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## **Supporting document 1**

**Risk and Technical Assessment Report – Application A1215**

**Cetylpyridinium chloride (CPC) as a processing aid**

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### **Executive summary**

FSANZ has assessed an application from Safe Foods Corporation to amend the Australia New Zealand Food Standards Code (the Code) to permit the use of cetylpyridinium chloride (CPC) as a processing aid.

Safe Foods Corporation markets an aqueous solution containing CPC (as the active constituent) and propylene glycol under the proprietary name Cecure (referred to hereafter as the CPC preparation). The CPC preparation is diluted with water to achieve a wash solution with a concentration of up to 1% (w/v<sup>1</sup>) CPC for use as an antimicrobial agent to treat the inner (cavity) and outer surfaces of raw poultry carcasses and pieces.

FSANZ has undertaken an assessment to determine whether CPC achieves the technological purpose, as a processing aid, of an antimicrobial treatment for raw poultry and to identify any potential public health and safety concerns associated with its use.

As an acceptable daily intake (ADI) for propylene glycol has been established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), an assessment of potential public and safety concerns in relation to propylene glycol from the use of the applicant's CPC preparation was also undertaken.

Raw poultry inherently carries a wide range of microorganisms, some of which are potential human pathogens. The application of CPC to the surface of skin-on raw poultry carcasses and pieces, at levels ranging from 0.1 to 1% (w/v) concentration in the wash solution, was demonstrated to effectively reduce the prevalence and levels of microorganisms, including relevant pathogens. FSANZ therefore concludes that the proposed use of CPC as an antimicrobial agent for raw poultry is technologically justified.

As CPC performs the antimicrobial function at the time of treatment (during the processing of poultry) and does not perform a technological purpose in the food for sale, it functions as a processing aid as defined in the Code.

There is a relevant specification for CPC in the Food Chemicals Codex (United States Pharmacopeial Convention 2020), a primary source of specifications listed in Schedule 3 of the Code.

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<sup>1</sup> weight per volume

Propylene glycol is added to Safe Foods' CPC preparation to act as a wetting agent or humectant in the processing of the CPC preparation and to maintain solubility and stability in the preparation after processing. Propylene glycol is currently permitted for use both as a food additive permitted at GMP and as a processing aid, in accordance with the Code.

In short-term dietary toxicity studies of CPC in rats and dogs, reduced food consumption and decreased body weight and body weight gain were observed at higher concentrations. These effects may possibly be due to issues with palatability of the test item. Increased caecum weights were observed in rats. The cause of this finding was unclear but it was not possible to definitively conclude that these changes were not treatment-related or adverse. In addition, haematological changes were observed in dogs. The no observed adverse effect level (NOAEL) in a 90-day dietary toxicity in dogs was 8 mg/kg bw/day.

*In vitro* genotoxicity studies of the final CPC preparation found no evidence of mutagenicity or clastogenicity. Proprietary *in vitro* and *in vivo* genotoxicity studies of CPC unavailable to FSANZ were reviewed by the EU Scientific Committee on Consumer Safety (SCCS), and considered to demonstrate that CPC does not have genotoxic potential. No long-term studies of toxicity or carcinogenicity are available for review, but no histopathological changes indicative of lesions that could lead to neoplasia were identified in the short-term dietary toxicity studies reviewed by FSANZ.

Limited details summarising developmental toxicity studies of CPC in rats and rabbits were submitted to FSANZ. In addition, the EU SCCS review of CPC considered results of a proprietary developmental toxicity study in rats. These summaries state that no developmental toxicity was observed, but the full study reports were not available to FSANZ for evaluation. A summary of a combined developmental and reproductive toxicity study of a vinyl copolymer containing CPC in rats, conducted over three generations, states that no effects on fertility or developmental toxicity were observed. No histopathological changes in reproductive tissues were reported in the short-term dietary toxicity studies reviewed by FSANZ.

Given the limited data on long-term toxicity, carcinogenicity and developmental and reproductive toxicity available to FSANZ, it is not appropriate to establish a health-based guidance value (HBGV) for CPC. However, the NOAEL of 8 mg/kg bw/day identified in the 90-day dietary toxicity study in dogs is considered a suitable point of departure for use in a margin of exposure (MOE) assessment. This NOAEL is also protective of the changes observed in the rat studies.

For propylene glycol, an acceptable daily intake (ADI) of 0 – 25 mg/kg bw has been established by JECFA.

A dietary exposure assessment was undertaken for both CPC and propylene glycol based on residue levels in poultry from use of the applicant's CPC preparation. The assessment for propylene glycol also included dietary exposure from existing food additive uses. For CPC, estimated dietary exposures ranged between 0.0025 and 0.014 mg/kg bw/day across mean and high (90<sup>th</sup> percentile) exposures for all scenarios and Australian and New Zealand population groups assessed. When compared with the NOAEL, these dietary exposures equate to MOEs between 600 and 3200. The MOEs are sufficiently large to account for the uncertainties in the database for CPC, and indicate that there are no safety concerns from the proposed use of CPC as a poultry treatment. For propylene glycol, estimated dietary exposures from the applicant's CPC preparation and additive sources combined ranged between <1 and 27 mg/kg bw/day for mean and high exposures across all scenarios and population groups assessed. This equates to between 1 and 110% of the ADI. The upper end of this range is based on a very conservative estimate, primarily as that estimate is

based on maximum industry use levels in 100% of food products in each food class, a single day of food consumption data, and a restricted age group. The contribution from the applicant's CPC preparation was <1% of the ADI.

Studies on the potential for the proposed use of CPC to engender resistance to the compound or cross resistance to antimicrobial compounds of importance to human health demonstrate that the proposed use of CPC does not introduce an unacceptable risk of the development of antimicrobial resistance in the six pathogens tested: *Salmonella* Typhimurium, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Listeria monocytogenes* and *Campylobacter jejuni*.

In conclusion, there were no public health and safety concerns identified from the estimated dietary exposure to either CPC or the propylene glycol in the applicant's CPC preparation at the proposed use levels.

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# 1 Introduction

FSANZ received an application from Safe Foods Corporation (Safe Foods) to amend the Australia New Zealand Food Standards Code (the Code) to permit the use of cetylpyridinium chloride (CPC) as a processing aid. The applicant states that CPC would be used as an antimicrobial surface (including the abdominal cavity) treatment for raw poultry.

Safe Foods markets an aqueous solution containing CPC (as the active constituent) under the proprietary name Cecure (referred to hereafter as the CPC preparation). The CPC preparation is a colourless to light yellow liquid. The CPC preparation would be diluted with water to achieve a wash solution with a concentration of up to 1% (w/v<sup>2</sup>) CPC for use as an antimicrobial agent to treat raw poultry carcasses and pieces.

The CPC preparation also contains propylene glycol, a food additive and processing aid permitted for use in a range of food categories in the Code. An acceptable daily intake (ADI) for propylene glycol has been established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Propylene glycol was therefore included in the scope of FSANZ's assessment.

The objectives of this food technology and risk assessment were to:

- determine whether CPC achieves the technological purpose, as a processing aid, of an antimicrobial treatment for raw poultry
- identify any potential public health and safety concerns associated with the proposed use of CPC and with propylene glycol from the applicant's CPC preparation.

## 2 Food technology assessment

### 2.1 Identity

CPC is the chloride salt form of cetylpyridinium, a quaternary ammonium compound with broad-spectrum antimicrobial activity (PubChem 2004). The identity of CPC is outlined further in Table 1.

**Table 1 Identity of Cetylpyridinium chloride**

<b>IUPAC<sup>3</sup> name</b>	Cetylpyridinium chloride 1-hexadecylpyridin-1-ium;chloride
<b>Synonyms</b>	1 – palmitylpyridinium chloride, Acetoquat CPC, Ammonyx CPC, Ceepryn chloride, Cetamium, Dobendan, Pristacin, Pyrispet
<b>Molecular formula</b>	C <sub>21</sub> H <sub>38</sub> NCl
<b>Molecular weight</b>	340 g/mol
<b>CAS<sup>4</sup> number</b>	123-03-5
<b>EC number<sup>5</sup></b>	204-593-9

<sup>2</sup> weight per volume

<sup>3</sup> International Union of Pure and Applied Chemistry

<sup>4</sup> Chemical Abstracts Service

<sup>5</sup> European Community number

## 2.2 Production of CPC and the CPC preparation

Safe Foods provided the manufacturing process for CPC in section A.4 of the application. CPC is commercially available from a number of chemical suppliers.

FSANZ understands that in order to prepare the applicant's CPC preparation, propylene glycol is added to the CPC monohydrate as a solvent to dissolve the crystallised form and produce an aqueous solution. Propylene glycol is therefore used as a processing aid in the processing of the CPC preparation. Safe Foods states that propylene glycol also functions in the CPC preparation to maintain the solubility and stability.

Propylene glycol is listed as an 'additive permitted at GMP' in section S16—2. This means that it can be used as a food additive in the CPC preparation subject to the requirement that that use be consistent with GMP. As it is an additive permitted at GMP, section 1.3.3—4 of the Code permits the use of propylene glycol as a processing aid in any food (including the CPC preparation) provided that the propylene glycol is used only at a level necessary to achieve the relevant technological purpose in the processing of that food.

## 2.3 Product specification

Processing aids must meet relevant specifications in Schedule 3. There is a specification for CPC in the Food Chemicals Codex (United States Pharmacopeial Convention 2020). The Food Chemicals Codex is a primary source of specifications listed in Schedule 3 of the Code.

The application includes the specification and certificates of analysis from two suppliers indicating the CPC used by Safe Foods meets the Food Chemicals Codex specification.

## 2.4 Technological purpose and justification

The requested technological purpose for the use of CPC is that of an antimicrobial agent to treat the inner and outer surfaces of raw poultry. Raw poultry inherently carries a wide range of microorganisms, some of which are potential human pathogens. Pathogens of particular concern in poultry include *Salmonella* species and *Campylobacter* species. These two organisms are the leading cause of zoonotic intestinal infections in developed countries, including Australia, and have frequently been isolated from raw and undercooked poultry meat and implicated in foodborne illness (Bell et al 2021; Lee and Yoon 2021). Efforts to reduce foodborne illness due to *Salmonella* and *Campylobacter* have been recognised as a high priority in Australia, given effect through *Australia's Foodborne Illness Reduction Strategy 2018–2021+*.<sup>6</sup>

The major steps in the processing of poultry following de-feathering are evisceration (removal of internal organs), chilling, portioning (if not selling as a whole carcass), storage and distribution (FSANZ 2005). The CPC preparation is diluted with potable water and that solution is used to treat raw poultry carcasses and poultry pieces. Safe Foods stated that the diluted CPC preparation would be applied at the poultry processing premises either by:

- spraying the solution onto whole carcasses following evisceration, either prior to entry to the chiller or post chilling
- dipping of poultry pieces into the solution following evisceration and chilling of whole carcasses.

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<sup>6</sup> <https://foodregulation.gov.au/internet/fr/publishing.nsf/Content/aus-foodborne-illness-reduction-strategy-2018-2021-Jun-2018>

The poultry carcasses or pieces are then rinsed in potable water following the treatment outlined above.

The CPC preparation is diluted with potable water to achieve a wash solution with an appropriate concentration of CPC. The technical data sheet for the CPC preparation states that the concentration of CPC in the wash solution applied to the poultry may range from less than 0.05% up to approximately 1.0%. It recommends a concentration range of 0.2-0.5% CPC for application as a standard poultry carcass rinse. The volume of the final solution typically sprayed onto a carcass is estimated by the Safe Foods to be 946 ml, at an average concentration of 0.5% CPC.

As indicated above and stated in the application, edible offal has been removed from the bird when the CPC solution is typically applied. FSANZ therefore assessed the use of CPC on poultry carcasses and pieces, but not offal.

Upon topical administration, the positively charged CPC ion is posited to interact with negatively charged microbial cell surface compounds such as lipoteichoic acid (in Gram-positive bacteria), lipopolysaccharides (in Gram-negative bacteria) and the phospholipids of the cell membrane, disrupting its integrity and leading to cell death (Yegin et al 2019). Direct inhibitory effects on glucose and lactose metabolic pathways, and against bacterial biofilms, have also been observed (Pitten and Kramer 2001).

#### **2.4.1 Biocidal efficacy**

The efficacy of CPC has previously been assessed by the European Food Safety Authority (EFSA) expert panels on biological hazards (BIOHAZ) and food contact materials, enzymes, flavourings and processing aids (CEF) (EFSA, 2012). In its assessment, EFSA deemed efficacy to be demonstrated where the biocide achieved a statistically significant reduction in the prevalence and/or numbers of pathogenic target microorganisms compared to the control (e.g. water), and where the reduction had a positive impact on cases of human illness (EFSA, 2010). Since direct evidence for a reduction in illness was not available, EFSA relied on results of previous microbiological risk assessments which showed that reducing microbial contamination by as little as 0.5 log<sub>10</sub> could reduce consumer risk of illness to a significant extent. In this assessment, FSANZ has adopted the approach developed by EFSA.

