EXECUTIVE SUMMARY

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

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NATURE OF BUSINESS: FOOD SAFETY COMPANY/ PROCESSING AID SUPPLIER

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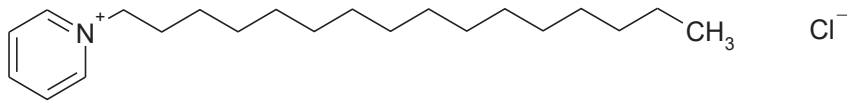
1. Purpose of the Application.

The subject of this application is an aqueous solution containing cetylpyridinium chloride ("CPC") as the active ingredient, and food-grade propylene glycol ("PG"). The mixture is commercially available under the trade name Cecure®. Cecure® is a patented food processing aid that is formulated and supplied as a concentrated solution of CPC dissolved in an aqueous solution with food-grade PG. Cecure® is diluted to $\leq$ 1% concentration in potable tap water for use as an antimicrobial treatment for raw poultry. Cecure® is not a chlorine-based disinfectant and therefore can be used in situations where chlorine-based disinfectants are not permitted.

2. Physical and Chemical Characteristics.

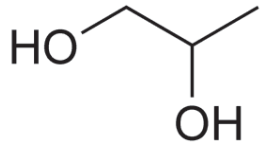
A. Cetylpyridinium Chloride. The IUPAC name for CPC is 1-hexadecyl pyridinium chloride; the CAS Number is 123-03-5; and, the EC Number is 204-593-9.

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 with a molecular formula of $C_{21}H_{38}NCl{:}H_2O$ and 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%. CPC is a white powder, with a melting point of 77°C to 83°C, a pH of 6.0 to 7.0 (1% aqueous solution), and is freely soluble in water, alcohol and chloroform, but is insoluble in ether and does not dissolve in food products. As noted above, Cecure® is not a chlorine-based compound.

B. Propylene Glycol. The IUPAC name for PG is Propane-1,2-diol; the CAS Number is 57-55-6; and, the EC Number is 200-338-0. 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. PG is a colorless, clear, viscous liquid. PG has a melting point of -59°C, a boiling point of 188.2°C, and is freely soluble in water, alcohol, acetone, chloroform, and diethyl ether.

C. Impurities and Breakdown Products. There are no known impurities, by-products, contaminants, or reaction products of concern in concentrated or diluted Cecure®. CPC is not an oxidant, or acidic in nature and will not alter the structure or function of proteins, lipids, or carbohydrates. In addition, Cecure® has a neutral pH and will not alter the sensory characteristics of the product being treated.

The PG molecule does not break down on the treated poultry product or in the processing environment. However, 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. The PG molecule is chemically inert and only serves to enhance the stability and solubility of CPC in solution, and to reduce the absorption of CPC on the treated poultry.

D. Manufacturing Process. The Petitioner does not manufacture CPC, as it is a readily available item of commerce that may be obtained from a variety of suppliers throughout the world. CPC can be prepared by the interaction of cetyl chloride and pyridine under pressure at an elevated temperature. In aqueous solution, CPC is synthesized by alkylation of pyridine with cetyl chloride

to yield the monohydrate of the quaternary salt of pyridine and cetyl chloride. The Cecure® concentrate solution is manufactured by mixing the CPC and PG with water according to Good Manufacturing Practices ("GMPs"). The concentrated solution is diluted with additional potable water at the point of use to yield the appropriate product application solution (≤ 1.0% CPC).

3. Intended Use of Cecure® with Respect to Target Pathogenic Organisms.

Cecure® will be used as a processing aid to control the following microorganisms on raw poultry: *Salmonella*, *Campylobacter*, *Listeria*, *Staphylococcus aureus*, *Escherichia coli* (including 0157:H7), *Pseudomonas*, total coliforms, as well as viruses. An extensive amount of work to support these claims has been published in the scientific literature and are summarized in the application (reprints of many of these studies can be found in Annex A of the application). These studies cover virtually every aspect of this technology from *in vitro* studies done in laboratory settings, to field trials with prototype application equipment, to actual results from commercial poultry processing facilities in the U.S.

A. Types of Food for Cecure® Application and Conditions of Use. The Cecure® solution (≤ 1.0%) can be 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. 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.

4. Existing Authorization.

Cecure® is approved for the usage described above 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 for this usage for raw poultry, and in some cases for treatment of other foods, in several 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.

5. Toxicological Data.

A. *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. This information has been summarized below in Table I. The Applicant has also commissioned several additional toxicity studies not publicly available in literature. These studies are also incorporated into Table 1.

Table I. Toxicology studies on CPC.

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

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)
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, 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

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)
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 determined to be 25 mg/kg bw/day
1979	CPC (0.5%)	Yamaguchi and Yamashita	Ames Test	Not mutagenic to *Salmonella typhimurium*

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)
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 Rat Mouse Rabbit Guinea Pig Dog Cat	 LD_{50} 5080 LD_{50} 1360 LD_{50} 1000 LD_{50} 3860 LD_{50} 1000 LD_{50} 1000
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;	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)

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)
			Inhalation by Pregnant Rats	
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
2001	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	Redfield Laboratories	14-day Palatability Study of CPC in Sprague-	NOEL = 100 NOAEL = 500

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)
	(100-2000 ppm in diet)	Study Number 161-002.	Dawley Rats (up to 500 ppm CPC)	
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
2005	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.	90-day 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.	90-day Toxicity Feeding Study of CPC in Beagle Dogs (up to 1000 ppm)	NOEL = 250 NOAEL = 375

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.

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.

By comparison, the highest estimated daily intake (EDI) of CPC (calculated from poultry consumption values and CPC residue levels expected on the poultry skin) is 2.418 µg CPC /kg b.w./day (Australia's EDI). This level is less than the dietary exposure accepted by the FDA based on the toxicity studies presented. In addition, the EDI value of 2.418 µg CPC/kg b.w./d (or 0.00242 mg CPC /kg b.w./d) 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 above toxicity studies.

History of Safe and Effective Use. Cecure® application systems are now installed and operating in 49 poultry slaughter facilities in the U.S. and other countries. Cecure® has proved to be efficacious in its in-plant decontamination results, with an excellent record of safe use within the plants. Based on the foregoing, the Petitioner respectfully submits that the use of Cecure® as a decontaminant treatment on pre-chill poultry, or post-chill poultry carcasses or parts, under the treatment conditions described herein, is safe.