National Organic Standards Board
Handling Subcommittee
Petitioned Material Proposal
Cetylpyridinium Chloride (CPC)
February 15, 2022

Summary of Petition, Petition addendum #1
Cetylpyridinium chloride (CPC), CAS #123-03-5, is being petitioned by Safe Foods Corporation as an antimicrobial processing aid specifically for application onto poultry or poultry parts at slaughter or processing plants. As such it is being petitioned to be listed on the National List at 7 CFR 205.605(b), synthetic nonagricultural (nonorganic) substance allowed in or on processed products labeled as "organic" or "made with organic (specified ingredients)." CPC would be added to water used as a drench or dip to reduce populations of foodborne pathogens such as Salmonella and Campylobacter that may be present on raw poultry. The petitioner's proposed listing is "*Cetylpyridinium chloride – Antimicrobial food treatment for use according to FDA limitation.*" The petition was received on 12/4/2019 (referred to as "petition") and amended on 4/24/2021 (referred to as "addenda"). A Technical Review (TR) was completed and found sufficient on 8/5/2021 (referred to as "TR"). The Handling Subcommittee is bringing this petition forward for full NOSB review at its Spring 2022 meeting.

Summary of Review:
The Handling Subcommittee has reviewed the relevant information on the cetylpyridinium chloride petition and discussed a range of specific issues.

One critical issue outlined in this proposal relates to the fact that CPC residues have been discovered on treated surfaces and poultry skin, exposing consumers to unlabeled pesticide residues.

Another relates to continued concern about sanitizer usage and regulation in organics and whether or not expansion of the sanitizer toolkit to support food safety requirements is essential for organic production. Previously, the NOSB has heard from an expert panel on sanitizers on the need for appropriate sanitizer rotations to prevent pathogen resistance and what material rotations can ensure appropriate efficacy. CPC is a powerful antimicrobial and raises questions about its fit with organic production. Significantly, another antimicrobial petition – for peroxylactic acid (POLA) – is currently before the NOSB on a different timeline, and its relevance to the CPC review is expected.

The fact that CPC requires the use of an inert – propylene glycol (PG) – to complete its formulation, as outlined in full in the TR, raises another important question. Under OFPA reviews for handling do not include any guidance provisions for inerts like PG. However, because the inert PG is a functional requirement of the CPC formulation, the Subcommittee is facing – and has discussed – what is an unprecedented evaluation pathway for this material in its full application.

Nonetheless, the Subcommittee has reviewed CPC on the merits for its compatibility with OFPA and organic systems.

Reference Material:
Petition: https://www.ams.usda.gov/sites/default/files/media/CPC_PetitionAddendum1.pdf
Addendum: https://www.ams.usda.gov/sites/default/files/media/CPC_PetitionAddendum1.pdf
Technical Report (TR):
https://www.ams.usda.gov/sites/default/files/media/NOPCetylpyridiniumChlorideHandlingTR.pdf

Other – Biomonitoring California – Quaternary Ammonium Compounds (QACs):
https://biomonitoring.ca.gov/events/biomonitoring-california-scientific-guidance-panel-meeting-march-2021

Category 1: Classification

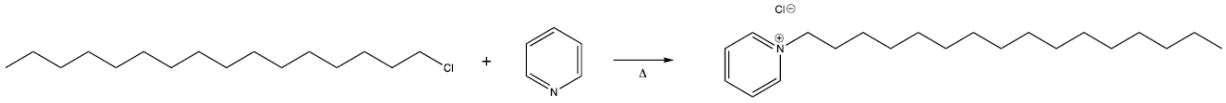
1. Substance is for: ____X___ **Handling** _____ **Livestock**

2. For HANDLING and LIVESTOCK use:
   a. Is the substance _____ **Agricultural** or ___X____ **Non-Agricultural?**
   Describe reasoning for this decision using NOP 5033-2 as a guide:

CPC is a non-agricultural synthetic substance.

