplied as a solution of CPC dissolved in an aqueous solution with PG. PG acts as a wetting agent or humectant and also functions in the solution to maintain the solubility and stability of the Cecure® formulation. Cecure® is diluted to ≤ 1% in potable tap water for use as a decontaminant treatment for raw poultry carcasses and parts. Since the components

of Cecure® are not oxidants, or acidic in nature, Cecure® will not alter the structure or function of proteins, lipids, or carbohydrates in food treated with the processing aid.

A.4. Manufacturing Process

Cetylpyridinium chloride (CPC), the active ingredient in Cecure®, is manufactured by the addition reaction of pyridine and cetyl chloride resulting in the quarternized nitrogen compound. The typical manufacturing process uses a 10-30% molar excess of pyridine. The mixture is heated to ~100°C for 12-18 hours to complete the reaction. The reaction mixture is cooled to ~50°C and a solvent is added to induce crystallization of "crude" CPC. Typical solvents used for crystallization are ethanol, acetone, or 2-butanone. Crude CPC is isolated by filtration and subjected to a second crystallization to increase the purity to meet USP specifications. It is during this second crystallization that a small amount of water is added to form CPC monohydrate. CPC monohydrate crystallizes in a large crystal, thus improving filtration rate and purity. CPC monohydrate is dried under vacuum to remove residual solvents.

The source of water in the Cecure® formulation is from CPC monohydrate. The water composes 1-3% of the Cecure® formulation.



No allergens are used in the manufacturing process or produced in the CPC or commercial product (Cecure®) manufacturing facilities, therefore no carry-over of allergens is expected to occur at any point in the manufacturing of the processing aid.

A.5. Specification for identity and purity

CPC meets the specifications specified in the published monograph in the United States Pharmacopeial Convention (2014) Food chemicals codex.[13] Approved vendors for CPC Monohydrate used in the Cecure® formulation are Jubilant and Tatva. The USP monograph and Certificates of Analysis from each vendor are located in Appendix I.

Propylene glycol meets specifications specified in the published monograph in the U.S. Pharmacopeia Food chemicals codex.[14] There are no known allergens present in the processing aid preparation or in its packaging.

A.6. Analytical methods for detection

Analytical methods to detect residues of CPC and PG are based on HPLC and Gas Chromatography ("GC") respectively. The analytical methods and validation of the methods are described in detail in Annex B.

In summary, for the CPC analysis of a Cecure®-treated whole bird, the skin is removed and heated at 375ºF (190.6ºC). The CPC from the skin is then extracted with ethanol and resulting solution centrifuged to remove solids. The solids-free solution is analyzed by HPLC to determine CPC concentration. A series of calculations are used to determine residual CPC on the whole bird. A similar method is used for the analysis of CPC on Cecure-treated poultry parts. The detailed method for whole birds is located in Annex B.

Analysis for residual PG is performed in a similar manner with the exception being the raw skin is used for the analysis and the instrument used for analysis is GC. The detailed method can be found in Annex B.

B. INFORMATION RELATED TO THE SAFETY OF THE PROCESSING AID

B.1. General information on the industrial use of the chemical

CPC, the active ingredient in Cecure® antimicrobial solution, is a cationic quaternary ammonium compound found in many types and brands of worldwide, commercially available products such as mouthwash (Crest Pro-Health®, Scope®, Reach ACT®, Cepacol®, Viadent®, Oasis®, Dr. Fresh®, Swish®, BreathRX®, and BetaCell®); toothpaste (Crest Sensitivitiy® and Crest Plus Scope®); lozenges, throat sprays, and anti-snore throat sprays (Cepacol®, Breathe Right®, Rite Aid, CVS, Walgreens brand, Oasis®, BreathRX®, SinoFresh®, Ayr No-Drip Sinus®, and Septolete Plus); as well as baby teething gels (Anbesol, Calgel, Dentinox, Rinstead, and Woodward's) and baby wipes (Penaten lotion-filled baby wipes).

Cecure® is not a chlorine-based decontaminant and therefore can be used in situations where chlorine-based decontaminants are not permitted.

Cecure® is used in the poultry industry as a food processing aid to control the following microorganisms on raw poultry carcasses and poultry parts: *Salmonella*, *Campylobacter*, *Listeria*, *Staphylococcus aureus*, *Escherichia coli* (including 0157:H7), *Pseudomonas*, total coliforms, viruses, and other naturally occurring microorganisms on raw poultry carcasses (FDA, 1998; Breen *et al*., 1995 and 1997; Kim and Slavik, 1995; Pohlman *et al*., 2002).

B.2. General information on the use of the chemical as a food processing aid in other countries

Cecure® is approved for use as a food processing aid on poultry products in the U.S., by the U.S. Food and Drug Administration ("FDA") and by the United States Department of Agriculture/Food Safety Inspection Service ("USDA/FSIS"). Cecure® is also approved in other countries, including Canada, Mexico, Panama, Costa Rica, Colombia, Israel, Peru,

Russia, South Africa, Saudi Arabia, and Jordan. Table 2 below summarizes the countries and various food groups for which Cecure® is approved.

Table 2. Cecure® Decontaminant Approvals

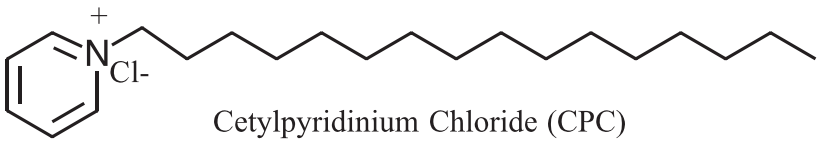
Country	Food Group(s) Approved
Argentina	Raw poultry applications
Canada	Raw poultry carcasses (and parts)
Colombia	All meat applications
Costa Rica	All food groups
Ecuador	All food groups
El Salvador	All food groups
Guatemala	All food groups
Israel	Raw poultry carcasses
Jordan	Raw poultry applications
Mexico	All meat applications
Panama	All food groups
Peru	All food groups
Russia	Raw poultry carcasses
Saudi Arabia	Raw poultry applications
South Africa	Raw poultry applications
U.A.E.	Raw poultry applications
Uruguay	Raw poultry applications
U.S.A.	Raw poultry carcasses and poultry parts

The Cecure® solution (≤ 1.0%) is used to treat the inner and outer surfaces of raw pre-chill, poultry carcasses after the last inside/outside bird washer ("IOBW") at ambient temperature. Optionally, Cecure® can be applied to post-chill (immersion or air-chilled), whole poultry carcasses or to poultry parts. For post-chill application of whole carcasses or parts, the temperature of the Cecure® solution will typically be lower than with a pre-chill application due to the colder temperature of the product being treated. Cecure® is typically applied using a spray cabinet that drenches the carcasses as they move on the shackle line. It can also be applied using a dip application depending on the point of application and the poultry products being treated. The Cecure® system captures and recycles the solution, so water usage

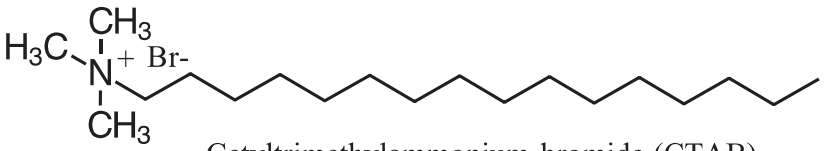
is not significantly affected by treatment volume. This provides processors with cost savings for both chemical and water usage.

B.3. Toxicokinetics and Metabolism of chemical processing aid

CPC. CPC is a quaternary ammonium compound (QAC) that is heterocyclic. When classified according to the four QAC clusters developed by EPA, CPC falls in *Group IV: Heterocyclic ammonium compounds*.[15] Literature studies on toxicokinetics and metabolism of this group were not readily available. However, studies of more commonly used QACs (groups I and II) used as preservatives in pharmaceutical uses, or as sanitizers, or in other industrial applications were more readily available. The compounds include benzyl alkonium, monoalkonium, and dialkonium quaternary salts. While these compounds have been extensively studied, most of their structures do not closely resemble CPC. However, Cetyltrimethylammonium bromide (CTAB), a straight-chain (monoalkomium quaternary salt) cationic surfactant classified in group I, shows some similarities to CPC. Figure 1 below shows the chemical structures of CPC and CTAB.



Cetylpyridinium Chloride (CPC)



Cetyltrimethylammonium bromide (CTAB)

Figure 1: Chemical structures of CPC and CTAB

When compared to CPC, both CTAB and CPC have the C-16 cetyl chain. The cation portion of the molecule has similar molecular weight with the CPC cation being 305 atomic mass units (AMU) and CTAB cation being 284 AMU, the difference being roughly two carbons in the non-cetyl part of the molecule. No other commercial quaternary ammonium salts, either benzyl, mono, or dialkonium, contain the C-16 alkyl chain.

Quaternary ammonium compounds consist of three main components: 1) four moieties covalently attached to nitrogen, 2) a quaternized nitrogen, and 3) a counter anion. Table 3 outlines the three components for CTAB and CPC.

Table 3. Components of CTAB and CPC

QAC Component	CTAB	CPC
Nitrogen moieties	3 methyl groups 1 cetyl group	1 pyridinyl 1 cetyl group
Quaternized nitrogen	Four moieties	Four moieties
Counter anion	Bromide	Chloride

Counter anion comparison – Both bromide in CTAB and chloride in CPC are halogen-based anions. The difference between bromide and chloride is size (molecular weight). The difference in size generally impacts the solubility of the QAC. The two halogen counter anions would not impact efficacy, toxicity, or metabolism of either CTAB or CPC.