The applicant provided results of published and in-house scientific studies on the efficacy of CPC for treating raw poultry. In line with the EFSA analysis (EFSA, 2012), appropriately controlled studies on the application of CPC to broiler carcasses, chicken skin, or skin-on chicken pieces were assessed and are summarised below and in **Error! Reference source not found.**

In initial laboratory scale experiments, CPC was shown to achieve reductions in levels of bacteria between 0.59 and 4.9 log units when applied at concentrations in the range 0.1-0.8% by spray or immersion for periods of time between 3 seconds and 10 minutes to chicken pieces inoculated with 10<sup>6</sup>–10<sup>7</sup> CFU *Salmonella* or *Campylobacter* (Arritt et al 2002; Breen et al 1997; Li et al 1997).

Subsequent trials confirmed that the laboratory-scale results could be translated to pilot-scale and commercial poultry processing plants (Beers et al 2006; and the applicant's in-house studies as provided to FSANZ and separately reported in EFSA 2012).

Beers and co-workers evaluated the effect of spray treatment with 0.5–0.7% CPC on levels of bacteria on visibly-contaminated broiler carcasses in three commercial poultry plants. Initial contamination levels of around 2–3 log CFU *E. coli* and *Campylobacter* were reduced by



1.2–2.9 log for *E.coli* and 0.5–2.1 log for *Campylobacter* when CPC was applied at 130-220 ml per kilogram of carcass. The incidence of carcass contamination with *Campylobacter* was reduced from >83% to <10%, while *Salmonella* incidence was reduced from 5-33% to 1–10% after CPC treatment.

In a series of in-plant trials, the applicant further assessed the efficacy of CPC in drench application to artificially-inoculated poultry carcasses at a range of concentrations and volumes and for a range of times (Table 2, and EFSA 2012). Reductions in levels and incidence of *E. coli*, *Salmonella* and *Campylobacter* support the findings of the earlier studies that demonstrate the efficacy of CPC when applied at concentrations in the range 0.1–1.0%.

In summary, the efficacy of pathogen reduction by CPC was found to be dependent on the volume and concentration of the active constituent, the exposure time, and the pressure of the spray treatment (where applicable). Significant reductions of up to 5 log units in levels of *E. coli*, *Salmonella* and *Campylobacter* were reported when CPC was applied at levels in the range 0.1–1.0% (w/v). The applicant's in-plant trials for the purpose of US and EU regulatory approvals are consistent with the results of earlier published laboratory and pilot plant scale studies.

It is concluded that the proposed use of CPC during processing can effectively reduce pathogen contamination on a variety of poultry products and can contribute, as part of a multi-hurdle approach, to the safety of poultry products for consumers.

#### **2.4.2 Potential for ongoing antimicrobial function**

Several studies—in both laboratory and commercial poultry processing settings—indicate that CPC does not perform an ongoing technological purpose as an antimicrobial in poultry products after the initial treatment. Using aerobic plate count (APC) as a measure of total bacterial load, CPC was shown to extend the shelf life of products by reducing the initial bacterial load on boneless, skinless thigh meat (Bai et al., 2007), skin-on carcass pieces (Baker et al., 2010) and whole broiler carcasses (Baker et al., 2007; Gilbert et al., 2015). In each of these studies, CPC treatment did not affect the rate of growth of the residual bacterial population during refrigerated storage, after the initial treatment, indicating that any residual CPC did not function as an antimicrobial. As CPC performs the antimicrobial function in the processing (washing) of poultry and does not perform a technological purpose after the initial treatment, it functions as a processing aid as defined in the Code.

**Table 2 Summary of CPC/CPC preparation efficacy studies**

Product treated	Reference (study design)	Process controls	Effectiveness (log reduction or incidence)
Poultry skin inoculated with <i>Campylobacter jejuni</i>	Arritt et al (2002) (laboratory-scale)	Sprayed with 0.1% and 0.5% (w/v) CPC at ~8psi pressure for 3 seconds	1.4 and 2.7 log reduction, resp., compared to water control
Pre-chill (immersion) broilers contaminated with ingesta	Beers et al (2006) (in-plant trial)	Sprayed with 0.5–0.7% (w/v) CPC	1.2–2.9 log for <i>E.coli</i> ; 0.5–2.1 log for <i>Campylobacter</i> . <i>Salmonella</i> : incidence reduced from 5–33% to 1–10%. <i>Campylobacter</i> : incidence reduced from >83% to <10%.
Poultry skin inoculated with <i>Salmonella</i> Typhimurium	Breen et al (1997) (laboratory-scale)	Skin (2.5x2.5 cm) immersed in 0.1–0.8% (w/v) CPC for 1, 3 or 10 min	Reduction dependent on time and CPC concentration. From 0.59 log (0.1%, 1 min) to 4.6-4.9 log (0.4% (w/v), 3 min; 0.2% (w/v), 10 min)
Pre-chill broilers inoculated with <i>Salmonella</i> Typhimurium	Li et al (1997) (laboratory-scale)	Sprayed with 0.1% (w/v) CPC at 207, 345 or 827 kPa pressure for 30 or 90 seconds.	Between 0.59 log CFU/bird (0.1% (w/v) CPC, 30 sec, 207kpa) and 1.6 log CFU/bird (0.1% (w/v) CPC, 90 sec, 827kpa) compared to water control
Pre- and post-chill carcasses	Safe Foods #60302 (in-plant trial) (see EFSA 2012)	Drench application: 0.9L of 0.1% (w/v) or 3.8L of 0.6% (w/v) CPC for 5 or 60 sec	Volume and concentration dependent reduction of <i>E. coli</i> . Between 0.37 log (0.1% (w/v), 0.9L, post-chill carcass) and 2.0 log (0.6% (w/v), 0.9L, pre-chill carcass)
Pre- and post-chill carcasses	Safe Foods #60401 (in-plant trial) (see EFSA 2012)	Drench application: 4.3L of 0.05% (w/v) CPC / bird for 60 sec or 2.2L of 0.6% (w/v) CPC / bird for 60 sec	Reduction of <i>E. coli</i> dependent on CPC volume and concentration. Up to 2.6 log—no remaining <i>E. coli</i> (0.6% (w/v), 2.2L, pre-chill carcass)
Pre- and post-chill carcasses	Safe Foods #60407 (in-plant trial) (see EFSA 2012)	Drench application: 0.4% (w/v) CPC; 2.2–5.7L/bird, 60 sec.	Reduction of <i>E. coli</i> dependent on CPC volume and concentration. Up to 2.0 log—no remaining <i>E. coli</i> (0.4% (w/v), 4.9L, pre-chill carcass)
Post-chill carcasses artificially inoculated	Safe Foods #60607 (in-plant trial) (see EFSA 2012)	Drench application: 0.95L of 0.2–1.0% (w/v) CPC for 60 sec	Reduction of <i>E. coli</i> dependent on CPC concentration. From 0.48 log (0.2% w/v) to 3.7 log—no remaining <i>E. coli</i> (1.0% w/v)
Pre-chill carcasses inoculated with <i>E. coli</i> & <i>Salmonella</i> Typhimurium	Safe Foods #60613 (in-plant trial) (see EFSA 2012)	Drench application: 0.95–1.9L of 0.2–1.0% (w/v) CPC for 60 sec	Reduction dependent on CPC volume and concentration. <i>E. coli</i> from 2.2 log (0.95 L of 0.2% w/v) to 4.8 log—no remaining <i>E. coli</i> (0.95L or 1.9L of 0.6–1.0% w/v). <i>Salmonella</i> from 2.8 log (0.95 L of 0.2% w/v) to 5.0 log—no remaining <i>Salmonella</i> (0.95L or 1.9L of 0.6–1.0% w/v).
Pre-chill carcasses	Safe Foods #61010 (in-plant trial) (see EFSA 2012)	Drench application: 3.8L of 0.2% or 1.0% (w/v) CPC for 60 sec	<i>E. coli</i> : 1.5 log (0.2% w/v) to 1.6 log—no remaining <i>E. coli</i> (1.0% w/v). <i>Campylobacter</i> : 0.72 log—no remaining <i>Campylobacter</i> (0.2% and 1.0% w/v CPC).
Pre-chill carcasses	Safe Foods #70414 (in-plant trial) (see EFSA 2012)	Drench application: of 0.6% (w/v) CPC	<i>E. coli</i> : 1.0 log reduction—no remaining <i>E. coli</i> .

## 2.5 Analytical methods for detection

Analytical methods for detection of CPC in poultry carcasses following treatment with the CPC preparation, developed by the applicant, were submitted to FSANZ as confidential commercial information (CCI). The applicant provided a summary of the analytical method, whereby for whole carcasses, the skin is removed and heated, the CPC extracted with ethanol and the resulting solution centrifuged to remove solids. The solids-free solution is analysed by HPLC to determine residual CPC. A similar method is used for poultry pieces.

## 2.6 Food technology conclusion

Raw poultry inherently carries a wide range of microorganisms, some of which are potential human pathogens. Analysis of the evidence provides adequate assurance that the application of CPC to the surface of skin-on raw poultry carcasses and pieces at levels ranging from 0.1 to 1% in the wash solution can effectively reduce the prevalence and levels of microorganisms, including relevant pathogens. FSANZ therefore concludes that the proposed use of CPC as an antimicrobial agent for skin-on raw poultry is technologically justified.

As CPC performs the anti-microbial function at the time of treatment (during the processing of poultry) and does not perform a technological purpose in the food for sale, it functions as a processing aid as defined in the Code.

There is a relevant specification for CPC in the Food Chemicals Codex (United States Pharmacopeial Convention 2020), a primary source of specifications listed in Schedule 3 of the Code.

Propylene glycol is added to Safe Foods' CPC preparation to act as a wetting agent or humectant in the processing of the CPC preparation and to maintain solubility and stability in the preparation after processing. Propylene glycol is currently permitted for use both as a food additive permitted at GMP and as a processing aid, in accordance with the Code.

## 3 Hazard assessment

The hazard assessment for this application primarily focuses on the active constituent, CPC as well as the CPC preparation, in particular, the propylene glycol.

The applicant submitted a number of proprietary toxicity studies it had commissioned on CPC or the CPC preparation. These were a 14-day palatability study, 28-day and 90-day dietary toxicity studies in rats and dogs, an *in vitro* chromosome aberration study and a bacterial reverse mutation assay. As these studies are considered Confidential Commercial Information, only limited details are included in this report. In addition, a number of industry reports and studies from the published literature were provided. Some of these studies were on other products containing CPC as well as other substances, and therefore of limited relevance for evaluating the safety of CPC itself.

Several proprietary toxicity studies of CPC that are not available to the applicant or FSANZ have been reviewed by overseas bodies. Limited details of these studies are included in the sections below, but cannot be verified by FSANZ.

### 3.1 Industrial use of the chemical

CPC is a cationic quaternary ammonium compound found in many types of commercially

available products around the world such as mouthwash, toothpaste, sore throat lozenges and throat sprays, as well as oral gels for teething, cold sores, ulcers and other abrasions, baby wipes and antiseptic wipes.

### **3.2 Use of the chemical as a food processing aid in other countries**

The CPC preparation is approved for use in the USA as an antimicrobial agent applied in a pre-chiller or post-chiller solution to raw poultry carcasses. The most recent US FDA approval documentation was published in 2007. The CPC preparation is also approved as an antimicrobial treatment of raw poultry carcasses in Canada, Russia, Mexico, Panama, Costa Rica, Colombia, Ecuador, El Salvador, Guatemala, Uruguay, Israel, Jordan, Peru, Saudi Arabia, South Africa, and the United Arab Emirates.

### **3.3 Toxicokinetics and metabolism**

Full reports of toxicokinetic and metabolism studies with CPC were not submitted by the applicant, and no publicly available studies were identified in a literature search by FSANZ.

A submission on CPC-containing mouthrinses to the Plaque Subcommittee of the US Food and Drug Administration (FDA) Dental Panel, provided by the applicant, includes limited summaries of pharmacokinetic studies in rats and dogs (Genco 1995). In the rat, approximately 85% of a single dose of radiolabelled CPC was detected in the faeces and approximately 10% in the urine. The dog study was reported to be inconclusive because only 56.5% of the radiolabelled CPC was recovered from the urine, faeces, cage rinses, organs and carcass. These results are also reported by the US FDA in a safety assessment of the use of CPC as an antigingivitis/antiplaque agent in mouth rinses (US FDA 2003).

These proprietary pharmacokinetic studies with CPC, unavailable to the applicant or to FSANZ, have also been considered by the European Scientific Committee on Consumer Safety (SCCS) in a safety assessment of the use of CPC in mouthwashes, other oral hygiene cosmetic products, skin lotions and creams, and antiperspirant deodorants.

The SCCS reported that two toxicokinetic studies with CPC in rats and three in dogs were submitted, but it was unable to evaluate these studies because parts of the reports were poorly legible. The SCCS commented that the available data suggested > 10% oral absorption in rats and dogs and that as well as urinary excretion, biliary excretion of CPC occurs in rats (SCCS 2015).

Public summaries of some of these studies (one in rats and two in dogs) are also available as part of a REACH<sup>7</sup> registration dossier for CPC on the European Chemical Agency (ECHA)'s website.