   b. If the substance is **Non-agricultural**, is the substance _____ **Non-synthetic** or __X__ **Synthetic?**
   Is the substance formulated or manufactured by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral sources? [OFPA §6502(21)] If so, describe, using NOP 5033-1 as a guide:

According to the TR, "Cetylpyridinium chloride is a synthetic substance produced by reacting pyridine and cetyl chloride (1-chlorohexadecane) at an elevated temperature and pressure. The majority of commercial pyridine is produced through the Chichibabin reaction between acrolein, formaldehyde, and ammonia. According to the petition, the pyridine for this synthesis is produced exclusively from bioethanol components (USDA 2019). Bioethanol is formed through the fermentation of biomass such as corn or sugarcane to form biologically sourced ethanol... Once formed, ethanol and methanol can be oxidized to produce acetaldehyde and formaldehyde, respectively... Acetaldehyde and formaldehyde can then be combined to produce acrolein, which can be further reacted with formaldehyde and ammonia to form pyridine via the Chichibabin reaction…." Although not likely to be present in the final product, precursors to manufacture CPC include formaldehyde and acetaldehyde, both probable or known carcinogens ((https://oehha.ca.gov/proposition-65); https://www.epa.gov/iris), and acrolein is a respiratory irritant (https://oehha.ca.gov/chemicals/acrolein).



Equation 5

The pyridine ring is reacted with cetyl chloride to form CPC (Equation 5 from the TR). The source of cetyl chloride (CC) (synonym: 1-Chlorohexadecane/ CAS # 4860-03-1) is not described in the petition or TR. Manufacturing information about CC was not available from the petition, TR, PubChem, EPA, or ECHA. Cetyl chloride is considered an irritant with a "Warning" label but does not appear very toxic (https://pubchem.ncbi.nlm.nih.gov/compound/1-chlorohexadecane).

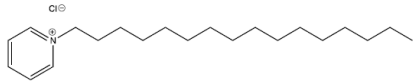


Figure 1. The chemical structure of cetylpyridinium chloride

Category 2: Adverse Impacts

1. What is the potential for the substance to have detrimental chemical interactions with other materials used in organic farming systems? [§6518(m)(1)]

As petitioned for use only as a drench or dip for poultry carcasses or parts, it is unlikely that that CPC will interact with other materials used in organic farming systems.

2. What is the toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment? [§6518(m)(2)]

CPC is a quaternary ammonium compound (QAC) used as a microbicide. QAC use in general has increased due to COVID-19 safety protocols. To date, no QACs are present on the National List. In contrast to many other sanitizers on the National List, CPC is not an oxidant. It "has been reported to be more effective against Gram-positive bacteria." As paraphrased from the TR: Gram-positive bacteria have membrane surfaces that bear a negative charge. The positively charged pyridinium portion of the substance binds to the negatively charged bacterial membrane through electrostatic interactions. The electrostatic attraction improves the ability of the substance to rearrange membrane lipids. Additionally, the binding of the positively charged pyridinium portion of the substance disrupts membrane function and bacterial metabolism, which may deactivate bacteria. Once initial bacterial populations have been reduced, cetylpyridinium-chloride-treated meat products have been shown to maintain reduced bacterial populations when stored between 14 and 42 days.

At high concentrations, CPC is toxic to humans. CPC is identified as a hazardous substance according to the Global Harmonized System of Classification and Labeling of Chemicals (GHS) and summarized in Table 3 from the TR:

Table 3. GHS classification of cetylpyridinium chloride

Hazard class	Hazard statement	Pictogram
Acute toxicity, oral, category 4	H302—Harmful if swallowed	
Skin corrosion/irritation, category 2	H315—Causes skin irritation	
Serious eye damage/eye irritation, category 1	H318—Causes serious eye damage	
Acute toxicity, inhalation, category 2	H330—Fatal if inhaled	
Specific target organ toxicity, single exposure, respiratory tract irritation, category 3	H335—May cause respiratory irritation	