Quaternized Nitrogen – The element of nitrogen is a common feature of all QACs. Regardless of physical or chemical properties, the nitrogen does not impact these properties for either CTAB or CPC.

Nitrogen Moieties – Nitrogen moieties are the most important aspects of structure activity relationships. Of the four nitrogen moieties, typically just one or two moieties is responsible for the activity of the compound. The remaining moieties that do not impart activity are used

to fine tune the physical properties of the compound. As these moieties are selected, economies are oftentimes a consideration. Thus, methyl and ethyl groups are often times selected to complete the set of four moieties.

In the case of CTAB and CPC, the moieties which mainly impacts functionality is the cetyl (C16) group. This moiety functions by penetrating the cell membrane of pathogens resulting in death by leakage.

Therefore, the difference in CTAB and CPC is the three methyl groups from CTAB and the pyridinyl group from CPC. The base nitrogen containing compounds are trimethylamine for CTAB and pyridine for CPC. The paragraphs below describe the metabolism of these two nitrogen-containing compounds.

Tezel reports in his 2009 Ph.D. dissertation that there are two potential routes for aerobic metabolism of CTAB[16]. One pathway is initiated with ω-hydroxylation on the terminal carbon. This begins β-oxidation of the C-16 side chain to produce eight units of the two-carbon acetate ion. Residual trimethylamine is demethylated to ammonia and three units of methanol.

A second pathway is α-hydroxylation on the carbon adjacent to the nitrogen moiety. Hydroxylation on this carbon leads to the breakage of the carbon-nitrogen bond, producing the aldehyde hexadecanal and trimethylamine. Hexadecanal is oxidized to Hexadecanoic acid, which then undergoes β-oxidation to produce eight units of the two-carbon acetate ion. Residual trimethylamine is demethylated to ammonia and three units of methanol.

In the case of CPC, pyridine would be the amine produced from carbon-nitrogen bond cleavage. Kaiser et.al. report that pyridine is metabolized by a reduction followed by oxidative ring cleavage between C2 and C3[17]. The intermediate is further metabolized to ammonia and dicarboxylic acids such as succinic or glutaric acid.

A toxicological evaluation of QACs by the Danish Veterinary and Food Administration included the review of a study of CTAB, showing poor intestinal absorption of QACs in rats.[18,19] In the CTAB study, rats received carbon 14-labeled (radioactive) hexadecyl trimethyl ammonium bromide (CTAB). After 8 hours of administering the dose, about 80% of the radioactivity was found in the gastrointestinal tract, and only small amounts were found in the blood plasma. After 12 hours, about 2% was excreted in the bile. The combination of high levels of radioactivity found in the gastrointestinal tract and the low levels found in the plasma and bile indicated poor intestinal absorption of CTAB. Within three days of ingestion, 92% of the radioactivity was excreted via the feces and 1% via urine.

Given the above observations, CPC is expected to be mostly excreted from the body in urine and feces without further breakdown.

Propylene Glycol (PG). When consumed, PG is rapidly metabolized in a manner similar to sugar, where it breaks down into lactic acid, which is excreted from the body in urine (Propylene Glycol Sector Group of Cefic, 2008)[20]. According to JECFA, PG is rapidly absorbed after oral administration and appears in the bloodstream.[21] In a dog study evaluated by the 1974 JECFA committee, a dose of 8mL/kg b.w. was administered to dogs, it took 24 hours for the PG to be completely eliminated from the blood stream.[22] The normal metabolic pathway for PG was shown to result in production of lactic acid. This determination, along with the results of long-term toxicity studies showing no adverse effects in dogs led to the JECFA's evaluation determining the estimated acceptable daily intake (ADI) for man to be 0 to 25 mg/kg b.w. EFSA's re-evaluation of PG (also known as propane-1,2-diol) in 2018 to evaluate its safety when used as a food additive concluded that there was no reason to revise the ADI from 25 mg/kg bw per day.[23]

B.4. Information on the toxicity of the chemical processing aid

CPC. Due to the long history (> 70 years) of safe use of CPC as a disinfectant in mouthwashes, toothpastes, throat sprays, throat lozenges, etc., numerous toxicity studies have been conducted on the compound over the years. Many of these reports have been published in the literature and include studies on acute toxicity, short-term toxicity, subchronic toxicity, genotoxicity, carcinogenicity, reproductive development toxicity, and pharmaceutical use. The Applicant has also commissioned several additional toxicity studies not publicly available in literature. The available historical toxicity data on CPC were submitted by the applicant to the U.S. FDA in a Food Additive Petition (FAP No. 2A4736) in 2002 to support the approval of Cecure® (CPC) as a processing aid. This information was used to determine that CPC is safe for use on poultry treated prior to the chiller location in the plant. This information has been incorporated into Tables 4 and 5 below and the full toxicology studies are provided in **Annexes C and D** to this application. An additional Food Additive Petition submission in 2006 (FAP 6A4767) provided additional toxicology and efficacy studies for expanded use of Cecure®(CPC) in treatments either prior to or after the chiller location. These studies are also provided in **Annexes C and D** to this application.

Published Toxicity Studies.

Previous evaluations of CPC have been as part of pharmaceutical formulations of oral hygiene products, therefore, most of the published toxicity studies include other ingredients in mixture with CPC, as shown in Table 4). However, several short-term and subchronic toxicity studies (summarized in Tables 4 and 5 below and provided in full in Annex C) have been conducted on aqueous CPC solutions. These studies include the 1942 study by Warren et. al.,

the 1995 report by Genco to the members of the Plaque Subcommittee of the FDA Dental Panel, and the 1969 study by Weeks and Rowe (USAEH-HT).

Short-term and subchronic toxicity. In the study by Warren et. al., oral doses of 1, 10 or 100 mg/kg bw/day CPC were administered to groups of rabbits over a period of 28 days. While temporary diarrhea was initially observed in the animals, no overall effect on body weight gain was reported, and there was no evidence of pathological changes. In addition, findings of histological examinations were concluded no to be toxicologically significant. In the 1995 report by Genco, CPC administered orally to dogs and rats at doses of 5 to 500 mg/kg bw/day showed morbidity and death at 125 mg/kg bw/day and above. At lower doses (50 mg/kg bw/day) gastric irritation was observed. The 90-day CPC feeding study by Weeks and Rowe (USAEH-HT, 1969) on six groups of rats administered at concentrations ranging from 0 to 10,000 mg/kg (or 1% CPC), showed no gross effects in organ weight at 125 ppm (or 6.25 mg/kg bw/day), and increased caecal weights were observed at 300ppm (15 mg/kg bw/day) and above in females and 800ppm (40 mg/kg bw/day) in males. No adverse effects on growth below 2000 ppm (equivalent to a dosage of 100 mg/kg bw/day) were reported. Unspecified changes in the liver and kidney were observed at the 100 mg/kg bw/day dose level. However, kidneys, lungs, liver, spleen, caecum and testis were observed to be microscopically normal at all dose levels.

Chronic toxicity and carcinogenicity. Two chronic toxicity studies are reported by Genco and BIBRA summarized a carcinogenicity study done on rats with CPC in vinyl copolymer. The BIBRA reports that the study is limited in its utility to assess carcinogenicity due to the small number of animals and tissue examined.

Reproductive and developmental toxicity and genotoxicity. Studies reproductive and developmental toxicity and genotoxicity for CPC-only solutions were not readily available in the literature. Table 4 presents studies in BIBRA and by Proctor and Gamble, which are done on CPC in combination with other ingredients. However, the applicant also commissioned studies that address genotoxicity, and several studies on short-term and subchronic toxicity. These studies are discussed in detail below.

Summary of Proprietary CPC Toxicology studies

Several short term and subchronic toxicity studies were commissioned by the applicant, namely, a 14-day palatability study, two 28-day toxicity feeding studies, and two 13-week toxicity feeding studies of CPC in rats and dogs. In addition, two genotoxicity studies were commissioned, namely, a bacterial reverse mutation test and an in-vitro chromosome aberration study in Chinese Hamster ovary cells.

Short-term and subchronic toxicity studies

In the 14-day study conducted in Sprague-Dawley rats, dietary CPC levels of 0, 100, 500, 1000, 1500 and 2000 ppm were administered daily orally through feed to six groups of 5 male and 5 female rats each (Redfield Laboratories, 2002). Daily observations were performed, and the body weights and feed consumption recorded every 2 to 3 days. The objective of this study was to determine the palatability of CPC by ingestion. Results showed thinness in one female from group 6 (2000 ppm), which corresponded with lower feed consumption. Dose-responsive decrease in body weight was also observed in males and females, with significant effect starting at group 4 (1000 ppm) in males, and group 5 (1500 ppm) in females. Changes in body weight were considered not an adverse effect if the reduction was within -10% of the control group. A No-Observable-Effect-Level (NOEL) of 100 ppm CPC in the diet, and a No-

Observable-Adverse-Effect-Level (NOAEL) of 500ppm CPC in the diet was established from this study.

In a 28-day study conducted in Sprague-Dawley rats, dietary CPC levels of 0, 125, 250, 375, 500, 750 and 1000 ppm were administered daily orally through feed to seven groups of 10 male and 10 female rats each (Redfield Laboratories, 2002). Daily observations were made, and the body weights and feed consumption measured weekly. In addition, hematology, clinical chemistry, and urinalysis parameters were evaluated at termination of the study. All animals were subjected to gross necropsy. Specified tissues were also analyzed microscopically. The objective of this study was to determine the potential adverse effects of ingesting CPC in the diet, and in growth and organ development. Results showed dose-responsive decrease in body weight in males and females throughout the study, with significantly lower values observed in Group 6 (750 ppm) and 7(1000 ppm) when compared to the control group. A corresponding feed consumption decrease in these groups was considered dose responsive. No clinical observations were considered test article (CPC)-related, and necropsy revealed no findings that were CPC-related. No other parameters were affected by exposure to the test article. A No-Observable-Effect-Level (NOEL) of 250 ppm CPC in the diet, and a No-Observable-Adverse-Effect-Level (NOAEL) of 1000ppm CPC in the diet was established from this study.