In the absence of the full toxicokinetic study reports for review FSANZ is unable to draw conclusions as to the absorption, distribution, metabolism and excretion of CPC. However, it is noted that reviews by overseas authorities indicate oral absorption greater than 10% of CPC in rats and dogs with elimination occurring via the urine, bile and faeces. Information on metabolism does not appear to be available.

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<sup>7</sup> EU Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals.

## **3.4 Toxicity studies**

### **3.4.1 Acute toxicity studies**

#### ***Studies in animals***

The LD<sub>50</sub> of CPC in male Sprague-Dawley rats following oral administration was reported to be 200 mg/kg bw. Large oral doses were reported to cause erosion of the gastric mucosa, and at fatal doses peripheral paralysis and central nervous stimulation were observed (Nelson and Lyster 1946). In another study, the LD<sub>50</sub> of CPC in male rats was calculated to be 428 mg/kg bw when administered in water and 192 mg/kg bw in 50% DMSO. In female mice, LD<sub>50</sub>s were 195 and 108 mg/kg bw, respectively (Rosen et al. 1965).

In a more recent study, an LD<sub>50</sub> of 400 mg/kg bw for male and female rats combined was reported. Clinical signs in animals that died and survivors included diarrhoea, lethargy, piloerection, dyspnea, and chromodacryorrhoea. Necropsy of the dead animals found abnormalities of the lungs, liver, spleen, pancreas, pleural cavity and gastrointestinal tract (Zeeland Chemicals 1995).

In rabbits, CPC doses of 300, 400, 500, 600 and 700 mg/kg bw caused mortality in 0, 1, 5, 4 and 4 of 6 animals, respectively. Most of the rabbits developed diarrhoea (Warren et al. 1942).

*Other studies not available to FSANZ*

In a proprietary GLP acute oral toxicity study not available to FSANZ but reviewed by the SCCS, the LD<sub>50</sub> in female Sprague-Dawley rats was estimated to be 560 mg/kg bw with approximate 95% confidence intervals of 950 mg/kg and 300 mg/kg (SCCS 2015).

#### ***Reports in humans***

A textbook provided by the applicant states that the fatal dose of CPC and other quaternary ammonium compounds has been estimated as being between 1 and 3 g. The principal signs following ingestion are stated to be vomiting, collapse and coma due to caustic effects (Arena and Drew 1986).

### **3.4.2 Short-term studies of toxicity**

#### ***Studies commissioned by the applicant***

##### ***Rats***

*14-day palatability study in rats (Redfield Laboratories 2002a) Regulatory status: GLP; non-guideline*

Sprague-Dawley rats (5/sex/group) were administered 0, 100, 500, 1000, 1500 or 2000 ppm CPC in the diet for 14 days. Clinical signs were recorded daily and body weight and feed consumption was measured every 2 to 3 days.

Thinness was observed in one female in the high dose group, which corresponded with lower feed consumption. Dose-dependent reductions in body weight were observed in males and females, with a significant effect starting at 1000 ppm in males and 1500 ppm in females. The no observed adverse effect level (NOAEL) in this study was considered to be 500 ppm CPC in the diet.

*28-day dietary toxicity study in rats (Redfield Laboratories 2002b) Regulatory status: GLP; consistent with OECD test guidelines*

CPC was administered in the diet to Sprague-Dawley rats (10/sex/group) at concentrations of 0, 125, 250, 375, 500, 750 or 1000 ppm for 28 days. Clinical signs were monitored daily. Body weights and feed consumption were measured weekly. Haematology, clinical chemistry and urinalysis parameters were assessed at the end of the study. All animals underwent gross necropsy and specified tissues were analysed microscopically.

Dose dependent decreases in body weight and body weight gain were reported, significantly lower than controls at dietary concentrations of 750 and 1000 ppm in both sexes. A corresponding decrease in feed consumption in these groups was considered dose responsive. No clinical observations were considered test article-related and necropsy found no treatment-related changes.

The study authors concluded that the no observed effect level (NOEL) was 250 ppm CPC. The NOAEL was considered by the authors to be 1000 ppm.

*13-week dietary toxicity study in rats (Charles River Laboratories 2006a) Regulatory status: GLP; conducted in accordance with OECD Test Guideline 408*

Sprague-Dawley rats (20/sex/group) were fed diets containing 0, 125, 250, 500 or 1000 ppm CPC for 91 days. Clinical observations and measurements of body weight, feed consumption, ophthalmology, neurology, haematology, coagulation, clinical chemistry and urinalysis were performed. Complete necropsy was performed on day 92, organ weights and gross lesions were recorded and histopathology was performed.

One male in the 250 ppm group was found dead on study day 66. This death was considered to be unrelated to the test item as histopathological examination indicated inflammation of the heart as the probable cause of death. No treatment-related clinical signs were observed in all other animals. Mean body weights were decreased in males given 1000 ppm from study day 8 and in females given 1000 ppm from study day 22. Feed consumption was also significantly lower in high dose animals. It was not clear if these effects were due to palatability issues or caused by the test item. No changes in ophthalmology, neurological functions were reported. Intermittent changes in clinical pathology were not considered to be adverse and no gross lesions were recorded at necropsy.

The study authors concluded that the NOEL in this study was 250 ppm, and the NOAEL was 1000 ppm. However, FSANZ considers that the NOAEL in this study was 250 ppm.

## **Dogs**

*28-day dietary dose range-finding study in dogs (Charles River Laboratories 2006b) Regulatory status: Non-GLP, non-guideline*

Beagle dogs (1/sex/group) were given diets containing 0, 250, 500, 1000 or 1500 ppm CPC for 28 days. Animals were monitored daily for clinical signs. Body weights, feed consumption, haematology, clinical chemistry, coagulation and urinalysis parameters were recorded. All animals were subjected to gross necropsy on day 29. Organ weights were recorded and histopathology was performed on all tissues from control and high dose dogs, and the kidney from dogs given 250, 500 or 1000 ppm.

All animals survived to scheduled termination. The incidence of abnormal stool (soft or watery) was increased in treated animals compared with controls. The study authors noted that it was unclear whether this was related to the test article. Animals administered 1500

ppm had a decrease in body weight from study day 8 to 28. Feed consumption was consistently less in both sexes in this group. The study authors considered that these effects may have been due to palatability issues with the test item rather than an effect of the test item itself. No treatment-related changes in haematology, coagulation or urinalysis parameters were observed. Alanine aminotransferase (ALT) was increased above the test facility normal ranges in the male administered 1000 ppm, and in the females administered 1000 and 1500 ppm, but was not considered adverse as there were no accompanying histopathological lesions.

The study authors concluded that the NOEL was 500 ppm. The NOAEL was 1000 ppm based on decreased body weights and feed consumption at 1500 ppm.

FSANZ notes that this study is of limited value for regulatory purposes given the use of a single animal of each sex and the inability to achieve a clear separation of increasing doses, most likely due to palatability issues.

*13-week dietary toxicity study in dogs (Charles River Laboratories 2006c) Regulatory status: GLP; conducted in accordance with OECD TG 409 and FDA Redbook*

Beagle dogs (4/sex/group) were administered diets containing 0, 250, 375, 500 or 1000/500 ppm CPC for 90 days. Clinical signs were monitored, body weights, and feed consumption were recorded. Physical, ophthalmology, cardiology and neurological exams were performed and clinical pathology was evaluated. Post-mortem, organ weights were recorded and macroscopic and microscopic evaluations were performed.

Thinness was observed in males in the 375, 500 and 1000 ppm groups, as well as females given 1000 ppm. Mean body weights decreased in males given 1000 ppm from day 8 – 36. Due to corresponding decreases in feed consumption in this group, the test item was withdrawn from days 29 – 42 in males and days 29 – 41 to females, and after the dosing break the test item concentration was adjusted to 500 ppm. All animals had normal physical exams and no treatment-related changes in neurological, ophthalmology, cardiology, clinical chemistry and urinalysis. Changes in haematology parameters were observed at higher doses. No histopathological changes were reported.

The study authors concluded that the NOEL in this study was 250 ppm. It was concluded that the NOAEL was 375 ppm. FSANZ considers the NOAEL to be 250 ppm, equal to 8 mg/kg bw/day, based on changes in body weight and haematology parameters in males administered 375 ppm.

### ***Studies of CPC not commissioned by the applicant***

#### ***Rats***

*90-day oral toxicity study in rats (USAEHA 1969) Regulatory status: non-GLP, non-guideline*

In a 90-day study, groups of 6 male and 6 female rats (strain and age unspecified) were fed diets containing 0, 125, 300, 800, 2000, 5000 or 10,000 ppm CPC. These concentrations resulted in doses of 0, 6.6, 15.8, 44.9 or 128.4 mg/kg bw/day in the 0, 125, 300, 800 or 2000 ppm group males, respectively. In females, the doses at these concentrations were 0, 9.7, 29.4, 56.8 or 144.6 mg/kg bw/day, respectively. Doses at 5000 and 10,000 ppm were not reported but were equivalent to approximately 250 or 500 mg/kg bw/day, respectively. CPC was dissolved in ethanol prior to addition to the feed, and the ethanol was removed from feed by evaporation.

All animals fed diets containing 5000 or 10,000 ppm CPC died within the first three weeks of

the study. Mean body weight, body weight gain and food utilisation were significantly lower than controls in rats given 2000 ppm. No significant differences in food consumption were observed. In males, increased liver, kidney and testes weights relative to body weight were observed at the high dose compared with controls. Relative caecum weight (full or empty unspecified) was increased in males given 800 and 2000 ppm. In females, relative liver and kidney weights were increased at 2000 ppm, and relative caecum weight was increased at concentrations  $\geq$  300 ppm. As the dietary concentration of CPC increased, the total number of microorganisms recovered in the caecal contents was decreased. No substantial differences in the genera of caecal bacterial flora were observed. No treatment-related gross or histopathologic changes were observed in the liver, kidneys, lung, spleen, caecum and testes.

The study authors concluded that the NOAEL in this study was 125 ppm, equal to 7 mg/kg bw/day, based on increased caecal weights in females at 300 ppm (equal to 29 mg/kg bw/day).

### **Rabbits**

*4 week oral toxicity study in rabbits (Warren et al. 1942); Regulatory status: non-GLP, non-guideline*

Rabbits (age and sex unspecified) were orally administered (method not reported) 0 (6 animals), 10 (12 animals) or 100 (10 animals) mg/kg bw/day CPC for four weeks. At the end of the treatment period 50% of animals in each group were killed and examined for gross pathological changes, and tissues (unspecified) were taken for histological examination. The remainder of the animals were killed and examined following a two week treatment-free period.

No treatment-related gross pathological conditions were observed. Many liver sections showed varying degrees of vacuolisation of the cytoplasm of hepatocytes. This was diffuse and not limited to any particular portion or zone of the lobule. This change was also observed in two control animals so it was uncertain whether it was treatment-related. Vacuolisation was observed in the kidney, in the cytoplasm of the cells lining the tubules. This change was observed to some extent in all groups but was more pronounced in animals in the high dose group. Some cloudy swelling of tubular cells was also observed, but there was no degeneration of the nuclei or pathological changes in the glomeruli. There were no histopathological changes in any other tissues. The study authors concluded that the results of this study indicate that administration of CPC at doses up to 100 mg/kg bw/day for four weeks did not induce any significant toxic effects.

FSANZ notes that this study is not suitable for regulatory purposes due to the limited details reported.

### **Studies of CPC not available to FSANZ**

Several proprietary short-term studies of CPC that are unavailable to FSANZ have been reviewed by the SCCS. The SCCS reviews of these studies are briefly summarised below (SCCS 2015).

In a 28-day oral toxicity study, Sprague-Dawley rats (8/sex/group) were administered 0, 25, 50, 100, 200 or 400 mg/kg bw/day CPC by oral gavage. Mortality occurred in some or all animals at doses  $\geq$  100 mg/kg bw/day. Body weight gain was reduced at all dose levels. The target organ was considered to be the stomach, with histopathological changes indicative of localised irritation (acanthosis and necrosis/erosion observed in the non-glandular region of the stomach at doses  $\geq$  50 mg/kg bw/day. The NOAEL was considered to be 25 mg/kg



bw/day.

In a 28-day oral toxicity study in dogs (3/sex/group), CPC was administered via a gelatin capsule at doses of 0, 5, 25, 125, 250 or 500 mg/kg bw/day. All animals in the high dose group died or were killed in extremis during the study, as well as two animals of each sex at 250 mg/kg bw/day and two males and one female at 125 mg/kg bw/day. Clinical signs observed at  $\geq 25$  mg/kg bw/day included dehydration, abnormal head movements, decreased activity, decreased defecation, emesis, mucoid diarrhoea, discoloured faeces and pytalism. Decreased body weight or body weight gain and decreased food consumption were observed at  $\geq 25$  mg/kg bw/day. Local effects were observed in the gastrointestinal tract including erosion, ulcers and/or acute/subacute inflammation in the oesophagus, stomach, duodenum, ileum, colon and/or rectum in both sexes at doses  $\geq 125$  mg/kg bw/day, with localised effects in the stomach observed in one male in both the 5 and 25 mg/kg bw/day groups. Atrophy of the thymus and decreased relative thymus weight were observed at 125 and 250 mg/kg bw/day. The NOAEL for systemic toxicity was considered to be 250 mg/kg bw/day based on mortality and decreased thymus weight and thymus atrophy at 125 mg/kg bw/day. The NOAEL for local effects was  $< 5$  mg/kg bw/day based on effects in the gastrointestinal tract at all dose levels.