Class 1 reflects the highest danger and Class 4 reflects the lowest danger. CPC represents higher risks (Class 1-2) for skin corrosion/irritation, ocular damage, and inhalation toxicity. Like many toxicants, the dose makes the poison, and lower health-based benchmarks have been established for CPC where adverse effects in humans, when exposed, would be unlikely to occur. QACs exposure in general was reviewed by the California Biomonitoring Science Guidance Panel, which raised some concerns about long-term exposure and recommended biomonitoring of QACs to better understand exposure trends. Of note, no occupational air monitoring data was reported in the petition, TR, or by EPA, NIOSH, ECHA, or aggregated data bases such as EWG. Similar to other sanitizers, it appears that there is little data to assess inhalation exposures in occupational environments where this sanitizer is approved for use. While exposures may be low because relatively dilute solutions are used as a microbicide, and because

QACs, in particular, are not highly volatile, information on potential exposures would be valuable. Toxicology data submitted by the petitioner does not address inhalation exposures.

CPC is approved for use in many consumer products, including mouthwash, toothpaste, and other products contacting oral cavities in humans. These uses almost certainly result in ingestion and dermal exposures that are deemed safe by FDA. As excerpted in the petition "…the FDA concluded that the no-observable effect level (NOEL) for the dog [study] … was 8 mg/kg body weight per day. By applying a 1000-fold safety factor to this value, the FDA determined the acceptable daily intake (ADI) for a 60-kg human as 0.48 mg/p/d." This is quoted as an excerpt from FDA Code of Federal Register (CFR 173.375). The FDA ADI converts to 0.008 mg/kg-bw, which are more common units used by EPA.

According to the TR: "FDA has approved the use of cetylpyridinium chloride "as an antimicrobial agent…to treat the surface of raw poultry carcasses" (21 CFR 173.375). The FDA requires cetylpyridinium chloride to be combined with propylene glycol (PG), which must be included "at a concentration of 1.5 times that of cetylpyridinium chloride." When used as an antimicrobial additive in poultry processing, the FDA has outlined its use in §173.375." Note, propylene glycol is on EPA List 4 and is on the National List at 205.603(a): only for treatment of ketosis in ruminants.

As described in the TR, CPC is petitioned for use as a drench or dip followed by a chiller solution or a potable water wash when used in post-chiller applications, as stipulated by FDA regulations (21 CFR 173.375). The continued processing is expected to remove the majority of CPC from treated surfaces. However, residual CPC has been detected on treated surfaces at the processing endpoint and is expected to be found in concentrations of 2.–25.9 mg/kg on poultry skin. The maximum reported concentration of 25.9 mg/kg found on the meat surface would result in an average concentration of 2.3 mg/kg of CPC on treated meat. In the information reviewed, CPC was not found in non-surface meat. The TR concludes that CPC exposure is not expected to pose safety concerns (EFSA 2012). Importantly, organic consumers would be exposed to unlabeled pesticide residues (and propylene glycol) in the food. For the proposed use PG will be regulated as an "inert" substance from the EPA List 4. Note, the List 4 is not supported by EPA and is a legacy guideline for organic pesticides.

As described in the TR (Table 2), CPC is "highly toxic to fish, crustaceans, molluscs, and other aquatic life."

According to the petition, "At the end of a processing day, the entire CPC application system is shut down and any solution remaining in the recycle tank is sent to a purge tank. The frequency of this purging varies from one plant to another, although a daily purging is typical. The purged solution is filtered to remove any remaining CPC using disposable carbon filters. The activated carbon treatment provides for complete removal of CPC from the aqueous treatment solution." The TR describes similar procedures.