The second 28-day study was conducted in Beagle dogs, with the objective of determining the palatability and potential adverse effects of administering CPC in the diet to the dogs for 28 days (Charles River Laboratories, 2006). The results would be used to determine the dosage for a 13-week study following this study. The dietary CPC levels administered daily in the feed to five groups of 1 male and 1 female dog each were 0, 250, 500, 1000 and 1500 ppm.

Clinical observations, and measurements of body weight, feed consumption, hematology, clinical chemistry, coagulation, and urinalysis parameters were recorded and evaluated. All animals were subjected to gross necropsy on day 29. Organ weights were recorded, and histopathology was performed on all tissues from all the animals in groups 1 and 5, and the kidneys from all animals in groups 2 to 4. Results showed no early deaths. There was an increase in abnormal stool (soft and watery) in both males and females, but it was unclear whether this observation was a CPC-related effect. No other clinical observation was considered test-article related. A decrease in body weight was observed in males and females in group 5 (1500 ppm) from Study Day 8 to 28. The feed consumption was consistently less in both males and females in this group throughout the study, and the report suggests it may be more related to palatability than the effect of the test article itself. No changes were observed in hematology, coagulation, or urinalysis evaluation. A significant increase in Alanine aminotransferase (ALT) above the normal testing facility ranges (17 to 51 U/L) was noted in both males and females in group 4 (1000ppm) and females in group 5 (1500 ppm) on Day 29. However, the change was not considered adverse due to the fact that no histopathological lesion was associated with this change. The No-Observable-Effect-Level (NOEL) for this study was 500 ppm, while No-Observable-Adverse-Effect-Level (NOAEL) was 1000ppm CPC in the diet.

The 13-week toxicity feeding study on Beagle dogs was performed to determine potential adverse effects of ingested CPC in the dogs after 13 weeks of administration in the diet (Charles River Laboratories, 2006). As mentioned previously, the corresponding 28-day study on Beagle dogs was used to determine the dosage level for this study. The dosage levels for the five groups of 4 males and 4 females each were 0, 250, 375, 500, and 1000/500ppm. Clinical

observations, and measurements of body weight, feed consumption, physical, ophthalmology, cardiology, and neurological exams, and clinical pathology evaluations were performed. Post-mortem exams included organ weights, macroscopic and microscopic evaluations. Results showed thinness in the males in groups 3 to 5 (375-1000 ppm), and in females in group 5 (1000 ppm). Mean body weights decreased for group 5 males from day 8 to 36, which corresponded to a decrease in feed consumption in the high-dose males during the first month of administration. Due to the observed decrease in feed consumption, the study was modified by stopping the administration of the test-article from days 29 to 42 in males and days 29 to 41 in females, and after the dosing holiday, the dose was adjusted to 500 ppm. After this change, the body weights of the males and females were no longer statistically different from controls, except on Day 78 (for males). Other body weight effects observed were not considered statistically significant or were sporadic. Changes (decrease) in red blood cells, hemoglobin, and hematocrit counts in groups 4 (500 ppm) and 5 (1000 ppm) males were small and therefore not considered adverse. No toxicologically significant changes were observed in serum chemistry and urinalysis. All animals had normal physical exams and no neurological or ophthalmic changes were considered test article-related. Although cardiology changes were statistically significant, none of them were dose-related or considered toxicologically significant. No evidence of histopathology or immunotoxicity was observed due to the test article. The No-Observable-Effect-Level (NOEL) for this study was 250 ppm, while No-Observable-Adverse-Effect-Level (NOAEL) was 375 ppm CPC in the diet.

The second 13-week toxicity feeding study was performed on Sprague-Dawley rats to determine potential adverse effects of ingested CPC in the rats after 13 weeks of administration in the diet (Charles River Laboratories, 2006). Five groups of 20 males and 20 females each

received daily doses 0, 125, 250, 500, and 1000 ppm CPC over 91 consecutive days. Clinical observations, and measurements of body weight, feed consumption, ophthalmology, neurology, hematology, coagulation, clinical chemistry, and urinalysis were performed. Complete necropsy was performed on day 92, and organ weights and histopathology of all tissues of all animals and all gross lesions were recorded. Results showed one early death of a male in group 3 (250 ppm) on day 66. The probable cause of death was determined to be inflammation of the heart, and therefore not test article-related. No clinical observations were considered test article-related in all other animals. The mean body weight in males in group 5 (1000 ppm) decreased significant from day 8, and in females from day 22. Feed consumption also decreased significantly for group 5 males and females throughout the study. It was not clear if this was due to the test article itself or palatability issues. No changes in ophthalmology, neurological functions, or urinalysis were noted, and no gross lesions were recorded at necropsy. There were also no microscopic findings related to the test article. Intermittent changes in clinical pathology were not considered biologically significant or adverse, and there were no clinically adverse observations. The No-Observable-Effect-Level (NOEL) for this study was 250 ppm, while No-Observable-Adverse-Effect-Level (NOAEL) was 1000 ppm CPC in the diet.

Genotoxicity Studies

A bacterial reverse mutation test using Cecure® (CPC) was performed to evaluate the test article for the ability to induce mutations, therefore determining the mutagenic potential either in presence or absence of exogenous metabolic activation systems (Next Century Inc., 2002). The increase in base pair mutations due to the test article can be detected by the ability of the test article to restore functional capability to bacteria to synthesize an essential amino acid.

Revertant bacteria are characterized by their ability to grow in the absence of the amino acid originally required by the parent tester strain. In bacterial reverse mutation tests, a combination of Salmonella and E. coli tester strains with several genetically engineered features that make them more selective for detection of mutations are used. In this study, Cecure® solution was tested in the Salmonella typhimurium strains TA1535, TA97a, TA98, TA100 and with Escherichia coli WP2 uvrA pKM101 in a plate incorporation assay, with and without metabolic activation by Aroclor®-induced rat liver S9 at the following concentrations: 5, 10, 50, 100, 500, 1000, 2500 and 5000 µg per plate. Deionized water was used as solvent. Based on the toxicity observed in the first trial, in the repeat test the following concentrations were evaluated: 5, 10, 50, 100 and 500 µg per plate without S9; 100, 500, 1000, 2500, 5000 µg per plate with S9. In both trials, all concentrations were tested in triplicate. Treatment with Cecure® was toxic in the absence of S9 at concentrations 1000 µg per plate. No treatment related increase of revertant colonies was observed with or without S9 in any tester strain. Based on the study findings, the test article, Cecure® was concluded to be negative for the induction of mutagenicity in the bacterial reverse mutation test.

An in-vitro chromosome aberration test in Chinese hamster ovary (CHO) cells was performed to evaluate the ability of the test substance (Cecure®) to induce structural chromosomal aberration in CHO cells (Next Century Inc., 2001). CHO cells are determined to be a sensitive indicator of in-vitro induced chromosomal damage. In this study, Cecure® was evaluated in the presence and absence of a metabolic activation system (Aroclor®- induced rat liver S9), and a minimum of 5 concentrations levels were tested in duplicate treatments. Deionized ultra-filtered water was used as the test article solvent, diluent, and negative control. Concentrations of 0.1, 0.5, 1.0, 2.5 and 5.0 mg/L were used in the first trial and were compared

to negative controls. Concentrations of 0.025, 0.05, 0.10, 0.25, and 0.5 mg/L in the absence of metabolic activation system and 0.05, 0.1, 0.25, 0.5, and 1.0 mg/L in the presence of metabolic activation system were tested in comparison to negative controls. Results showed that higher doses resulted in excessive toxicity, assessed as percent confluence. In both experiments, treatment with Cecure® did not increase the frequency of aberrant cells or structural chromosomal aberrations.

Table 4. Published Toxicology studies on CPC (provided in full in Annex C).