### **Studies of mixtures containing CPC**

The applicant also submitted a number of short-term toxicity studies of pharmaceutical formulations containing CPC together with other ingredients. These studies are of limited value for the assessment of CPC given the presence of other compounds and the low concentration of CPC in these formulations. These studies are briefly summarised in Table 3.

**Table 3 Short-term toxicity studies of pharmaceutical formulations containing CPC plus other ingredients**

<b>Author/Testing party</b>	<b>Test item</b>	<b>Species</b>	<b>Study type/doses</b>	<b>Summary of results</b>
<b>Scientific laboratories (1969)</b>	Cepacol anaesthetic gargle (0.05% CPC)	Rats	30-day oral toxicity study (non-GLP; non-guideline)  Up to 10 mL/kg bw/day administered by oral gavage	No treatment-related effects reported.
<b>Richardson-Merrell SpA (1972)</b>	Cepacaine cough drops dissolved in water (1.68 mg CPC per tablet)	Rats	1-month oral toxicity study (non-GLP; non-guideline)  Up to 7 mg/kg bw/day CPC administered by oral gavage	No treatment-related effects reported.
<b>Richardson-Merrell SpA (1972)</b>	Cepacaine cough drops dissolved in water (1.68 mg CPC per tablet)	Rats	95-day oral toxicity study (non-GLP; non-guideline)  Up to 7 mg/kg bw/day CPC administered by oral gavage	No treatment-related effects reported.
<b>Richardson-Merrell SpA (1972)</b>	Cepacaine spray (0.05 % CPC)	Rats	18-day local tolerability study  100 mg cepacaine (route not specified; presumed oral)	No signs of intolerance in the trachea, pharynx, larynx or mouth.

<b>Proctor and Gamble (1979)</b>	Scope mouthwash (0.045% CPC)	Rats	91-day oral toxicity study (GLP status unspecified)  Up to 20 mL/kg bw/day administered by oral gavage	No treatment-related effects reported.
<b>Scientific Laboratories (1965)</b>	Cepa-Truss troche (1:1500 CPC)	Dogs	1-month oral toxicity study (non-GLP; non-guideline)  1 troche/kg bw/day	No treatment-related effects reported.
<b>Scientific Laboratories (1969)</b>	Cepacol anaesthetic gargle (0.05% CPC)	Dogs	1-month oral toxicity study (non-GLP; non-guideline)  Up to 10 mL/kg bw/day administered by oral gavage	No treatment-related effects reported.

### 3.4.3 Long-term studies of toxicity and carcinogenicity

No chronic toxicity or carcinogenicity studies of CPC were submitted by the applicant, and no full reports of chronic toxicity or carcinogenicity studies are publicly available.

A submission on CPC-containing mouthrinses to the Plaque Subcommittee of the US Food and Drug Administration (FDA) Dental Panel provides limited details of studies of 6 months and 1 year in duration (Genco 1995). In these studies CPC was administered by oral gavage to animals (species and number unspecified) at doses ranging from 5 – 75 mg/kg bw/day. Significant decreases in body weight and body weight gain were noted in animals of both sexes administered 40 and 75 mg/kg bw/day. At necropsy, gastrointestinal irritation, manifested as thickening of the stomach mucosa, was observed at 40 and 75 mg/kg bw/day and in some animals administered 15 mg/kg bw/day.

Additional details of this study are included in the SCCS evaluation of CPC and in a public summary of the study REACH registration dossier for CPC on the ECHA website. The SCCS notes that the study was conducted in Sprague-Dawley rats (20/sex/group). Decreased body weight gain was also observed in females at 15 mg/kg bw/day. A higher incidence of a distended caecum was observed in males at 15 – 75 mg/kg bw/day and in females at 75 mg/kg bw/day. Histopathology showed acanthosis in the non-glandular stomach at doses  $\geq$  15 mg/kg bw/day (SCCS 2015). The summary of the study on ECHA's website notes that the distention of the caecum may not have been a direct effect of the test material or due to gastric irritation, but may have been caused by alterations in the gut microflora due to chronic feeding of the test material.

A toxicity profile of CPC prepared by BIBRA summarises limited details of a 1 year study in which CPC incorporated in a vinyl copolymer was administered via the diet to rats (10/sex/group; strain not specified) at levels providing doses of 7 or 35 mg/kg bw/day (BIBRA 1988). No clinical effects or blood changes were observed. Examination of most of the major tissues revealed no gross or microscopic abnormalities, including no evidence of carcinogenicity. As noted by BIBRA, this study would have limited power to detect carcinogenic activity as it did not follow current test guidelines regarding animal numbers, study duration and the range of tissues that should be examined.

FSANZ notes that these reports are not suitable for regulatory purposes given the very limited details provided and the inability to access the original study reports.

### **3.4.4 Developmental and reproductive studies in animals**

No developmental or reproductive toxicity studies of CPC were submitted by the applicant, and no full reports of such studies are publicly available.

A submission from Proctor and Gamble to the US FDA's OTC Review Panel on Oral Cavity Drug Products provides limited details of a teratogenicity study of CPC as well as CPC and domiphen bromide (DB) at a 9:1 ratio (Proctor & Gamble 1979). Groups of 15 pregnant New Zealand specified pathogen free (SPF) rabbits were administered 0, 2.5, 12 or 100 mg/kg bw/day CPC, or the same levels of CPC to which one-ninth as much DB had been added (0, 0.28, 1.33 or 11.08 mg/kg bw/day) by oral gavage from gestation days 7 – 18. The highest dose was lethal to most dams and was discontinued. The six remaining untreated dams scheduled for inclusion in the two high dose groups were given either 25 mg/kg bw/day CPC or 25 mg/kg bw/day CPC plus 2.85 mg/kg bw/day DB. At the end of the treatment 1/15 dams given 12 mg/kg bw/day CPC and 1/6 dams given 25 mg/kg bw/day died. Gross necropsy of these animals indicated severe irritation of the gastrointestinal tract, marked by diarrhoea and gastric ulceration.

Loss of body weight was observed in dams in the 25 mg/kg bw/day CPC, 25 mg/kg bw/day CPC + 2.8 mg/kg bw/day DB and 12 mg/kg bw/day CPC groups, which was associated with anorexia. Six dams aborted fetuses: one given 2.5 mg/kg bw/day CPC, two given 12 mg/kg bw/day CPC, two given 25 mg/kg bw/day CPC and one given 25 mg/kg bw/day CPC + 2.8 mg/kg bw/day DB. These abortions were considered probably related to maternal toxicity, which included anorexia and weight. No significant differences in the average number of corpora lutea were observed. The high dose CPC group showed a higher incidence of resorptions which did not reach statistical significance, considered likely to be due to maternal toxicity. Significant differences in the number of implants in the high dose CPC and CPC + DB groups, compared to controls, were not considered treatment-related as dosing occurred post-implantation. Reductions in the number of live fetuses in the two high dose groups were considered likely to be a result of the lower number of implants or maternal toxicity. Female foetal weights in the high dose CPC group were lower than controls. No significant differences in the average number of male or female fetuses were observed. The test items were reported to be increasingly toxic to the dams with increasing dose with secondary toxicity in the embryos or fetuses, with further details not provided. There were no differences in the incidence of foetal soft tissue or skeletal abnormalities between controls and treated groups, and no treatment-related teratogenic effects were observed.

An abstract reports details of a teratology study in which CPC was administered to pregnant rats (strain and group sizes not reported) at doses ranging up to 27.33 mg/kg bw/day from gestation days 6 – 15 (Gilman and De Salva 1979). Dams were killed on gestation day 20 and the fetuses were examined. Mean body weights of dams were reduced in dams given 27.33 mg/kg bw/day, but no clinical manifestations of skeletal deformity were observed.

BIBRA's CPC toxicity profile summarises a study in which CPC incorporated in a vinyl copolymer was administered in the diet to groups of four female rats (strain not specified) at levels providing 7 or 35 mg/kg bw/day for three months prior to mating and during pregnancy and lactation (BIBRA 1988). At weaning, offspring were given the same diet as their mothers for three months prior to mating and throughout pregnancy and lactation. Third generation offspring were also fed the CPC diet and mated after three months. Fertility and the incidence of malformations were within normal limits in each generation.

The SCCS review of CPC summarises details of a developmental toxicity study in Sprague-Dawley rats, in which CPC was administered by gavage at doses of 0, 5, 15 or 60 mg/kg bw/day during gestation days 6 – 16. Maternal toxicity (reduced body weight gain, decreased defecation and laboured breathing) was observed at 60 mg/kg bw/day, but there was no

evidence of developmental toxicity at any dose (SCCS 2015).

The REACH registration dossier for CPC notes that in the 6-month oral gavage toxicity study in rats (doses up to 75 mg/kg bw/day) no histopathological changes were observed in the reproductive organs.

FSANZ notes that these reports are not suitable for regulatory purposes given the very limited details provided and the inability to access the original study reports.

### **3.4.5 Genotoxicity**

#### ***Studies of the CPC preparation commissioned by the applicant***

*Bacterial reverse mutation assay with the CPC preparation (Next Century Incorporated 2002)  
Regulatory status: GLP; Conducted in accordance with OECD TG 471 (1997)*

The CPC preparation was tested in a bacterial reverse mutation assay in *Salmonella typhimurium* strains TA97a, TA98, TA100 and TA1535 plus *Escherichia coli* WP2 uvrA (pKM101) in the presence and absence of metabolic activation (rat liver S9 mix). The vehicle control was water.

No treatment-related increases in the number of revertant colonies were observed in the presence or absence of metabolic activation in any strain.

It was concluded that the CPC preparation was not mutagenic under the conditions of the study.

*In vitro mammalian chromosome aberration assay with the CPC preparation (Next Century Incorporated 2001) Regulatory status: GLP; Conducted in accordance with OECD TG 473 (1997)*

The CPC preparation was evaluated for its ability to induce chromosome aberrations in Chinese Hamster Ovary (CHO) cells *in vitro*. The assay was performed using duplicate cultures. Water was used as the vehicle control.

Treatment with the CPC preparation did not increase the frequency of cells with chromosome aberrations or structural chromosomal aberrations.

It was concluded that the CPC preparation was not clastogenic under the conditions of this study.

#### ***Other studies***

The applicant also submitted a number of other studies that provide some limited additional information on the potential genotoxicity of CPC, and an additional study was identified by FSANZ in a literature search. These studies are briefly summarised below.

In a study of a representative Xerox reprographic toner containing 2% CPC, a thermoplastic polymer (major component) and carbon black, negative results were reported in a range of tests, listed below (Lin 1999). The results of these assays are of uncertain relevance for the assessment of CPC given the test item contained a number of ingredients in addition to CPC itself.

- Bacterial reverse mutation assay with *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 at concentrations up to 1000 µg/plate in the presence and absence of metabolic activation (S9 mix).
- Mouse lymphoma assay in L5178Y TK+/- cells at concentrations up to 400 µg/mL in the absence of S9 and up to 300 µg/mL in the presence of S9.
- Sister chromatid exchange assay in CHO cells at concentrations up to 100 µg/mL in the presence and absence of S9.
- BALB/3T3 in vitro cell transformation assay at concentrations up to 0.16 µg/mL.
- Micronucleus assay in bone marrow of rats exposed to toner via inhalation (whole body exposure) at concentrations up to 1343 mg/m<sup>3</sup>, 6 hours/day, 5 days/week for 13 weeks.

Cepacol mouthwash (0.05% CPC; 16.8% ethanol) produced positive responses in the *Drosophila melanogaster* Wing Spot test (Rodrigues et al. 2007). Induction of mitotic recombination was detected in flies exposed as larvae to feed rehydrated with the test item at concentrations of 75% and 100%. Subsequent studies with ethanol or CPC tested individually at the same concentrations as those present in the mouthwash showed that ethanol produced a positive response but CPC did not. The study authors concluded that the genotoxic effects of Cepacol mouthwash observed in this study were likely to be due to the ethanol content rather than CPC.

Buccal mucosa cells obtained from healthy human volunteers (15/group) before and after two weeks of using one of five mouthwashes twice a day were evaluated for the presence of micronucleated cells (Carlin et al. 2012). The mouthwashes tested included Cepacol (0.05% CPC; 17.6% ethanol; 225 ppm sodium fluoride), Plax alcohol free (0.05% CPC; 225 ppm sodium fluoride) and Plax whitening (0.05% CPC; 17.6% ethanol; 225 ppm sodium fluoride; 1.5% hydrogen peroxide). Compared with baseline, no significant differences in the frequency of micronucleated cells following two weeks of using the CPC-containing mouthwashes. In addition, comet assays were performed *in vitro* with the mouthwashes on peripheral blood cells obtained from three healthy human volunteers. Exposure to Cepacol and Plax alcohol free for 1 hour did not induce DNA strand breaks as measured by comet tail moment. Plax whitening induced a significant increase in tail moment, which was attributed to the presence of hydrogen peroxide in this mouthwash.