Table 2. Aquatic toxicity values of cetylpyridinium chloride

Species	Endpoint	Concentration
Australorbis sp. (snail)	Lethal	5 mg/L
Penaeus monodon (jumbo tiger prawn)	LC_{50}	0.8 mg/L
Penaeus japonicus (Kuruma shrimp)	LC_{50}	3.1 mg/L
Penaeus semisulcatus (shrimp)	LC_{50}	1 mg/L
Fenneropenaeus penicillatus (redtail prawn)	LC_{50}	0.56 mg/L
Metapenaeus ensis (greasyback shrimp)	LC_{50}	2.1 mg/L
Macrobrachium rosenbergii (great river prawn)	LC_{50}	0.13 mg/L
Oncorhynchus mykiss (rainbow trout)	LC_{50}	0.15 mg/L
Cyprinus carpio (carp)	Not reported	0.01 mg/L
Daphnia magna (water flea)	EC_{50}	0.00736 mg/L

Sources: Vallejo-Freire et al. 1954, Liao et al. 1990, Fisher 2007, Parchem 2015, ECOTOX 2021

3. Describe the probability of environmental contamination during manufacture, use, misuse or disposal of such substance? [§6518(m)(3)]

According to the petition, "the CPC is captured in carbon barrels and disposed of either in approved landfills or by incineration. Disposal of the carbon barrels by either method does not allow for free CPC to enter the environment. Typically, a plant will use and dispose of one carbon filter (55-gallon drum or 209-L drum) every two months. The filtered, CPC-free liquid is then combined with the plant wastewater. In addition, available data for commercial CPC applications indicate that CPC, if present at all in the effluent from wastewater treatment facilities following the capture and recycling processes, will be there in vanishingly low levels and will be of no environmental significance" and "under the Notice and Comment rulemaking for CPC use, the FDA issued a Finding of No Significant Impact (FONSI) for CPC application to raw poultry."

Based on the information provided, environmental contamination resulting from use as a processing aid in poultry manufacturing lines is unlikely as long as the controls described in the petition and TR are followed. As noted above and described in the TR, precursor materials are likely to include formaldehyde and acetaldehyde, both probable or known carcinogens ((https://oehha.ca.gov/proposition-65); https://www.epa.gov/iris) and acrolein is a respiratory irritant (https://oehha.ca.gov/chemicals/acrolein). CPC manufacture and use is regulated, but inappropriate handling or accidents could result in human exposures or environmental emissions along the supply chain. It is impossible to quantify the probability of such events.

4. Discuss the effect of the substance on human health. [§6517 (c)(1)(A)(i); §6517 (c)(2)(A)(i); §6518(m)(4)].

See above.

5. Discuss any effects the substance may have on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock. [§6518(m)(5)]

Not applicable.

6. Are there any adverse impacts on biodiversity? (§205.200)

Not applicable.

Category 3: Alternatives/Compatibility

1. Are there alternatives to using the substance? Evaluate alternative practices as well as non-synthetic and synthetic available materials. [§6518(m)(6)]

Non-synthetic alternatives include plain water and organic acids (e.g., including citric acid, lactic acid, and tartaric acid). These materials may affect food quality or are not efficacious for an industrial poultry production line, or, in the case of lactic acid, is more commonly used in livestock.

Several existing materials on the National List are currently used as poultry processing aids and comply with food safety requirements. Peroxyacetic acid, in particular, is widely used. According to the TR, peroxyacetic acid is an oxidant microbicide applied as both a pre- and post-chill treatment as a spray or dip. Chlorine materials include chlorine dioxide and hypochlorous acid and acidified sodium chlorite (ASC), a related material. ASC is approved for poultry processing. As noted in the TR, the oxidizing nature of chlorine materials makes them susceptible to deactivation when interacting with organic matter.

2. **For Livestock substances, and Nonsynthetic substances used in Handling**: In balancing the responses to the criteria above, is the substance compatible with a system of sustainable agriculture? [§6518(m)(7)]

No. This synthetic material offers some benefits for pathogen control on poultry carcasses and parts. However, existing materials have supported a robust and growing organic poultry industry and currently allow compliance with food safety standards. Importantly, use of this material will result in unlabeled pesticide residues on organic food and exposures to organic consumers without their knowledge, factors antithetical to organic principles.

Category 4: Additional criteria for synthetic substances used in Handling (does not apply to nonsynthetic or agricultural substances used in organic handling):
Describe how the petitioned substance meets or fails to meet each numbered criterion.