Year of Study	Subject of Study	Testing Party or Author of Referenced Citation	Nature of Study	Results of Study (LD_{50} expressed in mg/kg b.w.) (NOEL and NOAEL expressed in mg/kg)
1942	CPC (2.5%)	Warren *et al*.	Acute Toxicity Rabbit	LD_{50} 400
1942	CPC (2.5%)	Warren *et al*.	28-day Oral Administration Study of CPC in Rabbits – (up to 10 to 100 mg/kg b.w.)	No gross pathological changes
1946	CPC (2.5 - 450 mg/kg)	Nelson and Lyster	Acute Toxicity Rat	LD_{50} 200
1955	CPC (0.001% CPC in mixture; 0.001% CPC solution,0.002% CPC solution)	Smith and Lofty	Effects of CPC on growth and chromosomal changes in meristems grown in the presence of CPC	Chromosomal abberations observed in Vicia faba (bean)
1965	CPC	Rosen *et al*.	Acute Toxicity Male Rat Female Mouse	LD_{50} 428 LD_{50} 195
1965	CPC in Cepa-Tuss Troches (1:1500 CPC per troche)	Wm. S. Merrell Company (Scientific Laboratories)	Sub-acute (1 month) Toxicity study in dogs, oral administration of a single dose given as three individual doses in 8-hr day	No significant effect related to treatment was reported. Occasional vomiting and some salivation in high dose group observed.
1969	CPC in Cepacol gargle (0.05% CPC as active ingredient)	Wm. S. Merrell Company (Scientific Laboratories)	Single daily doses for 30 days administered to dogs and rats (up to 10ml/kg bw/day)	Salivation and occasionally vomiting observed in dogs, formulation considered non-toxic to dogs; Mild respiratory disease observed in some rats,

Year of Study	Subject of Study	Testing Party or Author of Referenced Citation	Nature of Study	Results of Study (LD_{50} expressed in mg/kg b.w.) (NOEL and NOAEL expressed in mg/kg)
				formulation considered non-toxic to rats.
1972	CPC (0.05 mg CPC in Cepacaine	Wm. S. Merrell Company (Richardson-Merrell S.p.A (Italy)	30-day Toxicity Study in Male and Female Wistar-Morini albino rats (up to 10 ml/kg bw/day)	Rats tolerated all the doses upto 10 ml/kg bw/day well in both solution and spray form
1970	CPC (0.01-1%)	Weeks and Rowe (cited in BIBRA)	90-day Toxicity Feeding Study of CPC in Male and Female Rats (up to 1000 mg/kg)	NOEL= 800 (M); 300 (F) NOAEL= 2000 (M and F)
1970	CPC in vinyl-Copolymer (7 or 35 mg/kg b.w./day)	Villa *et al*. (cited in BIBRA)	1 Year Feeding Study in Male and Female Rats (up to 35 mg/kg b.w.)	No evidence of carcinogenicity
1970	CPC in vinyl-copolymer (7 or 35 mg/kg b.w./day)	Villa *et al*. (cited in BIBRA)	Feeding Study in Female Rats 3 Months Prior to Mating and Throughout Gestation and Lactation (up to 35 mg/kg b.w.); Repeated in 2nd and 3rd Generations	Fertility and incidence of malformations within normal limits in each generation
1979	CPC (27.33 mg/kg b.w./day)	Gilman and DeSalva	Rat Teratology Study for Days 6 to 15 of Gestation (up to 68 mg/kg b.w.)	27.33 mg/kg b.w. resulted in lower body weight; no skeletal deformity
1979	CPC (0.045%) in Scope mouthwash; CPC in combination with Domiphen bromide	Proctor & Gamble	Subchronic Oral Toxicity Studies on Rabbits (reference to Warren, 1942 study); and Teratology Studies on Rabbits from Day 7 to Day 18 of Gestation	Female foetal weights lower in high-dose CPC groups than controls. No foetal skeletal or soft tissue abnormalities observed. Therefore, non-effect dose for developmental effects

Year of Study	Subject of Study	Testing Party or Author of Referenced Citation	Nature of Study	Results of Study (LD_{50} expressed in mg/kg b.w.) (NOEL and NOAEL expressed in mg/kg)
				determined to be 25 mg/kg bw/day
1979	CPC (0.5%)	Yamaguchi and Yamashita	Ames Test	Not mutagenic to *Salmonella typhimurium*
1986	CPC in cationic detergents	Arena and Drew	Fatal dose by ingestion in humans	1 to 3 grams
1995	CPC (200-500 mg/kg)	Zeeland Chemicals	Acute Toxicity Male Rat Female Rat	 LD_{50} 460 LD_{50} 335
1995	CPC (5 to 500mg/kg, in mouthwash)	Genco	Subchronic Toxicity in Rats and Dogs of CPC administered orally at dose levels between 5 to 500 mg/kg	Morbidity and death observed at 125, 250, and 500 mg/kg. Gastric irritation observed at lower doses (50 mg/kg per day and higher)
1996	CPC (100%, monohydrate)	Lewis	Acute Toxicity ipr-Rat ipr-Mouse ivn-Dog orl-Rabbit ipr-Rabbit scu-Rabbit ivn-Rabbit ipr-Guinea Pig	 LD_{LO} 15 LD_{LO} 3 LD_{LO} 100 LD_{LO} 400 LD_{LO} 5 LD_{LO} 200 LD_{LO} 20 LD_{LO} 5

Year of Study	Subject of Study	Testing Party or Author of Referenced Citation	Nature of Study	Results of Study (LD_{50} expressed in mg/kg b.w.) (NOEL and NOAEL expressed in mg/kg)
1999	2% CPC in repro- graphic toner product	Lin	Bacterial Reversion (Ames Test); Mouse Lymphoma Assay; Sister Chromatid Exchange Assay in Chinese Hamster Ovary; *In vitro* BALB/3T3 Cell Transformation Assay; Inhalation by Pregnant Rats	CPC was Inactive in all assays; no mutagenic or teratogenic response in urine, feces, or bone marrow of animals in subchronic inhalation studies (1.2 g/m^3)
2003	CPC (0.045-1%)	U.S. FDA (21 CFR 356)	Ingredient in Mouthwash Products for Human Use	0.045 to 0.1% with minimally 72 to 77% chemically available CPC is safe
2007	CPC (0.05% in Cepacol mouthwash product)	Rodrigues et. al.	Genotoxicity of mouthwash on *Drosophila melanogaster* using the wing-spot test	Genotoxic responses observed in 75-100% Cepacol® attributed to ethanol content in mouthwash. Pure CPC at the same concentration showed no genotoxic response

NOEL = no observed effect level; NOAEL = no observable adverse effect level; mg/kg b.w. = milligrams per kilogram of body weight; mg/kg = milligrams per kilogram; g/m^3 = grams per cubic meter; U.S. FDA = United States Food and Drug Administration.

Table 5. Proprietary CPC toxicology studies commissioned by Safe Foods Corporation (provided in full in Annex D).

Year of Study	Subject of Study	Testing Party or Author of Referenced Citation	Nature of Study	Results of Study (LD_{50} expressed in mg/kg b.w.) (NOEL and NOAEL expressed in ppm)
2002	Cecure® (1% CPC in PG and water)	Next Century Incorporated Project Number 01-08-001.	Bacterial Reverse Mutation Test: Plate Incorporation and Preincubation Method for Liquids	No evidence of mutagenic activity
2001	CPC (1% CPC in PG and water)	Next Century Incorporated Project Number 01-08-002.	*In vitro* Chromosome Aberration in Chinese Hamster Ovary Cells for Liquids	No clastogenic activity detected
2002	CPC (100-2000 ppm in diet)	Redfield Laboratories Study Number 161-002.	14-day Palatability Study of CPC in Sprague-Dawley Rats (up to 500 ppm CPC)	NOEL = 100 NOAEL = 500
2002	CPC (125-1000 ppm in diet)	Redfield Laboratories Study Number 161-001.	28-day Toxicity Feeding Study of CPC in Sprague-Dawley Rats (up to 1000 ppm CPC)	NOEL = 250 NOAEL = 1000
2006	CPC (250-1500 ppm in diet)	Charles River Laboratories Study Number LFE00004.	28-day Toxicity Feeding Study of CPC in Beagle Dogs (up to 1500 ppm CPC)	NOEL = 500 NOAEL = 1000
2006	CPC (125-1000 ppm in diet)	Charles River Laboratories Study Number LFE00001.	13-Week Toxicity Feeding Study of CPC in Sprague-Dawley Rats (up to 1000 ppm)	NOEL = 250 NOAEL = 1000
2006	CPC (250-1000 ppm in diet)	Charles River Laboratories Study Number LFE00002.	13-Week Toxicity Feeding Study of CPC in Beagle Dogs (up to 1000 ppm)	NOEL = 250 NOAEL = 375

NOEL = no effect level; NOAEL = no observable adverse effect level; mg/kg b.w. = milligrams per kilogram of body weight, ppm = parts per million; g/m^3 = grams per cubic meter; U.S. FDA = United States Food and Drug Administration.

A large amount of toxicity data has been submitted regarding CPC. Based on the entirety of the genotoxicity testing conducted by Safe Foods Corporation, in addition to the testing in the literature, CPC has no significant potential for genotoxic activity. The 2006 subchronic feeding studies in rats and dogs indicate a NOAEL of at least 375 mg/kg in the diet for both species. If a 1000-fold safety factor is applied to this value, an allowable dietary concentration of 0.375 mg/kg (375 μg/kg) in the diet may be calculated.

B.5. Safety assessment report by other national or supranational agencies responsible for food safety.

Safe Foods submitted a dossier to the European Commission and received a favorable opinion from the European Food Safety Authority (EFSA) regarding the safety of Cecure® for human consumption. In the published 2012 Scientific Opinion of EFSA, the Agency found that, "… there are no safety concerns for humans from the proposed use of Cecure®…" and "… both Cecure® and CPC were found to be efficacious in reducing contamination with pathogenic organisms on fresh broiler carcasses." [24]

As noted in Section B.2 above, Cecure® has undergone rigorous reviews by other food safety agencies, including the U.S. FDA, Russian Ministry of Health, and Health Canada, and received approval for its safe use as a processing aid on poultry products. Documentation of these agencies' assessments or regulations approving the use of Cecure® (or their translations into English where needed) are provided in Annex E to this application.

F. Information related to the dietary exposure of the processing aid.

F.1. A list of foods likely to contain the processing aid

The applicant's requested use of Cecure® antimicrobial solution is for use on poultry carcasses and parts during processing at the poultry processing facilities. Therefore, foods expected to contain residues of the processing aid are poultry products only.

A very small percentage of poultry offal is considered edible, namely the heart, gizzard and liver. However, due to how Cecure® is typically applied, either immediately after the inside/outside bird washer (IOBW) for pre-chiller applications, or following the immersion or air chiller for post-chiller applications, the edible offal is already removed from the bird at this point, and is therefore not expected to be in contact with the Cecure® solution. The only surface that comes into contact with Cecure® within the cavity is therefore the frame of the bird. While the bird cavity does not contain skin, it contains residual fats and the skeletal frame to protect breast and back meat from residual CPC.