Two additional studies submitted by the applicant were not reviewed by FSANZ as they were not considered to provide relevant information. Yamaguchi and Yamashita (1979) assessed the impact of co-exposure to CPC or other detergents on the mutagenicity of autooxidised linolenic acid in a bacterial reverse mutation assay. However CPC was not tested alone in this study. The other study assessed the effects of CPC on chromosome aberrations at anaphase in root meristems of *Vicia faba* (broad bean), which are of uncertain relevance for mammalian cells (Smith and Lotfy 1955).

#### **Studies of CPC not available to FSANZ**

Several additional proprietary genotoxicity studies of CPC were reviewed by the SCCS: a bacterial reverse mutation test, *in vitro* mammalian cell gene mutation and chromosome aberration tests and an *in vivo* mouse bone marrow micronucleus test (SCCS 2015). An additional bacterial reverse mutation assay is summarised in the REACH registration dossier for CPC. No evidence of genotoxicity was reported in any of these studies.

### **3.5 Potential for allergenicity**

No reports of food allergy attributed to consumption of CPC or the CPC preparation were identified in a literature search.

A single case report of an immediate hypersensitivity reaction to a throat spray containing CPC was identified (Shima et al. 2015). A 67 year old male with a history of using throat lozenges and throat sprays developed generalised wheals, swelling of the eyelids and lips and dyspnoea twenty minutes after taking prescription medicine and using a throat spray. He recovered after receiving systemic corticosteroid therapy. Drug lymphocyte stimulation tests for two of the medications he was taking, loxoprofen sodium and cefcapene pivoxil hydrochloride, were negative. Prick tests for all components of the throat spray (glycerol, propylene glycol, l-menthol, citric acid, sodium citrate and CPC) did not induce a positive reaction after 15 minutes. An intradermal test with a 1% CPC solution induced a wheal 23 mm in diameter and erythema > 50 mm in diameter after 15 minutes, accompanied by throat irritation. The individual's forearm was severely swollen and tender several hours after the skin tests, and systemic corticosteroid therapy was administered. Signs and symptoms were relieved within a week. Prick and intradermal tests with CPC in five healthy subjects gave negative results, suggesting that the symptoms were not caused by a non-immunological reaction. The study authors concluded that the individual had an immediate hypersensitivity reaction caused by CPC in the throat spray.

Several case reports and studies have recorded incidents of allergic contact dermatitis attributed to the presence of CPC as part of the lubricant in latex and latex-free medical gloves (Castelain and Castelain 1993; Steinkjer 1998; Baeck et al. 2012; Pontén et al. 2012).

### **3.6 Safety assessments by international agencies or other national government agencies**

#### ***Antimicrobial uses of CPC for poultry***

The US FDA has assessed the safety of the CPC preparation as an antimicrobial agent in pre-chiller or post-chiller solutions for application to raw poultry carcasses. The US FDA established an acceptable daily intake (ADI) of 0.008 mg/kg bw/day CPC (equivalent to 0.48 mg/person/day for a 60 kg individual), based on the NOEL of 8 mg/kg bw/day in the 90 day dietary toxicity study in dogs and a 1000-fold safety factor. Mean and 90<sup>th</sup> percentile estimated daily intakes of CPC from the proposed use were 0.0275 and 0.065 mg/person/day, and it was concluded that the proposed use was safe for humans (US FDA 2007).

The applicant's CPC preparation was assessed by the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) in 2012. The CEF Panel concluded that there was no concern for genotoxicity of CPC. A health-based guidance value (HBGV) could not be established for CPC due to the lack of available studies of long-term, developmental and reproductive toxicity. However, a point of departure of 18 mg/kg bw/day was identified, which was the NOAEL from the 90-day dietary toxicity study in rats. The NOAEL was based on findings of increased caecal weight relative to body weight at higher doses, which the Panel considered could potentially be related to an effect on the composition of gastrointestinal microbiota. A comparison of this NOAEL with estimated dietary exposures gave margins of safety > 3000 and > 1000 for mean and 97.5<sup>th</sup> percentile exposures, respectively.

The applicant also provided documentation indicating that the safety of the CPC preparation as an antimicrobial treatment for poultry carcasses was assessed by Health Canada in 2008 and the Russian Ministry of Public Health in 2004.

#### ***CPC in oral hygiene products***

The safety of CPC as an antigingivitis/antiplaque agent in mouthrinse formulations has been

evaluated by the US FDA. It was noted that FDA spontaneous adverse reaction and adverse events reports suggest that clinical experience of long-term over the counter use of CPC-based products has not revealed overt toxic manifestations. Oral irritation as well as tooth and tongue staining may occur with such products, however. Based on the available toxicity studies, human clinical trials and adverse event data collected during more than 55 years of US marketing of mouthrinses containing CPC, the FDA concluded that CPC is safe in mouthrinse formulations at concentrations of 0.045 – 0.1% (US FDA 2003).

The EU SCCS has also assessed the safety of CPC as a preservative in mouthwashes up to a concentration of 0.1%, all other oral hygiene cosmetic products up to 0.5%, skin lotions and creams up to 0.2% and antiperspirant deodorants up to 2.0%. For dermal application, the NOAEL of 18 mg/kg bw/day identified by EFSA was used to derive a margin of safety (MOS). Oral gavage studies were considered more relevant for the assessment of the oral applications, however. The SCCS identified a NOAEL of 5 mg/kg bw/day from the 6-month study in rats for use in MOS calculations for use of CPC in oral hygiene cosmetic products including mouthwashes. The SCCS noted that aggregate exposure to CPC from cosmetic products together with treated poultry, based on worst case default assumptions for dermal and oral absorption, may be of concern for some consumers based on a MOS < 100. However the Committee considered that simultaneous exposure from all cosmetic products and treated poultry is unlikely (SCCS 2015).

The SCCS also reviewed cosmetovigilance data on undesirable events associated with oral care products containing CPC collected by European companies from the period 1<sup>st</sup> July 2013 to 31<sup>st</sup> December 2014. The overall European industry rate of reported incidents classed as 'likely' or 'very likely' to be due to products containing CPC was estimated to be 0.76 per million units sold. The overall rate for undesirable effects considered 'likely' or 'very likely' and classified as oral mucosal irritation was estimated at 0.35 per million units sold. The company data was reported to indicate that oral mucosal irritation associated with CPC-based oral rinses is typically mild, self-limiting and may be confounded by pre-existing conditions given the purposes mouthwashes are typically used for. The SCCS concluded that with the exception of potential skin, eye and oral mucosal irritation, the use of CPC in the products assessed is safe for consumers (SCCS 2015).

### ***Propylene glycol***

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established an acceptable daily intake (ADI) of 0-25 mg/kg bw for propylene glycol (WHO 1974). The Committee noted that propylene glycol is normally metabolised to lactic acid, and established the ADI based on the dose causing no toxicological effect in 2-year dietary toxicity studies in rats and dogs (2500 and 2000 mg/kg bw/day, respectively) and a 100-fold uncertainty factor. In the study in dogs, findings suggestive of increased erythrocyte destruction with a compensatory increased rate of haematopoiesis were observed at 5000 mg/kg bw/day. No other adverse effects were observed in this study. The ADI was maintained by JECFA at its 59<sup>th</sup> meeting (WHO 2002).

The European Scientific Committee on Food (SCF) evaluated propylene glycol as a food additive on several occasions and agreed with the ADI established by JECFA (reviewed in EFSA 2018). EFSA re-evaluated propylene glycol in 2018 and concluded that there was no reason to revise the ADI of 25 mg/kg bw/day (EFSA 2018).

The European Medicines Agency (EMA) considered the use of propylene glycol as an excipient in pharmaceutical products in 2017. The EMA concluded based on the available animal and clinical data that for adult patients and children ≥ 5 years of age, up to 500 mg/kg bw/day administered orally or intravenously could generally be considered safe even for long term periods. For children aged ≥ 1 month - < 5 years, it was considered safe to administer

doses up to 50 mg/kg bw/day (EMA 2017).

#### *Propylene glycol in the CPC preparation*

The US FDA also considered the use of propylene glycol in the CPC solution. It was noted that propylene glycol has generally recognised as safe (GRAS) status as an ingredient in human food for multiple uses and as a processing aid, provided it is used according to good manufacturing practices. No safety concerns were raised regarding the proposed use of propylene glycol in the CPC solution for treating poultry for human consumption. However, propylene glycol is toxic to cats and it was noted that it is common for poultry and poultry by-products to be used in animal feed, including cat food. The US FDA has established that the concentration of propylene glycol in cat food must be  $\leq 200$  ppm to be considered safe. It was concluded that potential propylene glycol residues in cat food from use of the CPC solution would not exceed 200 ppm at a maximum CPC concentration of 0.8%, a maximum limit of 5 gallons CPC solution per carcass and a minimum of 99% recovery of the applied solution (US FDA 2007).

EFSA's evaluation of the CPC preparation found mean and 97.5<sup>th</sup> percentile exposures to propylene glycol from the product were more than 22,000 and 7000 times, respectively, lower than the ADI established by JECFA. The CEF Panel concluded that there were no safety concerns for humans under the proposed use conditions (EFSA 2012).

### **3.7 Potential for development of antimicrobial resistance**

Any development of resistance to CPC could reduce the efficacy of poultry processing plant sanitisation measures, and potentially lead to the spread of CPC-resistant pathogens to food retail businesses and food preparation environments, commercial and domestic (Hora et al 2020). In addition, direct linkages have been observed between exposure to biocides and the development of antibiotic-resistant mutants in human pathogens, including *Salmonella*, *Campylobacter* spp. and *Listeria monocytogenes* (Bland et al 2022; Guérin et al 2021; Mavri and Smole Možina 2013; Webber et al 2015).

The applicant provided (as Confidential Commercial Information) the results of studies on the potential for the proposed use of CPC to engender resistance to the compound or cross-resistance to antimicrobial compounds such as those listed in the WHO list of critically important antimicrobials for human medicine (WHO 2019).

The studies evaluated the potential development of resistance in six pathogens: *Salmonella* Typhimurium, *Staphylococcus aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Listeria monocytogenes* and *Campylobacter jejuni*, following standard antimicrobial susceptibility testing protocols. Studies established the baseline susceptibility profiles of the target organism to CPC as well as a panel of antibiotics. Followed by an assessment of any change in susceptibility profiles after exposure to CPC, including whether the change was transient or stable. CPC susceptibility was based on measuring the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC).

The overall findings showed no evidence for the development of pathogen resistance to CPC, nor was there any stable reduction in susceptibility to the antibiotics tested.

It is concluded that the proposed use of CPC does not introduce an unacceptable risk of the development of antimicrobial resistance in the pathogens tested.

### **3.8 Discussion and conclusion**

Data on the absorption, distribution, metabolism and excretion of CPC are not available to



FSANZ for review, however public summaries of reviews of proprietary studies by overseas authorities suggest that oral absorption is greater than 10% in rats and dogs, with elimination occurring via urine, bile and faeces. No information on the metabolism of CPC was identified.

CPC is of moderate acute oral toxicity, with LD<sub>50</sub> values of 200 – 560 mg/kg bw reported. High doses in acute studies were reported to cause diarrhoea and erosion of the gastric mucosa.

In short-term dietary toxicity studies of CPC in rats and dogs, reduced food consumption and decreased body weight and body weight gain were observed at higher concentrations. These effects may possibly be due to issues with palatability of the test item. Increased caecum weights were observed in rats. The cause of this finding was unclear but it was not possible to definitively conclude that these changes were not treatment-related or adverse. In addition, haematological changes were observed in dogs. The no observed adverse effect level (NOAEL) in a 90-day dietary toxicity in dogs was 8 mg/kg bw/day.

FSANZ is also aware of publicly available summaries of proprietary 28-day, 6-month and 1 year studies in rats of CPC administered by oral gavage, and a 28-day study in rats involving administration via oral capsules. These studies were not available to FSANZ for review, but it is noted that toxicity and histopathological changes indicative of local irritant effects in the gastrointestinal tract were observed at doses  $\geq$  5 mg/kg bw/day. Similar histopathological changes were not observed in the dietary toxicity studies with CPC. FSANZ considers that the dietary toxicity studies are more relevant for risk assessment of dietary exposure to CPC from use an antimicrobial treatment for poultry carcasses than studies involving bolus administration.

*In vitro* genotoxicity studies of the final CPC preparation found no evidence of mutagenicity or clastogenicity. Studies of formulations containing CPC as an ingredient also found no evidence of genotoxicity attributable to CPC. In addition, proprietary *in vitro* and *in vivo* genotoxicity studies of CPC unavailable to FSANZ were reviewed by the EU SCCS, and considered to demonstrate that CPC does not have genotoxic potential. No long-term studies of toxicity or carcinogenicity are available for review, but no histopathological changes indicative of lesions that could lead to neoplasia through non-genotoxic mechanisms were identified in the short-term dietary toxicity studies reviewed by FSANZ.