1. The substance cannot be produced from a natural source and there are no organic substitutes; (§205.600(b)(1))

CPC is synthetic and cannot be produced from natural sources.

2. The substance's manufacture, use, and disposal do not have adverse effects on the environment and are done in a manner compatible with organic handling; (§205.600(b)(2))

If good manufacturing and handling practices are followed, it is unlikely that the environmental contamination will result from the petitioned use. Use of the material does result in periodic waste material that must be disposed of in a landfill. As noted above and described in the TR, precursor materials are likely to include formaldehyde and acetaldehyde, both probable or known carcinogens ((https://oehha.ca.gov/proposition-65); https://www.epa.gov/iris) and acrolein is a respiratory irritant (https://oehha.ca.gov/chemicals/acrolein). CPC manufacture and handling is regulated, but inappropriate handling or accidents could result in human exposures or environmental emissions along the supply chain. It is impossible to quantify the probability of such events.

3. The nutritional quality of the food is maintained when the substance is used, and the substance, itself, or its breakdown products do not have an adverse effect on human health as defined by applicable Federal regulations; (§205.600(b)(3))

The nutritional quality of the food is not affected by use of CPC. Use of this material will result in unlabeled pesticide residues (and propylene glycol) on organic food and exposures to organic consumers without their knowledge, factors antithetical to organic principles.

4. The substance's primary use is not as a preservative or to recreate or improve flavors, colors, textures, or nutritive value lost during processing, except where the replacement of nutrients is required by law; (§205.600(b)(4))

CPC is not used as a preservative or to recreate or improve flavors, colors, textures.

The substance is listed as generally recognized as safe (GRAS) by the Food and Drug Administration (FDA) when used in accordance with FDA's good manufacturing practices (GMP) and contains no residues of heavy metals or other contaminants in excess of tolerances set by FDA; (§205.600(b)(5))

CPC is unlikely to contain heavy metals. Propylene glycol (PG) must be used in the formulation, as required by the FDA. PG has historically been on the now obsolete EPA List 4; however, the National List does not contain a provision for inerts in Handling (§205.606(b)).

5. The substance is essential for the handling of organically produced agricultural products. (§205.600(b)(6))

The substance is not essential for organic poultry production. A robust and growing organic poultry industry is supported by existing materials.

6. In balancing the responses to the criteria in Categories 2, 3 and 4, is the substance compatible with a system of sustainable agriculture [§6518(m)(7)] and compatible with organic handling? (see NOSB Recommendation, Compatibility with Organic Production and Handling, April 2004)

The NOSB finds merits for this material, particularly around the need for alternative sanitizers in organic processing. However, existing materials have supported a robust and growing organic poultry industry and currently allow compliance with food safety standards. Importantly, use of this material will result in unlabeled pesticide residues on organic food and exposures to organic consumers without their knowledge, factors antithetical to organic principles. At this time, the Subcommittee is not recommending this material for inclusion on the National List.

Questions for Stakeholders

1. Do stakeholders agree that this review of CPC – without a deeper review of the inert propylene glycol – is appropriate?
2. Since the FDA requires that propylene glycol be in a CPC formulation, how should the committee evaluate future petitions that include inerts in the formulation given that there is no provision for such inerts within the handling section of the National List?
3. In the current food safety regulatory environment, do organic producers have effective tools for pathogens in poultry processing (specifically antimicrobials)?

Classification Motion
Motion to classify cetylpyridinium chloride (CPC) as a non-agricultural synthetic substance
Motion by: Wood Turner
Seconded by: Kyla Smith
Yes: 6 No: 0 Abstain: 0 Absent: 0 Recuse: 0

National List Motion
Motion to add cetylpyridinium chloride (CPC) with the following annotation: "CPC can only be used in formulation with propylene glycol per FDA requirements" at 7 CFR 205.605(b)
Motion by: Wood Turner
Seconded by: Kyla Smith
Yes: 0 No: 6 Abstain: 0 Absent: 0 Recuse: 0