F.2. Levels of residues of the processing aid for each food

Testing conducted by the Applicant (described in U.S. Food Additive Petition (FAP) 6A4767, and submitted as residue studies in **Annex B**), demonstrates that only a very small amount of the CPC used to treat the carcass actually ends up on the skin of the carcass. Several studies were conducted to determine the average residues found on poultry carcasses at different Cecure® concentrations, and the results of these studies is summarized in Table 6 below. On average, at 1% CPC concentration, the corresponding residue level on a poultry carcass was 12.4 mg/kg.

However, the "worst case" CPC residue on poultry carcasses treated with 1.0% CPC was determined to be 13.4 mg/kg using numerous studies and a prediction equation found in Figure 2 below. On this basis, using the skin weight as a fraction of carcass weight, the overall average

concentration of CPC per gram of poultry that is consumed with the skin on will be 8.8% (this represents the average percentage of skin on a typical broiler with a live weight of 2.44 kg) of 13.4 mg/kg, or **1.2 mg/kg.** This is the residue value (1.2 mg/kg) that will be used in dietary exposure calculations.

To determine how much residual CPC would be expected on the cavity of the bird during the spray treatment of the birds, a linear relationship between the internal and external application residues was assumed. The expected "worst case" residue on the carcass (external surface) as described above is expected to be 13.4 mg/kg. The volume of the Cecure® solution typically sprayed onto a carcass is estimated to be 0.25 gallons (946 ml), at an average concentration of 0.5% CPC. Most of the solution sprayed (based on number of nozzles and spray rate) is sprayed on the external surface, while an estimated 25ml (2.6% of the total volume) would be sprayed on the cavity. Using the linear relationship in residues between the outer and inner surfaces, while keeping the concentration constant, the estimated residue expected on the cavity surface was determined to be 0.35mg/kg (13.4 mg/kg x 0.026).

Dietary Exposure Calculation

The per-capita consumption of poultry in Australia is 2.015 g poultry/kg b.w./day[1], while New Zealand's is 1.798 g poultry/kg b.w./day[2] (OECD Data, 2018).[25] These per-capita consumption value assumes that all consumers consume poultry with the skin-on, and are therefore the worst-case figures. Based on the above per-capita consumption values, the

[1](44.13 kg per capita ÷ 60 kg b.w. x 1000g /kg) ÷ 365 days per year = 2.015 g poultry/ kg b.w. /day.

[2] (39.4 kg per capita ÷ 60 kg b.w. x 1000g /kg) ÷ 365 days per year = 1.799 g poultry/kg b.w. /day.

estimated daily intake (EDI) values of CPC for the Australian and New Zealand consumer of poultry are calculated separately as follows:

$EDI_{Australia}$= (2.015 g poultry/kg b.w./day) x (1.2×10^{-6} g CPC/g poultry)

= 2.418×10^{-6} g CPC/ kg b.w./day, or 2.418 µg/ kg b.w./day

= 0.00242 mg/ kg b.w./day

Similarly,

EDI_{NZ}= (1.799 g poultry kg b.w.//day) x (1.2×10^{-6} g CPC/g poultry)

= 2.159×10^{-6} g CPC/ kg b.w./day, or 2.159 µg/ kg b.w./day

= 0.00216 mg/ kg b.w./day

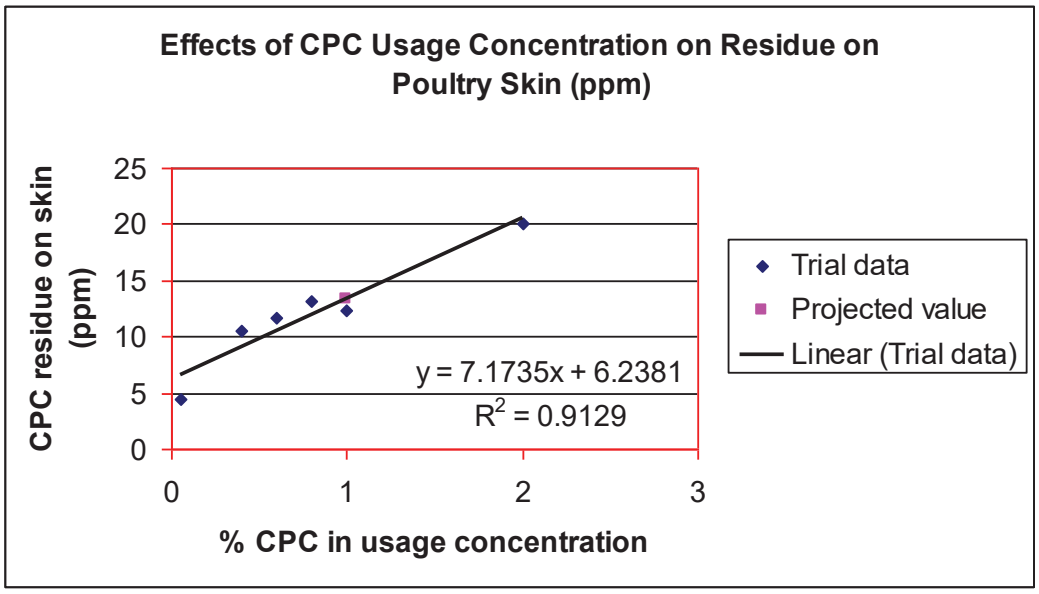
The above figures are well below the allowable dietary concentration of 375 µg/kg, which applies a 1000-fold safety factor to the NOAEL value determined in sub-chronic feeding studies of CPC summarized in Table 4 above. In addition, the higher EDI value of 2.418 µg/ kg b.w./day (or 0.00242 mg/ kg b.w./day) is well below the Acceptable Daily Intake (ADI) of 0.48 mg/p/d (or 480 µg/p/d) established by the FDA by taking into account the toxicity studies in Table 5.[26]

Table 6. Average CPC Residue Relative to CPC Concentration In the Treatment Solution

CPC Concentration in Treatment Solution (%)	Overall Average Residue on Poultry Skin (mg/kg)
0.05	4.39
0.4	10.53[3]
0.6	11.63
0.8	13.24
1.0	12.40
2.0	20.03

mg/kg = milligrams per kilogram.

Figure 2. Effects of CPC Usage Concentration on Residue on Poultry Skin



[3]The measured residue level for the 0.4% CPC treatment solution concentration, Study No. MCA-060407 (full report included in Annex B) has been excluded from the mean residue value. The results from this experiment were anomalous and do not appear to be representative of actual CPC residues for this treatment concentration, based on the entirety of the data.

F.3. Likely level of consumption of foods

As described in section F.2 above, the per capita poultry consumption of Australia and New Zealand, (OECD Data, 2018) was used as the likely level of poultry consumption in each country, as this gives a worst-case consumption estimate that assumes the whole population consumes poultry. The 2018 per capita poultry consumption in Australia was 44.13 kg, while that is New Zealand was 39.4 kg. This equates to daily consumption levels of 120.9 g/person and 107.9 g/person, in Australia and New Zealand respectively.

F.4. Percentage of food groups in which processing aid is likely to be found or percentage of market likely to use the processing aid

The processing aid is only expected to be found in poultry products, for which consumption values are as described in section F.3 above. If the processing aid was used in the largest poultry company in the region, the market share would be 40% of the market in Australia, and approximately 34% of the market in New Zealand.[27]

F.5. Information relating to the levels of residues in food in other countries

As stated in section F.2 above, Testing conducted by the Applicant (described in U.S. FAP 6A4767, included in Annex B), demonstrates that only a very small amount of the CPC used to treat the carcass actually ends up on the skin of the carcass. On average, after treatment with 1% CPC concentration, the corresponding residue level expected on the skin of the carcass was determined to be 1.2 mg/kg.

F.6. Information on likely current food consumption

Consumption of chicken and pork in Australia have continued to increase steadily over the last 40 years, while a steady decline has been observed in consumption of beef and sheep meat. Per capita chicken consumption in particular has increased sharply (by 149%) from 19 kg in 1980

to 47.4kg in 2018/2019.[28] Similarly, chicken is the highest consumed meat in New Zealand, at 37.5 kg/person, while total poultry (chicken, turkey and duck meat) per capita consumption averages 39 kg/person.[29] Chicken is now the largest consumed meat in Australia, New Zealand, and other countries as consumers have become more health conscious and reduced their intake of red meats in favor of white meats and other meat alternatives.

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Appendix I:

FCC Monograph for CPC

• **SODIUM**
Analysis: From the weight of the sample taken and the number of mL of 0.1 N perchloric acid consumed in the determination of *Degree of Substitution*, calculate the percent of sodium. Each mL of 0.1 N perchloric acid is equivalent to 2.299 mg of sodium (Na).
Acceptance criteria: NMT 12.4% on the dried basis

Add the following:

▪Cetylpyridinium Chloride

First Published: First Supplement, FCC 9

Pyridinium, 1-Hexadecyl-, Chloride, Monohydrate
1-Hexadecylpyridinium Chloride, Monohydrate

$C_{21}H_{38}ClN \cdot H_2O$ 358.00
CAS: [6004-24-6] (monohydrate)
[123-03-5] (anhydrous)

UNII: D9OM4SK49P [cetylpyridinium chloride]

DESCRIPTION

Cetylpyridinium Chloride occurs as a white powder. It is freely soluble in water, ethanol, and chloroform, but it is insoluble in diethyl ether.
Function: Antimicrobial agent
Packaging and Storage: Store in well-closed containers.