Limited details summarising developmental toxicity studies in rats and rabbits were submitted to FSANZ. In addition, the EU SCCS review of CPC considered results of a proprietary developmental toxicity study in rats. These summaries state that no developmental toxicity was observed, but the full study reports were not available to FSANZ for evaluation. A summary of a combined developmental and reproductive toxicity study of a vinyl copolymer containing CPC in rats, conducted over three generations, states that no effects on fertility or developmental toxicity were observed. No histopathological changes in reproductive tissues were reported in the short-term dietary toxicity studies reviewed by FSANZ.

Given the limited data available on long-term toxicity, carcinogenicity and developmental and reproductive toxicity, it is not appropriate to establish a health-based guidance value (HBGV) for CPC. However, the NOAEL of 8 mg/kg bw/day identified in the 90-day dietary toxicity study in dogs is considered a suitable point of departure for use in a margin of exposure (MOE) assessment. This NOAEL is also protective of the changes observed in the rat studies.

No reports of food allergy reactions to CPC were identified. A single case report of an immediate hypersensitivity reaction to a throat spray, attributed to CPC present in the spray, was found in the scientific literature. However, no reports of allergic reactions were identified in the US FDA's review of adverse event reports over more than 55 years of marketing of

CPC-containing mouthwashes, and the EU SCCS's review of cosmetovigilance data on oral care products containing CPC. Based on the available evidence the risk of food allergy from the proposed use of CPC is likely to be very low.

For propylene glycol, an ADI of 0 – 25 mg/kg bw has been established by JECFA and EFSA (WHO 1974; EFSA 2018). The US EPA concluded that as propylene glycol is toxic to cats, the concentration of propylene glycol in cat food treated with the CPC preparation must be  $\leq$  200 ppm to be considered safe. Pet food is not regulated by the Food Standards Code, however.

## 4 Dietary exposure assessment

### 4.1 Approach to estimating dietary exposure

Dietary exposure assessments require data on the concentrations of the chemicals of interest in the foods requested and consumption data for the foods that have been collected through a national nutrition survey. The dietary exposure assessments were undertaken using FSANZ's dietary modelling computer program, Harvest<sup>8</sup>.

For CPC, the dietary exposures were based on (1) maximum residue levels of CPC from use of the poultry wash solution (i.e. CPC after dilution with water for use) on all poultry (including game birds), and (2) average residue levels of CPC from the use of poultry wash solution on all poultry, combined with food consumption data from the most recent Australian and New Zealand national nutrition surveys. The dietary exposures were assessed against a NOAEL of 8 mg/kg bw/day, set by FSANZ.

As the CPC preparation also contains propylene glycol, this was also considered in the dietary exposure assessment. The assessment was based on the maximum residue levels of propylene glycol arising from use of the applicant's CPC preparation on all poultry (including game birds) combined with food consumption data from the most recent Australian and New Zealand national nutrition surveys. Propylene glycol is a permitted food additive and processing aid. The dietary exposure assessment considered baseline permissions of propylene glycol used as a food additive in Schedule 15 and 16 of the Code. The dietary exposures were assessed against JECFA's numerical ADI of 0 – 25 mg/kg bw/day.

More details of the general FSANZ approach to conducting the dietary exposure assessment for this application are in Appendix 1. A detailed discussion of the FSANZ methodology and approach to conducting dietary exposure assessments is set out in *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2009).

#### 4.1.1 Concentration data used

##### 4.1.1.1 CPC

The applicant noted that CPC is diluted to  $\leq$ 1% for use in the poultry wash solution. An average concentration of CPC in the wash solution is 0.5%. At a CPC concentration of 1% in the poultry wash solution, the corresponding average and maximum residue levels of CPC on the poultry carcass (i.e. skin on) provided by the applicant are 12.4 mg/kg and 13.4 mg/kg, respectively. These residues were following the standard application procedures assuming there is a rinsing step following the application of the poultry wash solution. The applicant provided information on the skin to total carcass weight of 8.8%, the average percentage of skin on a typical broiler. The applicant applied this percentage to the residue

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<sup>8</sup> Harvest is FSANZ's custom-built dietary modelling program that replaced the previous program, DIAMOND, which does the same calculations using a different software program.

on the skin to determine the concentration in the poultry (i.e. skin and meat combined, no bones) that would be consumed with the skin on of 1.2 mg CPC/kg (based on a maximum residue on the skin of 13.4 mg/kg). This level was used in the estimate of dietary exposure presented by the applicant. As a worst case scenario FSANZ assumed for its dietary exposure assessment that the resulting concentrations for CPC in poultry meat and fat are 1.1 mg/kg for the 'Average residue level' scenario and 1.2 mg/kg for the 'Maximum residue level' scenario. The CPC concentrations used in the dietary exposure assessment are noted in Table 4.

FSANZ undertook an evaluation of the proportion of skin on poultry to ensure the derived concentration to use in the dietary exposure assessment was representative of residues for a chronic risk assessment. It has been shown that the proportion of skin (with subcutaneous fat) in different types of poultry is variable, from approximately 10-12% in turkeys and 13% in broiler chickens to 19% in geese and 23% in Pekin ducks (Murawska, 2017). There can also be variability in the proportion of skin and visible fat depending on the total carcass weight of the broiler chicken (ranging 8-20%) (Fereidoun et al., 2007). The webpage of the Australian Chicken Meat Federation states that the skin content in poultry differs with the parts. For example breast meat contains 9% skin whereas the wing contains 29% of skin to its weight (<https://www.chicken.org.au/chicken-cuts/>).

Based on this information, FSANZ also reviewed how commonly different types of poultry were consumed to evaluate if basing the residue concentration on concentrations from chicken was also applicable to the chronic risk assessment. It was found from the nutrition survey data from both countries that chicken is the most commonly consumed type of poultry (38% or more of the population consuming) compared to other types of poultry (e.g. duck, turkey, quail, ostrich, goose, mutton bird) (less than 3% consumers) (Table A1.2 in Appendix 1, section A1.2). Therefore, any data for chicken is more likely to influence long term exposures, irrespective of some other poultry types having higher skin percentages (and therefore possibly higher residues for the skin and flesh combined).

The worst case scenario of around 30% of the carcass as skin would result in a residue in skin and flesh combined of around 4 mg/kg, which is higher than the 1.2 mg/kg noted in the application and used in the dietary exposure assessment. FSANZ did not assess residues around 4 mg/kg because consumers across their lifetime would not only eat poultry parts with a high proportion of skin (e.g. wings) and also the most commonly consumed poultry was chicken. Therefore, the residue of 1.2 mg/kg was considered to be applicable for the FSANZ risk assessment. However, it should be noted that, the residue may be higher than 1.2 mg/kg if parts are analysed separately, or if poultry other than chicken is analysed.

**Table 4 Concentrations of CPC\* used in the dietary exposure assessment**

Classification code	Classification name	CPC concentration (mg/kg)	
		Average residue level	Maximum residue level
PF	Poultry fat	1.1	1.2
PM	Poultry meat	1.1	1.2
PO0113	Poultry skin	12.4	13.4

\* As residues on the poultry, following treatment of the whole carcass, skin on with the CPC preparation that had a concentration of 1% CPC.

#### **4.1.1.2 Propylene Glycol**

The applicant's proprietary CPC preparation contains propylene glycol and therefore the applicant has submitted confidential data on the concentrations of propylene glycol on poultry carcasses resulting from the use of the poultry wash. The dietary exposure assessment also considered uses as of propylene glycol as a food additive. Propylene glycol is currently permitted as a food additive at GMP within 54 food classes in Schedule 16, and one quantified permission within Schedule 15.

Given the majority of permissions for use of propylene glycol are at GMP in Schedule 16 of the Code, numerical concentrations were required in order to determine a baseline estimate of dietary exposure to propylene glycol. A call for data from the food industry was undertaken to obtain data on use levels. Data were received from 9 companies or industry groups for 15 of the 54 food classes of relevance for food additive use permitted in Schedule 16. Concentration data provided were commercial in confidence and therefore are not provided as part of this report. A maximum permitted level (MPL) of 30,000 mg/kg for food class 4.1.2.1 Citrus Fruit exists in Schedule 15 of the Code. No industry use data were submitted for this category. Therefore the concentrations used in the dietary exposure assessment for this food class were assigned as 0 for the minimum scenario assuming no use by industry in citrus fruit to the MPL of 30,000 mg/kg for the maximum scenario as a worst case.

GS1 provides information about products, including food, via bar codes. GS1 data were provided to FSANZ for use in this assessment by the New Zealand Ministry for Primary Industries. The relevant food related data were extracted from the GS1 database in June 2021 and included a list of food products that report propylene glycol or INS number 1520 as an ingredient. Each food product was assigned the relevant food class code from Schedule 15 of the Code. There were food products identified in 10 of the food classes with GMP permissions in Schedule 16. These data were cross referenced with the use data provided by the food industry. There were some food classes where GS1 data indicated several food items that contained propylene glycol but where concentration of propylene glycol in those food items was not available from the Australian and New Zealand industry data provided.

A literature search was undertaken to find estimates of dietary exposure internationally, and these were reviewed to evaluate uses in food categories overseas. This included a recent European assessment by EFSA (2018). Use levels for a number of food categories were reported as part of the EFSA assessment. These international concentration data reported by EFSA were used to supplement the concentration data in the dietary exposure assessment for those food items where GS1 data indicated use but no use levels were available from industry for certain scenarios (outlined further below) if EFSA data were available for that food class. If no Australian or New Zealand industry data were provided, and GS1 data indicated no uses, the international data was not used in the assessment.

The estimated dietary exposures to propylene glycol were assessed based on use in the applicant's CPC preparation only, and baseline plus CPC preparation uses.

Within the baseline scenario for propylene glycol, four scenarios were assessed:

- i. Minimum concentrations for each food class from Australian and New Zealand industry use data only (Min ANZ only)
- ii. Maximum concentrations for each food class from Australian and New Zealand industry use data only (Max ANZ only)
- iii. Minimum concentrations for each food class from Australian and New Zealand use data supplemented with international data from the EFSA assessment where GS1 data indicated use in Australia or New Zealand (Min ANZ+Int)
- iv. Maximum concentrations for each food class from Australian and New Zealand use data supplemented with international data from the EFSA assessment where GS1

data indicated use in Australia or New Zealand (Max ANZ+Int).

Scenarios i and ii provide an indication of dietary exposure based on known uses in Australia and New Zealand where data were provided. The use of international data to supplement the models allows for estimates of exposure to be calculated from a broader range of foods where propylene glycol is being used in Australia and New Zealand but no local concentration data were provided.

A summary of the food classes with permissions for use of propylene glycol in Schedules 15 and 16, and where industry data or supplementary international data were used in the dietary exposure assessment, and where GS1 data showed uses, are shown in Appendix 1, section A1.3.

#### **4.1.2 Food consumption data used and population groups assessed**

The food consumption data used for the dietary exposure assessments were:

**2011-12 Australian National Nutrition and Physical Activity Survey (2011-12 NNPAS)**, one 24-hour food recall survey of 12,153 Australians aged 2 years and above, with a second 24-hour recall undertaken for 64% of respondents (ABS, 2014). Only those respondents who had two days of food consumption data (n=7,735) were used in the assessment of dietary exposures to CPC and propylene glycol.

**2008-09 New Zealand Adult Nutrition Survey (2008 NZ ANS)**: a 24-hour recall of 4,721 New Zealanders aged 15 years and above, with a second 24-hour recall undertaken for 25% of respondents. (Ministry of Health 2011a; Ministry of Health 2011b). Only the first day of food consumption data was used in this assessment.

**2002 New Zealand National Children's Nutrition Survey (2002 NZ CNS)**, one 24-hour food recall covering 3,275 New Zealand school children aged 5-14 years, with 25% of respondents also completing a second 24-hour recall. Only the first day of food consumption data was used in this assessment.

The design of these nutrition surveys and the key attributes, including survey limitations, are set out in Appendix 1.

One day of food consumption data from both of the NZ surveys were used for the dietary exposure assessment whereas the average of two days of data from the 2011-12 NNPAS was used for Australia. The two day average exposures better reflect longer term estimates of dietary exposure and therefore are a better estimate of chronic dietary exposure.

The hazard characterisation did not identify any population sub-groups for which there were specific safety considerations or where separate dietary exposure estimates were needed. Poultry is consumed by a large proportion of the Australian and New Zealand populations. Therefore, the whole survey population from each of the nutrition surveys were used for the dietary exposure assessment. The populations groups used in the dietary exposure assessment are outlined in Table 5.

#### **Table 5 Population groups used in the dietary exposure assessment**

Country	Survey	Age group	No. respondents (Day 1 only)	No. respondents (Day 1 and 2)
Australia	2011-12 NNPAS	2 years and above	n/a	7,735
New Zealand	2002 NZ CNS	5 – 14 years	3,275	n/a
	2008 NZ ANS	15 years and above	4,721	n/a

#### 4.1.3 Assumptions and limitations of the dietary exposure assessment

The aim of the dietary exposure assessment was to make the most realistic estimation of dietary exposures to CPC and propylene glycol as possible. However, where significant uncertainties in the data existed, conservative assumptions were generally used to ensure that the estimated dietary exposure was not an underestimate of exposure.