IDENTIFICATION

• **INFRARED ABSORPTION,** *Spectrophotometric Identification Tests,* Appendix IIIC
Reference standard: USP Cetylpyridinium Chloride RS
Sample and standard preparation: *K*
Acceptance criteria: The spectrum of the sample exhibits maxima at the same wavelengths as those in the spectrum of the *Reference standard.* [NOTE—This acceptance criteria is specific to the monohydrate form.]
• **HPLC PEAK IDENTITY**
Acceptance criteria: The retention time of the major peak of the *Sample solution* corresponds to that of cetylpyridinium chloride, as obtained in the test for *Pyridine.*
• **CHLORIDE,** Appendix IIIA
Sample solution: 2 mg/mL
Analysis: Test a 10-mL volume of the *Sample solution.*
Acceptance criteria: Meets the requirements, except that when silver nitrate TS is added, turbidity is produced rather than a curdy white precipitate.

ASSAY

• **PROCEDURE**
Sample solution: Transfer 200 mg of the sample to a suitable vessel containing 75 mL of water. Add 10 mL of chloroform, 0.4 mL of bromophenol blue solution (500 µg/mL), and 5 mL of a freshly prepared solution of sodium bicarbonate (4.2 mg/mL).
Analysis: Titrate the *Sample solution* with 0.02 M sodium tetraphenylborate VS until the blue color disappears from the chloroform layer. Add the last portions of the 0.02 M sodium tetraphenylborate VS dropwise, agitating vigorously after each addition. Each mL of 0.02 M sodium tetraphenylborate VS is equivalent to 6.800 mg of $C_{21}H_{38}ClN$.
Acceptance criteria: 99.0%–102.0% of $C_{21}H_{38}ClN$, calculated on the anhydrous basis

IMPURITIES

Inorganic Impurities
• **LEAD,** *Lead Limit Test, Flame Atomic Absorption Spectrophotometric Method,* Appendix IIIB
Acceptance criteria: NMT 2 mg/kg
Organic Impurities
• **RESIDUAL SOLVENTS**
Standard stock solution: 1.25 mg/mL ethyl acetate, 1.25 mg/mL methyl ethyl ketone, and 1.25 mg/mL ethyl acetate in dimethyl sulfoxide (DMSO)
Blank: Transfer 2.0 mL of DMSO into a headspace vial, and cap tightly.
Standard solution: Transfer 2.0 mL of the *Standard stock solution* into a headspace vial. Crimp a cap with a teflon seal tightly onto the vial, and mix the solution well.
Sample solution: Transfer 500 mg of the sample into a headspace vial, and add 2.0 mL of DMSO. Crimp a cap with a teflon seal tightly onto the vial, and mix the solution well.
Chromatographic system, Appendix IIA
Mode: Gas chromatography equipped with a headspace analyzer
Detector: Flame ionization
Column: 30-m × 0.32-mm (id) mid-polarity capillary column with 14% cyanopropylphenyl-86% methylpolysiloxane stationary phase and a 1-µm film thickness[1]
Column temperature: See the temperature program table below.

Temperature (°)	Rate (°/min)	Hold Time (min)
45	—	5
45→70	10	—
70→220	20	5

GC Conditions
Temperatures
Injection port: 220°
Detector: 280°
Carrier gas: He/N_2
Flow rate: 1.5 mL/min
Split ratio: 5:1
Make up flow with nitrogen: 20 mL/min
Incubation: 85° for 25 min
Injection syringe: Heated, gas-tight, 90°
Headspace conditions

[1] RTX-1701 capillary column (Restek Cat. No. 12054, Bellefonte, PA, USA), or equivalent.

Temperatures
Oven: 85°
Loop: 90°
Transfer line: 95°
Vial shaking: Low
Vial equilibration time: 25 min
Pressurization time: 1.0 min
Loop filling time: 0.5 min
Loop equilibration time: 1.0 min
Injection time: 1.0 min
Transfer line pressure: 15 psi
Vial pressure: 15 psi
System suitability
Sample: *Standard solution*
Suitability requirement 1: The resolution, R, between ethyl acetate and methyl ethyl ketone is NLT 2.0.
Suitability requirement 2: The relative standard deviation of the individual peak responses for acetone, ethyl acetate, and methyl ethyl ketone from replicate injections is NMT 10%.
Suitability requirement 3: The number of theoretical plates for the acetone peak is NLT 10,000.
Analysis: [NOTE—Condition the column at 220° for 30 min. Allow GC to equilibrate at 45° and obtain steady baseline before beginning analysis.] Separately inject equal volumes of the *Blank*, *Standard solution*, and *Sample solution*, record the chromatograms, and measure the peak responses. [NOTE—The approximate retention times for acetone, methyl ethyl ketone, and ethyl acetate are 3.8 min, 5.9 min, and 6.1 min, respectively. The approximate retention time for DMSO (diluent solvent) is 12.5 min.] Determine the concentration (mg/kg) of each analyte (acetone, methyl ethyl ketone, and ethyl aceate) in the portion of the sample taken:

$$\text{Result} = [(A_U \times C_S)/(A_S \times C_U)] \times F$$

A_U = peak area of the analyte from the *Sample solution*
C_S = weight of the analyte in the *Standard solution* (mg)
A_S = peak area of the analyte from the *Standard solution*
C_U = weight of the sample in the *Sample solution* (mg)
F = conversion factor to convert from mg/mg to mg/kg, 1×10^6

Acceptance criteria
Acetone: 200 mg/kg
Ethyl acetate: 5000 mg/kg
Methyl ethyl ketone: 600 mg/kg

- **PYRIDINE**

Buffer: 0.01 M potassium dihydrogen phosphate (KH_2PO_4) in degassed water, adjusted with phosphoric acid to a pH of 3.0
Diluent: Acetonitrile and water, 65:35 (v/v)
Mobile phase: Acetonitrile and *Buffer*, 65:35 (v/v)
Standard stock solution: 0.1 mg/mL of pyridine and 100 mg/mL USP Cetylpyridinium Chloride RS in *Diluent*
Standard solution: 1 µg/mL of pyridine and 1000 µg/mL USP Cetylpyridinium Chloride RS, prepared by diluting 1 mL of *Standard stock solution* to 100 mL with *Diluent*
Sample solution: 5000 µg/mL in *Diluent*
Chromatographic system, Appendix IIA
Mode: High-performance liquid chromatography
Detector: UV 254 nm
Column: 25-cm × 4.6-mm; packed with 5-µm C18 silica gel[2]
Column temperature: 30°
Flow rate: 1.0 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirement 1: The relative standard deviation of the pyridine peak responses from replicate injections is NMT 2.0%.
Suitability requirement 2: The resolution, R, between the pyridine peak and all other peaks is NLT 2.0.
Analysis: Equilibrate the system to obtain a steady baseline (typically at least 30 min). Separately inject equal volumes of the *Standard solution* and *Sample solution* into the chromatograph, and measure the responses for the major peaks on the resulting chromatograms. [NOTE—The approximate retention times for pyridine and cetylpyridinium chloride are 2.4 min and 4.5 min, respectively.] Calculate the percentage of pyridine in the sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of pyridine from the *Sample solution*
r_S = peak area of pyridine from the *Standard solution*
C_S = concentration of pyridine in the *Standard solution* (µg/mL)
C_U = concentration of the sample in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 0.012%

SPECIFIC TESTS

- **ACIDITY**

Analysis: Dissolve 500 mg of the sample in 50 mL of water, add several drops of phenolphthalein TS, and titrate with 0.020 N sodium hydroxide.
Acceptance criteria: NMT 2.5 mL of titrant is required for neutralization.

- **MELTING RANGE OR TEMPERATURE DETERMINATION,** *Procedure for Class I*, Appendix IIB

[NOTE—Omit the preliminary drying step.]
Acceptance criteria: 80°–84° [NOTE—This acceptance criteria is specific to the monohydrate form.]

- **RESIDUE ON IGNITION (SULFATED ASH),** Appendix IIC

Sample: 1–2 g
Analysis: Proceed as directed, but igniting at 600° ± 50° until the residue is completely incinerated.
Acceptance criteria: NMT 0.2%, calculated on the anhydrous basis

[2] Symmetry Shield RP 18 (Waters Corporation), or equivalent.

• **WATER,** *Water Determination, Method I,* Appendix IIB
Acceptance criteria: 4.5%–5.5% [NOTE—This acceptance criteria is specific to the monohydrate form.] ■1S (FCC9)

Chromic Chloride

First Published: First Supplement, FCC 8
Last Revision: First Supplement, FCC 9

Chromium chloride (III)
Chromium trichloride hexahydrate
Chromium chloride hexahydrate
Chromium chloride hexahydrate (III)

$CrCl_3 \cdot 6H_2O$ **Formula wt:** 266.45
CAS: [10060-12-5]

UNII: KB1PCR9DMW [chromic chloride]

DESCRIPTION

Chromic chloride hexahydrate occurs as very dark green to violet crystals or crystalline powder. It is hygroscopic, and freely soluble in water. It is soluble in ethanol; insoluble in ether and in acetone.

Function: Nutrient

Packaging and Storage: Store in tightly sealed containers in a cool, dry place, away from moisture.
[**CAUTION**—Avoid contact with skin and eyes. Avoid formation of dust and aerosols. Handle under appropriate exhaust ventilation.]

IDENTIFICATION

• **A. PROCEDURE**
Sample solution: Dissolve 1 g of the sample in water to a final concentration of 4 mg/mL.
Analysis: In a test tube, add 1 mL of 5 N sodium hydroxide and 10 drops of 30% hydrogen peroxide to 5 mL of the *Sample solution,* and heat gently for about 2 min.
Acceptance criteria: A yellow color develops.
• **B. CHLORIDE,** Appendix IIIA
Sample solution: 4 mg/mL
Acceptance criteria: Passes test

ASSAY

• **PROCEDURE**
Analysis: In a glass-stoppered, 500-mL conical flask, dissolve 0.4 g of the sample in 100 mL of water. Then, add 5 mL of 5 N sodium hydroxide, and mix. Pipet slowly 4 mL of 30% hydrogen peroxide into the flask, and boil the solution for 5 min. Cool the solution slightly, and add 5 mL of nickel sulfate solution (50 mg/mL). Boil the solution until no more oxygen is evolved, cool, and add 2 N sulfuric acid dropwise until the color of the solution changes from yellow to orange. Add to the flask a freshly prepared solution of 4 g of potassium iodide and 2 g of sodium bicarbonate in 100 mL of water, then add 6 mL of hydrochloric acid. Immediately insert the stopper in the flask, and allow to stand in the dark for 10 min. Rinse the stopper and the sides of the flask with a few mL of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS to an orange color. Add 3 mL of starch TS, and continue the titration to a blue-green endpoint. Each mL of 0.1 N sodium thiosulfate is equivalent to 8.882 mg of $CrCl_3 \cdot 6H_2O$.
Acceptance criteria: 98%–101.0%

IMPURITIES

Change to read:

Inorganic Impurities
• **ARSENIC,** *Elemental Impurities by ICP,* Appendix IIIC
Acceptance criteria: NMT 1 mg/kg
• **CADMIUM,** *Elemental Impurities by ICP,* Appendix IIIC
Acceptance criteria: NMT 1 mg/kg
• **LEAD,** *Elemental Impurities by ICP,* Appendix IIIC
Acceptance criteria: NMT 1 mg/kg
• **MERCURY,** *Elemental Impurities by ICP,* Appendix IIIC
Acceptance criteria: NMT 1 mg/kg
• ■**CHROMIUM(VI)**
[NOTE—Use high-purity deionized water (>18MΩ • cm at 25°) to prepare all solutions. Use solvents that are of sufficient purity for analysis of trace contaminants.]
Solution A: 15 mM ethylenediaminetetraacetic acid, disodium salt (disodium EDTA), adjusted to a pH of 7.0 using 50% (w/w) sodium hydroxide solution
Mobile phase: Combine equal volumes of 5 mM disodium EDTA, 5 mM sodium dihydrogen phosphate (NaH_2PO_4), and 15 mM sodium sulfate. Adjust the pH of the resulting solution to 7.0 using 50% (w/w) sodium hydroxide solution.
Standard stock solution: Use a commercially available standard solution containing 100 mg/L (100 µg/mL) of Cr(VI).[1] Dilute an aliquot of this solution with water to obtain a *Standard stock solution* containing 1.00 mg/L (1.00 µg/mL) of Cr(VI).
Standard solutions: Dilute individual aliquots of the *Standard stock solution* with *Solution A* to obtain *Standard solutions* containing the following Cr(VI) concentrations: 5.0 µg/L, 10.0 µg/L, 20.0 µg/L, and 40.0 µg/L.
Sample stock solution: Transfer 100 mg of the sample into a 100-mL volumetric flask, mix with the 5 mM EDTA solution, and dilute to volume.
Sample solution: Dilute 0.5 mL of the *Sample stock solution* to 100 mL with *Solution A.*
Chromatographic system, Appendix IIA
Mode: HPLC (coupled to ICP-MS with collision-reaction cell technology)
Detector: ICP-MS with collision-reaction cell technology [NOTE—The instrument and its operational parameters are described in the *Elemental spectrometric system* section below.]
Column: 4.6-mm × 30-mm anion exchange column with a polyhydroxymethylacrylate base resin[2]
Column temperature: Ambient
Flow rate: 1.2 mL/min
Injection volume: 100 µL
Elemental spectrometric system, Appendix IIIC

[1] Commercial solutions for use as ICP-MS standards can be purchased from Sigma-Aldrich or VHG Labs and various other sources.
[2] Agilent catalog number G3268A, or equivalent.

Certificates of Analysis for CPC

Tatva Chintan Pharma Chem Pvt.Ltd.

CERTIFICATE OF ANALYSIS

CERTIFICATE OF ANALYSIS			
NAME OF PRODUCT : CETYL PYRIDINIUM CHLORIDE MONOHYDRATE BATCH NO : ACPCL190170			CAS NO : 6004 –24-6 MFG. DATE : 09.05.2019 EXP. DATE : 08.05.2024
S.No.	TEST	SPECIFICATIONS	TEST RESULT
1	Appearance	White Powder	White Powder
2	**Identification**		
	(A) By IR	Conforms with std	Complies
	(B) By UV	Conforms with std	Complies
3	Moisture content (% w/w, by KF)	4.5 - 5.5%	5.18 %
4	Melting Range °C	80 to 84 °C	81°C to 84 °C
5	Pyridine	To pass test	Complies
6	Organic Volatile impurities	To pass test	Complies
7	Heavy metals, %	0.002 %(max.)	Less than 0.002 %
8	Residue on ignition (% on anhydrous basis)	0.2 %(max.)	0.07 %
9	Acidity	To pass test	Complies
10	Assay (% w/w, by chemical method, on anhydrous basis)	99 to 102 %	99.85 %
11	**Additional test (as per ph.Eur)**		
	(A) Assay (% w/w, by chemical method, on anhydrous basis)	96 to 101 %	98.76 %
	(B) Amines & Amine salts (By Titration)	To pass test	Complies (0.3ml)
	(C) Appearance of solution (1% soln. in water)	Clear, colorless, no visible insoluble materials	Complies
12	**Additional specifications**		
	(A) PYRIDINE content	120 mg/kg (max.)	6 PPM
	(B) Appearance of 40% solution Propylene Glycol	Colourless, to light yellow, no visible insoluble materials	Complies

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Tatva Chintan Pharma Chem Pvt.Ltd.

CERTIFICATE OF ANALYSIS

CERTIFICATE OF ANALYSIS			
NAME OF PRODUCT : CETYL PYRIDINIUM CHLORIDE MONOHYDRATE BATCH NO : ACPCL190145			CAS NO : 6004 –24-6 MFG. DATE : 03.05.2019 EXP. DATE : 02.05.2024
S.No.	TEST	SPECIFICATIONS	TEST RESULT
1	Appearance	White Powder	White Powder
2	**Identification**		
	(A) By IR	Conforms with std	Complies
	(B) By UV	Conforms with std	Complies
3	Moisture content (% w/w, by KF)	4.5 - 5.5%	5.10 %
4	Melting Range °C	80 to 84 °C	82°C to 84 °C
5	Pyridine	To pass test	Complies
6	Organic Volatile impurities	To pass test	Complies
7	Heavy metals, %	0.002 %(max.)	Less than 0.002 %
8	Residue on ignition (% on anhydrous basis)	0.2 %(max.)	0.07 %
9	Acidity	To pass test	Complies
10	Assay (% w/w, by chemical method, on anhydrous basis)	99 to 102 %	99.91 %
11	**Additional test (as per ph.Eur)**		
	(A) Assay (% w/w, by chemical method, on anhydrous basis)	98 to 101 %	99.02 %
	(B) Amines & Amine salts (By Titration)	To pass test	Complies (0.3ml)
	(C) Appearance of solution (1% soln. in water)	Clear, colorless, no visible insoluble materials	Complies
12	**Additional specifications**		
	(A) PYRIDINE content	120 mg/kg (max.)	5 PPM
	(B) Appearance of 40% solution Propylene Glycol	Colourless, to light yellow, no visible insoluble materials	Complies

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CERTIFICATE OF ANALYSIS

CERTIFICATE OF ANALYSIS			
NAME OF PRODUCT : CETYL PYRIDINIUM CHLORIDE MONOHYDRATE BATCH NO : ACPCL190162			CAS NO : 6004 -24-6 MFG. DATE : 07.05.2019 EXP. DATE : 06.05.2024
S.No.	TEST	SPECIFICATIONS	TEST RESULT
1	Appearance	White Powder	White Powder
2	**Identification**		
	(A) By IR	Conforms with std	Complies
	(B) By UV	Conforms with std	Complies
3	Moisture content (% w/w, by KF)	4.5 - 5.5%	5.05 %
4	Melting Range °C	80 to 84 °C	80°C to 84 °C
5	Pyridine	To pass test	Complies
6	Organic Volatile Impurities	To pass test	Complies
7	Heavy metals, %	0.002 %(max.)	Less than 0.002 %
8	Residue on ignition (% on anhydrous basis)	0.2 %(max.)	0.10 %
9	Acidity	To pass test	Complies
10	Assay (% w/w, by chemical method, on anhydrous basis)	99 to 102 %	100.62 %
11	**Additional test (as per ph.Eur)**		
	(A) Assay (% w/w, by chemical method, on anhydrous basis)	96 to 101 %	98.82 %
	(B) Amines & Amine salts (By Titration)	To pass test	Complies (0.3ml)
	(C) Appearance of solution (1% soln. in water)	Clear, colorless, no visible insoluble materials	Complies
12	**Additional specifications**		
	(A) PYRIDINE content	120 mg/kg (max.)	6 PPM
	(B) Appearance of 40% solution Propylene Glycol	Colourless, to light yellow, no visible insoluble materials	Complies