Assumptions made in the dietary exposure assessment included:

- Unless otherwise specified, all foods within a food class contain CPC at the concentrations listed in Table 4.
- Unless otherwise specified, all poultry contains propylene glycol at residue levels provided by the applicant.
- Treatment is applied to all poultry irrespective of if it was whole carcass or pieces.
- There is 100% market penetration of the use of CPC and propylene glycol on poultry (including game bird) carcasses.
- Rinsing of the treated poultry occurs after application of the CPC preparation.
- Poultry offal does not contain CPC nor propylene glycol from the CPC preparation, only the meat and skin, as it is noted in the application it is removed before the poultry wash is applied.
- Meats listed as 'unspecified' in the food consumption data are not poultry.
- Mixed dishes with unspecified contents (e.g. sushi, sandwiches, stir-fries) do not contain poultry.
- Where a food or food class was not included in the dietary exposure assessment, it was assumed to contain a zero concentration of CPC or propylene glycol.
- Where a concentration is assigned to a food class, this concentration is carried over to any mixed dishes where foods in this class have been used as an ingredient to capture exposure from all sources of the food in the diet.
- Where there were no industry data for the use of propylene glycol for the baseline estimate of dietary exposure provided for Australia and New Zealand, European data were used to supplement data gaps where the use of propylene glycol was known in Australian or New Zealand food products as shown by GS1 data. This was based on the assumption that food additive use levels are limited by a technological amount and would be similar in Australia, New Zealand and Europe.

In addition to the specific assumptions made in relation to this dietary exposure assessment, there are a number of limitations associated with the nutrition surveys from which the food consumption data used for the assessment are based. A discussion of these limitations is included in Section 6 of the *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2009).

## 4.2 Dietary exposure assessment results

In this assessment, dietary exposures have been estimated for 'consumers only' (i.e. consumers of foods containing CPC or propylene glycol). Nutrition survey respondents who had no consumption of these foods were excluded. The proportion of the population who are consumers varies between the different population groups assessed.

### 4.2.1 CPC

Over 40% of the New Zealand and Australian populations are estimated to be exposed to CPC through consumption of poultry.

The mean and P90 consumer dietary exposures to CPC for Australians aged 2 years and above range between 0.0025 – 0.0027 mg/kg bw/day and 0.0057 – 0.0062 mg/kg bw/day, respectively depending on the scenario. The lower end of the range is for the *Average residue level* scenario, with the upper end of the range being for the *Maximum residue level* scenario.

For New Zealanders aged 5 to 14 years, the mean and P90 consumer dietary exposures to CPC range between 0.0048 – 0.0052 mg/kg bw/day and 0.013 – 0.014 mg/kg bw/day, respectively. The mean and P90 consumer dietary exposures for New Zealanders aged 15 years and above range between 0.0033 – 0.0036 mg/kg bw/day and 0.0083 – 0.0090 mg/kg bw/day, respectively. For both New Zealand population groups the lower end of the range represents the *Average residue level* scenario and the upper end of the range represents the *Maximum residue level* scenario.

New Zealand population groups had higher mean and P90 dietary exposures to CPC compared to the Australian population group aged 2 years and above. New Zealand children aged 5-14 years had higher dietary CPC exposures than those for New Zealanders aged 15 years and above.

Further details are available in Table 6.

**Table 6 Estimated mean and P90 dietary exposures to CPC from poultry for Australian and New Zealand consumers, expressed in mg/kg bw/day**

Country	Population Group	Proportion consumers to respondents♦	Estimated consumer dietary exposure to CPC (mg/kg bw/day)			
			Mean		P90	
			Average residue level	Maximum residue level	Average residue level	Maximum residue level
Australia	2 years and above*	60.6	0.0025	0.0027	0.0057	0.0062
New Zealand	5-14 years▽	41.4	0.0048	0.0052	0.013	0.014
	15 years and above▽	39.6	0.0033	0.0036	0.0083	0.0090

♦ Consumers as a % of total respondents. A consumer is a respondent in the national nutrition survey who consumes a food containing CPC. A respondent is anyone in a national nutrition survey, irrespective of whether they consume a food that contains CPC or not. Number of respondents: Australia 2+ = 7735, New Zealand 5-14 years = 3275 and 15+ = 4721.

❖ Based on consumption data from Day 1 and 2.

▽ Based on consumption data from Day 1 respondents only.

## 4.2.2 Propylene Glycol

It is estimated that over 40% of the Australian and New Zealand populations would be exposed to propylene glycol through consumption of poultry, resulting from use of the applicant's CPC preparation. More specifically 61% of Australians aged 2 years and above, 41% of New Zealand children 5-14 years and 40% of New Zealanders 15 years and above.

Across the three population groups assessed the estimated mean consumer dietary exposures to propylene glycol from the CPC preparation only ranged between 0.013 and 0.022 mg/kg bw/day, and P90 dietary exposures ranged between 0.028 and 0.049 mg/kg bw/day.

When current (baseline) uses of propylene glycol were included in the dietary exposure assessment in combination with use of the applicant's CPC preparation, estimated dietary exposures ranged between <1 and 13 mg/kg bw/day at the mean for all population groups assessed. At the P90 exposures ranged between <1 and 27 mg/kg bw/day across all population groups assessed. Further details are shown in Table 7.

**Table 7 Estimated mean and P90 dietary exposures to propylene glycol from existing permissions (baseline) and the applicant's CPC preparation combined, for Australian and New Zealand consumers, expressed in mg/kg bw/day**

Country	Population Group	Scenario	Proportion consumers to respondents (Min-Max concentration scenario) (%) <sup>◆</sup>	Estimated consumer dietary exposure to propylene glycol (Min-Max concentration scenario) (mg/kg bw/day)	
				Mean	P90
Australia	2 years and above <sup>*</sup>	ANZ	94-95	1-6	1-14
		ANZ+Int	99-99	1-7	2-15
New Zealand	5-14 years <sup>▽</sup>	ANZ	85-88	<1-10	1-22
		ANZ+Int	99-99	1-13	3-27
	15 years and above <sup>▽</sup>	ANZ	73-76	<1-6	<1-13
		ANZ+Int	96-96	1-6	1-12

◆ Consumers as a % of total respondents. A consumer is a respondent in the national nutrition survey who consumes a food containing poultry. A respondent is anyone in a national nutrition survey, irrespective of whether they consume a food that contains propylene glycol from use of the applicant's CPC preparation or not. Number of respondents: Australia 2+ = 7735, New Zealand 5-14 years = 3275 and 15+ = 4721.

❖ Based on consumption data from Day 1 and 2.

▽ Based on consumption data from Day 1 respondents only.

## 5 Risk characterisation

### 5.1 CPC

The MOE's presented in Table 8 are based on the dietary exposures to CPC from poultry washes only. The MOE's are based on the NOAEL of 8 mg/kg bw/day established by FSANZ as a point of departure for the risk assessment.

For Australians aged 2 years and above the MOEs range from 1300 – 3200, with the P90 dietary exposure based on the maximum residue level being the lower end of this range and the mean dietary exposure based on the average residue level being the higher range.



For New Zealanders aged 5 to 14 years the MOEs ranged from 600 – 1700, with the P90 dietary exposures for the both the maximum and average residue scenarios being the lower end of the range and the mean dietary exposure for the average residue level being the higher end of the range. This population group had the lowest MOEs.

For New Zealanders aged 15 years and above the MOEs ranged from 900 – 2400. The lower end of the range represents the P90 dietary exposures based on the maximum residue level and the higher end of the range represents the mean dietary exposure based on the average residue level.

**Table 8 Estimated mean and P90 dietary exposures to CPC for Australian and New Zealand consumers, expressed as Margins of Exposure\***

Country	Population Group	Estimated consumer dietary exposure to CPC (expressed as Margins of Exposure)			
		Mean		P90	
		Average residue level	Maximum residue level	Average residue level	Maximum residue level
Australia	2 years and above*	3200	2900	1400	1300
New Zealand	5-14 years <sup>∇</sup>	1700	1500	600	600
	15 years and above <sup>∇</sup>	2400	2200	1000	900

◆ Consumers as a % of total respondents. A consumer is a respondent in the national nutrition survey who consumes a food containing CPC. A respondent is anyone in a national nutrition survey, irrespective of whether they consume a food that contains CPC or not.

❖ Based on consumption data from Day 1 and 2.

∇ Based on consumption data from Day 1 respondents only.

\* Based on a NOAEL of 8 mg/kg bw/day.

Taking into account the available toxicological information and the conservative nature of the dietary exposure assessment, the MOEs are sufficiently large to account for the uncertainties in the database for CPC, and indicate that there are no safety concerns from the proposed use of CPC as a poultry treatment.

## 5.2 Propylene glycol

FSANZ has used the propylene glycol ADI established by JECFA, of 0 to 25 mg/kg bw/day for risk characterisation purposes.

Estimated dietary exposures to propylene glycol from the applicant's CPC preparation use only at the mean and P90 were below 1% of the ADI for the population groups assessed.

When current (baseline) uses of propylene glycol were included in the dietary exposure assessment in combination with use of the CPC preparation use, estimated dietary exposures ranged between 1 and 50% of the ADI at the mean for all population groups assessed. At the P90 exposures ranged between 2 and 110% of the ADI across all population groups assessed. Further details are shown in Table 9.

**Table 9 Estimated mean and P90 dietary exposures to propylene glycol for Australian and New Zealand consumers from baseline and the applicant's CPC preparation combined, expressed as a percent of the ADI\***

Country	Population Group	Scenario	Estimated consumer dietary exposure to propylene glycol (Min-Max concentration scenario) (%ADI)	
			Mean	P90
Australia	2 years and above*	ANZ	4-25	3-55
		ANZ+Int	4-30	7-60
New Zealand	5-14 years <sup>▽</sup>	ANZ	1-40	2-90
		ANZ+Int	5-50	10-110
	15 years and above <sup>▽</sup>	ANZ	2-25	2-50
		ANZ+Int	2-25	5-50

\* Acceptable Daily Intake established by JECFA of 25 mg/kg bw.

❖ Based on consumption data from Day 1 and 2.

▽ Based on consumption data from Day 1 respondents only.

Whilst a slight exceedance of the ADI is observed for New Zealand children 5-14 years, this is not considered to be a public health and safety concern for a number of reasons. These include:

- That this exceedance is for children only, and the ADI applies to a chronic or lifetime exposure. Food consumption or dietary exposure data for the New Zealand population as a whole was not available. Estimated exposures for New Zealand adults were under the ADI. Estimated exposures for the Australian population 2 years and above were under the ADI.
- It is only for the 90<sup>th</sup> percentile exposure and it is not expected that a consumer would have a high dietary exposure every day over a lifetime.
- It is only for the maximum concentration scenario where maximum concentrations were assumed for all foods. It is unlikely that a consumer would always select every food in every food group with the highest concentration over a lifetime. It is also unlikely that all foods within a group would contain propylene glycol.
- It is only for the scenario where international concentration data are used for food groups where use in foods in Australia or New Zealand was identified but no use levels were provided by industry in Australia or New Zealand.
- The exposure is based on only one day of food consumption data. More days of consumption data better reflect dietary exposures over a long or chronic period of time. It is known that more consumption days has the effect of averaging dietary exposures and bringing in the tails of the exposure distribution, resulting in a lower high percentile exposure.
- The ADI is only slightly exceeded and the maximum dietary exposure estimate is more than 180-fold lower than the LOAEL of 5000 mg/kg bw/day. The EMA has concluded based on clinical data that for adults and children ≥ 5 years of age, up to 500 mg/kg bw/day propylene glycol could generally be considered safe, and up to 50 mg/kg bw/day can be considered safe for children aged ≥ 1 month - < 5 years. These doses are substantially higher than the maximum dietary exposure estimate.

## 5.3 Conclusions from the risk characterisation

### 5.3.1 CPC

The dietary exposure assessment for CPC assessed maximum residue and average residue levels of CPC on poultry from use of the poultry wash solution on all types of poultry. The MOEs calculated based on dietary exposures to CPC from the proposed use of the applicant's CPC preparation for mean and high exposures for all residue concentrations for all population groups assessed did not indicate any public health and safety concerns.

### 5.3.2 Propylene glycol

The dietary exposure assessment for propylene glycol assessed residues supplied by the applicant resulting from use of the applicant's CPC preparation, along with baseline dietary exposures. Dietary exposures to propylene glycol from the CPC preparation at mean and high exposures were below 1% of the JECFA ADI for the population groups assessed showing an extension of use of propylene glycol from the applicant's CPC preparation adds minimally to propylene glycol dietary exposures. Whilst the upper end of the range of estimated dietary exposures just exceeds the ADI, it is based on a very conservative estimate in relation to data and methodologies used and would be lower in reality. Overall, dietary exposures from baseline and the applicant's CPC preparation uses combined did not raise any concerns for public health and safety.

## 6 Conclusions from the risk and technical assessment

FSANZ has undertaken an assessment to determine whether CPC achieves the technological purpose, as a processing aid, of an antimicrobial treatment for raw poultry and to identify any potential public health and safety concerns associated with its proposed use.