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Certificate No. : TC-7137

Quality Control Laboratory
Certificate of Analysis

PRODUCT : **CETYL PYRIDINIUM CHLORIDE (BP/EP/USP)**

REPORT ISSUE DATE	: 11.06.2019	TANKER/CONTAINER NO.	: PONU0306803
DATE OF SAMPLING	: 08.06.2019	NO. OF PACKINGS	: 01 X 454 KG
LAB REF. NO.	: 2668-19	QUANTITY	: 454 KG
REPORT NO.	: CPC/204/2019	SUPPLIED TO	: M/S JUBILANT LIFE SCIENCES (USA),INC 790 TOWNSHIP LINE ROAD SUITE 175 YARDLEY, PA 19067 USA
BATCH NO.	: G-CPC0173-F-19		
SPECIFICATION;REV.No.	: FPS/CPC/J1D014/SPEC-03,000		
SAMPLING PLAN	: JLL/QCD/SOP/018		
EXPORTER'S REF.	: 571973		
SHIPMENT NO.	: 210674	MFG. DATE	: JUNE-2019
		RETEST DATE	: MAY-2022

S.No.	PARAMETER	UNIT	STP NO.	SPECIFICATION	TEST RESULT
1	Appearance	-	FPS/STP/0001	White powder	White powder
2	Identification				
	(a) By IR	-	FPS/STP/0061	Conforms to standard	Passes
	(b) By HPLC	-	FPS/STP/0251	The retention time of the major peak of the sample solution corresponds to that of the standard solution,as obtained in the assay.	Passes
	(c)* By chloride	-	FPS/STP/0344	To pass test	Passes
3	Water content , w/w (by KF)	%	FPS/STP/0003	4.5 - 5.5	4.94
4	*-Organic Impurities , w/w (by HPLC)	%	FPS/STP/0251		
	a) Any Individual unspecified impurity			0.10 (max.)	ND
	b) Total Impurities			1.0 (max.)	ND
5	*Organic Volatile impurities	-	FPS/STP/0343	To pass test	Passes
6	Residue on ignition ,w/w (calculated on anhydrous basis)	%	FPS/STP/0007	0.20 (max)	0.054
7	Acidity	-	FPS/STP/0250	To pass test	Passes
8	Assay, (by HPLC) (calculated on anhydrous basis)	%w/w	FPS/STP/0251	98 -102	100.18
9	**Additional test (as per Ph.Eur)**				
	*(a)Assay (by chemical method on anhydrous basis)	%w/w	FPS/STP/0345	96 - 101	97.14
	*(b)Amines and Amine salt(by titration)	-	FPS/STP/0346	To pass test	Passes
	(c)Appearance of 1% solution in water	-	FPS/STP/0347	Clear, colourless, no visible insoluble material	Clear, colourless, no visible insoluble material
10	**Additional test (as per safe food)**				
	(a) Pyridine content	mg/kg	FPS/STP/0348	120 (Max)	50.17
	(b) Appearance of 40% solution in Propylene Glycol	-	FPS/STP/0349	Colourless to light yellow, no visible insoluble material	Colourless, no visible insoluble material

REMARKS:
1. ND = Not Detected
2. The material conforms to specifications.
3. The result listed refers only to the tested sample (s)/product and applicable parameter (s). Endorsement of products is neither inferred nor implied.
4. Sample will be destroyed after one month from the date of issue of test certificate unless or shelf life of products.
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6. **" The tests marked with an * are not accredited by NABL ".**

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Quality Control Laboratory
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PRODUCT : CETYL PYRIDINIUM CHLORIDE (BP/EP/USP)

REPORT ISSUE DATE	: 11.06.2019	TANKER/CONTAINER NO.	: PONU0306803
DATE OF SAMPLING	: 30.05.2019	NO. OF PACKINGS	: 01 X 454 KG
LAB REF. NO.	: 2532-19	QUANTITY	: 454 KG
REPORT NO.	: CPC/188/2019	SUPPLIED TO	: M/S JUBILANT LIFE SCIENCES (USA),INC 790 TOWNSHIP LINE ROAD SUITE 175 YARDLEY, PA 19067 USA
BATCH NO.	: G-CPC0156-E-19		
SPECIFICATION;REV.No.	: FPS/CPC/J1D014/SPEC-03,000		
SAMPLING PLAN	: JLL/QCD/SOP/018		
EXPORTER'S REF.	: 571973		
SHIPMENT NO.	: 210674	MFG. DATE	: MAY-2019
		RETEST DATE	: APR-2022

S.No.	PARAMETER	UNIT	STP NO.	SPECIFICATION	TEST RESULT
1	Appearance	-	FPS/STP/0001	White powder	White powder
2	Identification				
	(a) By IR	-	FPS/STP/0061	Conforms to standard	Passes
	(b) By HPLC	-	FPS/STP/0251	The retention time of the major peak of the sample solution corresponds to that of the standard solution,as obtained in the assay.	Passes
	(c)* By chloride	-	FPS/STP/0344	To pass test	Passes
3	Water content , w/w (by KF)	%	FPS/STP/0003	4.5 - 5.5	5.07
4	*-Organic Impurities , w/w (by HPLC)	%	FPS/STP/0251		
	a) Any Individual unspecified impurity			0.10 (max.)	0.053
	b) Total Impurities			1.0 (max.)	0.10
5	*Organic Volatile impurities	-	FPS/STP/0343	To pass test	Passes
6	Residue on ignition ,w/w (calculated on anhydrous basis)	%	FPS/STP/0007	0.20 (max)	0.060
7	Acidity	-	FPS/STP/0250	To pass test	Passes
8	Assay, (by HPLC) (calculated on anhydrous basis)	%w/w	FPS/STP/0251	98 -102	99.51
9	**Additional test (as per Ph.Eur)**				
	*(a)Assay (by chemical method on anhydrous basis)	%w/w	FPS/STP/0345	96 - 101	97.62
	*(b)Amines and Amine salt(by titration)	-	FPS/STP/0346	To pass test	Passes
	(c)Appearance of 1% solution in water	-	FPS/STP/0347	Clear, colourless, no visible insoluble material	Clear, colourless, no visible insoluble material
10	**Additional test (as per safe food)**				
	(a) Pyridine content	mg/kg	FPS/STP/0348	120 (Max)	55.44
	(b) Appearance of 40% solution in Propylene Glycol	-	FPS/STP/0349	Colourless to light yellow, no visible insoluble material	Light yellow no visible insoluble material

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QCD002/FM/031;01.07.17 Page 1 of 1

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Certificate No. : TC-7137

Quality Control Laboratory
Certificate of Analysis

PRODUCT : **CETYL PYRIDINIUM CHLORIDE (BP/EP/USP)**

REPORT ISSUE DATE	: 21.12.2019	TANKER/CONTAINER NO.	: FBLU0000873
DATE OF SAMPLING	: 05.12.2019	NO. OF PACKINGS	: 01 X 454 KG
LAB REF. NO.	: 6234-19	QUANTITY	: 454 KG
REPORT NO.	: CPC/511/2019	SUPPLIED TO	: M/S JUBILANT LIFE SCIENCES (USA),INC 790 TOWNSHIP LINE ROAD SUITE 175 YARDLEY, PA 19067 USA
BATCH NO.	: G-CPC0471-K-19		
SPECIFICATION;REV.No.	: FPS/CPC/J1D014/SPEC-03,000		
SAMPLING PLAN	: JLL/QCD/SOP/018		
EXPORTER'S REF.	: 572158		
SHIPMENT NO.	: 210886	MFG. DATE	: NOV.- 2019
		RETEST DATE	: OCT - 2022

S.No.	PARAMETER	UNIT	STP NO.	SPECIFICATION	TEST RESULT
1	Appearance	-	FPS/STP/0001	White powder	White powder
2	Identification				
	(a) By IR	-	FPS/STP/0061	Conforms to standard	Passes
	(b) By HPLC	-	FPS/STP/0251	The retention time of the major peak of the sample solution corresponds to that of the standard solution,as obtained in the assay.	Passes
	(c)* By chloride	-	FPS/STP/0344	To pass test	Passes
3	Water content , w/w (by KF)	%	FPS/STP/0003	4.5 - 5.5	5.09
4	*-Organic Impurities , w/w (by HPLC)	%	FPS/STP/0251		
	a) Any Individual unspecified impurity			0.10 (max.)	ND
	b) Total Impurities			1.0 (max.)	ND
5	*Organic Volatile impurities	-	FPS/STP/0343	To pass test	Passes
6	Residue on ignition ,w/w (calculated on anhydrous basis)	%	FPS/STP/0007	0.20 (max)	0.063
7	Acidity	-	FPS/STP/0250	To pass test	Passes
8	Assay, (by HPLC) (calculated on anhydrous basis)	%w/w	FPS/STP/0251	98 -102	100.65
9	**Additional test (as per Ph.Eur)**				
	*(a)Assay (by chemical method on anhydrous basis)	%w/w	FPS/STP/0345	96 - 101	97.60
	*(b)Amines and Amine salt(by titration)	-	FPS/STP/0346	To pass test	Passes
	(c)Appearance of 1% solution in water	-	FPS/STP/0347	Clear, colourless, no visible insoluble material	Clear, colourless, no visible insoluble material
10	**Additional test (as per safe food)**				
	(a) Pyridine content	mg/kg	FPS/STP/0348	120 (Max)	9.84
	(b) Appearance of 40% solution in Propylene Glycol	-	FPS/STP/0349	Colourless to light yellow, no visible insoluble material	Light yellow no visible insoluble material

REMARKS:
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2. The material conforms to specifications.
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