Raw poultry inherently carries a wide range of microorganisms, some of which are potential human pathogens that may cause illness in consumers. Analysis of the evidence provides adequate assurance that the application of CPC at levels ranging from 0.1 to 1% (w/v) to the surface of raw poultry carcasses and skin-on poultry pieces can effectively reduce the prevalence and levels of microorganisms, including relevant pathogens. FSANZ therefore concludes that the proposed use of CPC as an antimicrobial agent for raw poultry is technologically justified.

Studies on the potential for the proposed use of CPC to engender resistance to the compound or cross resistance to antimicrobial compounds of importance to human health demonstrate that the proposed use of CPC does not introduce an unacceptable risk of the development of antimicrobial resistance in the six pathogens tested.

There were no public health and safety concerns identified from the estimated dietary exposure to either CPC or the propylene glycol in the applicant's CPC preparation at the proposed use levels.

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# Appendix 1: Dietary Exposure Assessments at FSANZ

A dietary exposure assessment is the process of estimating how much of a food chemical a population, or population sub group, consumes. Dietary exposure to food chemicals is estimated by combining food consumption data with food chemical concentration data. The process of doing this is called 'dietary modelling', where:

$$\text{Dietary exposure} = \text{food chemical concentration} \times \text{food consumption}$$

FSANZ's approach to dietary modelling is based on internationally accepted procedures for estimating dietary exposure to food chemicals. Different dietary modelling approaches may be used depending on the assessment, the type of food chemical, the data available and the risk assessment questions to be answered. In the majority of assessments FSANZ uses the food consumption data from each person in the national nutrition surveys to estimate their individual dietary exposure. Population summary statistics such as the mean exposure or a high percentile exposure are derived from the ranked individual person's exposures from the nutrition survey.

An overview of how dietary exposure assessments are conducted and their place in the FSANZ Risk Analysis Process is provided on the FSANZ website at:

<http://www.foodstandards.gov.au/science/riskanalysis/Pages/default.aspx>

FSANZ has developed a custom-built computer program 'Harvest' to calculate dietary exposures. Harvest replaces the program 'DIAMOND' that had been used by FSANZ for many years. Harvest has been designed to replicate the calculations that occurred within DIAMOND using a different software package.

Further detailed information on conducting dietary exposure assessments at FSANZ is provided in *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2009), available at:

[http://www.foodstandards.gov.au/science/exposure/documents/Principles%20 %20practices %20exposure%20assessment%202009.pdf](http://www.foodstandards.gov.au/science/exposure/documents/Principles%20%20practices%20exposure%20assessment%202009.pdf)

## A1.1 Food consumption data used

The most recent food consumption data available were used to estimate CPC and propylene glycol dietary exposures for the Australian and New Zealand populations. The national nutrition survey data used for these assessments were:

The 2011-12 Australian National Nutrition and Physical Activity Survey (2011-12 NNPAS)

The 2002 New Zealand National Children's Nutrition Survey (2002 NZ CNS)

The 2008-09 New Zealand Adult Nutrition Survey (2008 NZ ANS).

The design of each of these surveys varies somewhat and key attributes of each are set out below. Further information on the national nutrition surveys used to conduct dietary exposure assessments is available on the FSANZ website at

<http://www.foodstandards.gov.au/science/exposure/Pages/dietaryexposureandin4438.aspx>.

### **A1.1.1 2011–12 Australian National Nutrition and Physical Activity Survey (2011-12 NNPAS)**

The 2011–12 Australian National Nutrition and Physical Activity Survey (2011-12 NNPAS), undertaken by the Australian Bureau of Statistics, is the most recent food consumption data for Australia. This survey includes dietary patterns of a sample of 12,153 Australians aged from 2 years and above. The survey used a 24-hour recall method for all respondents, with 64% of respondents (n=7,735) also completing a second 24-hour recall on a second, non-consecutive day. The data were collected from May 2011 to June 2012 (with no enumeration between August and September 2011 due to the Census). Only those respondents who had two days of food consumption data were used to estimate CPC and propylene glycol dietary exposures for this assessment. The Day 1 and 2 average provides the best estimates of CPC and propylene glycol dietary exposures for Australians aged 2 years and above. Consumption and respondent data from the survey were incorporated into the Harvest program from the Confidentialised Unit Record Files (CURF) data set (ABS 2014). These data were weighted during the calculations undertaken in Harvest.

### **A1.1.2 2002 New Zealand National Children's Nutrition Survey (2002 NZ CNS)**

The 2002 NZ CNS was a cross-sectional and nationally representative survey of 3,275 New Zealand children aged 5–14 years. The data were collected during the school year from February to December 2002. The survey used a 24-hour food recall and provided information on food and nutrient intakes, eating patterns, frequently eaten foods, physical activity patterns, dental health, anthropometric measures and nutrition-related clinical measures. It was also the first children's nutrition survey in New Zealand to include a second day diet recall data for about 15% of the respondents, and dietary intake from both foods (including beverages) and dietary supplements. Only the Day 1 24-hour recall data for all respondents (excluding supplements) were used for this assessment. These data were weighted during the calculations undertaken in Harvest.

### **A1.1.3 2008-09 New Zealand Adult Nutrition Survey (2008 NZ ANS)**

The 2008 NZ ANS provides comprehensive information on the dietary patterns of a sample of 4,721 respondents aged 15 years and above. The survey was conducted on a stratified sample over a 12-month period from October 2008 to October 2009. The survey used a 24-hour recall methodology with 25% of respondents also completing a second 24-hour recall. The information collected in the 2008 NZ ANS included food and nutrient intakes, dietary supplement use, socio-demographics, nutrition related health, and anthropometric measures. Only the Day 1 24-hour recall data for all respondents (excluding supplements) were used for this assessment. These data were weighted during the calculations undertaken in Harvest.

## **A1.2 Poultry consumption data**

The nutrition survey data from Australia and New Zealand were queried to determine the proportion and amount of different types of poultry that were consumed. The results are shown in Table A1.1. These results are based only on where respondents reported eating a specific type of poultry; they do not include meat that was reported as 'unspecified' type as that may have been non-poultry meats.

**Table A1.1: Proportion of consumers and consumption amounts of different types of poultry for Australian and New Zealand population groups**

Country	Population Group	Poultry sub-type	Proportion consumers of poultry to respondents (%)	Consumption of poultry (g/day)	
				Mean – all respondents	Mean – consumers only
Australia	2 years and above*	Chicken	59.6	57	96
		Duck	<1	<1	53
		Quail	<1	N/A	NA
		Turkey	1.7	1	50
New Zealand	5-14 years▽	Chicken	41.1	37	90
		Duck	<1	<1	18
		Turkey	1.5	N/A	NA
		Ostrich	<1	<1	3
	15 years and above▽	Chicken	38.7	49	127
		Duck	<1	1	91
		Goose	<1	NA	NA
		Turkey	2.7	1	37
		Mutton-bird	<1	NA	NA

◆ Consumers as a % of total respondents. A consumer is a respondent in the national nutrition survey who consumed poultry. A respondent is anyone in a national nutrition survey, irrespective of whether they consume the food or not. Number of respondents: Australia 2+ = 7735, New Zealand 5-14 years = 3275 and 15+ = 4721

❖ Based on consumption data from Day 1 and 2.

▽ Based on consumption data from Day 1 respondents only.

N/A means not applicable, low number of consumers therefore values are not be reported.

### **A1.3 Food classes and uses of propylene glycol included in the dietary exposure assessment**

The information provided by the food industry on the concentration of propylene glycol in food classes is confidential. Therefore only an indication of the food classes where information was obtained can be provided. This is shown in Table A1.2. The table includes all food classes that have GMP permission in the Code in Schedule 16 and those with MPLs in Schedule 15. As industry use data from Australia and New Zealand were not available for all food classes, GS1 data were used to identify food classes where propylene glycol was noted as being used in foods on the ingredient list. Where this was the case (as noted by a tick in the GS1 column in Table A1.2) and there were no Australian or New Zealand use levels available, international data were reviewed to determine if a concentration was available to use in the dietary exposure assessment. If one was available and used, a tick is included in the international data use column in Table A1.2. Where there are crosses in all three columns, a zero concentration was assumed for these food classes in the dietary exposure assessment.

**Table A1.2: Food classes where different data sources were available and where concentration data were used in the dietary exposure assessment**

<b>Food class number</b>	<b>Food class name</b>	<b>Australia or New Zealand industry data provided</b>	<b>GS1 data indicated use</b>	<b>International* data used in the ANZ+Int scenarios</b>
0	Preparations of food additives	✓	✓	✗
1.1.1	Liquid milk (including buttermilk) (Only UHT goats milk)	✗	✗	✗
1.1.2	Liquid milk products and flavoured liquid milk	✓	✗	✗
1.2.2	Fermented milk products and renneted milk products	✗	✗	✗
1.3	Condensed milk and evaporated milk	✗	✗	✗
1.4.1	Cream, reduced cream and light cream (Only UHT creams and creams receiving equivalent or greater heat treatments)	✗	✗	✗
1.4.2	Cream products (flavoured, whipped, thickened, sour cream etc)	✗	✗	✗
1.5	Dried milk, milk powder, cream powder	✗	✗	✗
1.6	Cheese and cheese products	✗	✗	✗
2.1	Edible oils essentially free of water	✗	✗	✗
2.2.1.2	Butter products	✗	✗	✗
2.2.1.3	Margarine and similar products	✗	✗	✗
2.2.2	Oil emulsions (<80% oil)	✗	✗	✗
3	Ice cream and edible ices	✗	✓	✓
4.1.2.1	Citrus fruit	✗	✗	✗
4.1.3	Fruits and vegetables that are peeled, cut, or both peeled and cut	✗	✗	✗
4.3	Processed fruits and vegetables	✓	✗	✓
5.1	Chocolate and cocoa products	✗	✗	✗
5.2	Sugar confectionery	✓	✗	✗
5.4	Icings and frostings	✓	✓	✗
6.3	Processed cereal and meal products	✓	✗	✗
6.4	Flour products (including noodles and pasta)	✗	✓	✗
7	Breads and bakery products	✗	✓	✓
8.2	Processed meat, poultry and game products in whole cuts or pieces	✗	✓	✗
8.3	Processed comminuted meat, poultry and game products, other than products listed in item 8.3.2	✗	✓	✗
8.3.2	Sausage and sausage meat containing raw, unprocessed meat	✗	✓	✗
8.4	Edible casings	✗	✗	✗
8.5	Animal protein products	✗	✗	✗
9.2	Processed fish and fish products	✗	✓	✗
9.3	Semi preserved fish and fish products	✗	✗	✗
9.4	Fully preserved fish including canned fish products	✗	✗	✗
10.2	Liquid egg products	✗	✗	✗
10.3	Frozen egg products	✗	✗	✗
10.4	Dried or heat coagulated egg products	✗	✗	✗
11.1.1	Rainbow sugar	✗	✗	✗
11.3.1	Dried honey	✗	✗	✗

Food class number	Food class name	Australia or New Zealand industry data provided	GS1 data indicated use	International* data used in the ANZ+Int scenarios
11.4	Tabletop sweeteners	x	x	x
12.1.2	Reduced sodium salt mixture	x	x	x
12.1.3	Salt substitute	x	x	x
12.5	Yeast and yeast products	✓	x	x
12.6	Vegetable protein products	x	x	x
13.3	Formulated meal replacements and formulated supplementary foods	✓	x	x
13.4	Formulated supplementary sports foods	x	x	x
13.5	Food for special medical purposes	x	x	x
14.1.1.2	Carbonated, mineralised and soda waters	✓	x	x
14.1.2.1	Fruit and vegetable juices (For juice separated by other than mechanical means only)	✓	x	x
14.1.2.2	Fruit and vegetable juice products	✓	x	x
14.1.3	Water based flavoured drinks	✓	x	x
14.1.4	Formulated Beverages	✓	x	x
14.1.5	Coffee, coffee substitutes, tea, herbal infusions and similar products	x	x	x
14.2.3	Wine based drinks and reduced alcohol wines	x	x	x
14.2.4.1	Fruit wine products and vegetable wine products	x	x	x
14.2.5	Spirits and liqueurs	x	x	x
14.3	Alcoholic beverages not included in item 14.2	x	x	x
20	Foods not included in items 0 to 14			
20	<i>Pizza</i>	x	✓	x
20	<i>Savoury based snacks (potato crisps, corn chips)</i>	x	✓	✓
20	<i>Soup</i>	x	✓	✓
20	<i>Sauces/toppings</i>	✓	✓	x
20	<i>Desserts</i>	x	✓	✓
20	<i>Dips</i>	x	✓	x
20	<i>Cereal based bars</i>	x	✓	x
20	<i>Mixed meals</i>	x	x	x

\* From EFSA, 2018.

## A1.4 Limitations of dietary exposure assessments

Dietary exposure assessments based on 2011-12 NNPAS, 2002 NZ CNS and 2008 NZ ANS food consumption data provide the best estimation of actual consumption of a food and the resulting estimated dietary exposure assessment for the Australian population aged 2 years and above, as well as the New Zealand populations aged 5–14 years and 15 years and above, respectively. However, it should be noted that NNS data do have limitations. Further details of the limitations relating to dietary exposure assessments undertaken by FSANZ are set out in the FSANZ document, *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2009).