FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

Supporting document 4

Antimicrobial Resistance Assessment Report – Application A1015

Ethyl Lauroyl Arginate as a Food Additive

Potential for microbial resistance

Microorganisms have the ability to adapt to a variety of physical and chemical environments. Tolerance, or resistance, of microorganisms to specific antimicrobial agents may be due to intrinsic factors, such as the nature and properties of cellular membranes, or be acquired through genetic mutation and/or acquisition of transferable genetic material (e.g. plasmids and transposons) (McDonnell and Russell, 1999). Variable levels of resistance of microorganisms to a wide range of antimicrobial agents, including disinfectants and preservatives, have been reported in the scientific literature (Potenski *et al*., 2003; Kramer *et al*., 2006; Capita *et al*., 2007; Plumridge *et al*., 2008).

Microorganisms that show a low-level resistance to an antimicrobial agent may be preferentially selected over sensitive populations, particularly when exposed to sub-lethal levels (i.e. below the minimum inhibitory concentration). If microorganisms were to develop resistance to an antimicrobial agent, their growth would no longer be inhibited in products where the antimicrobial had been added, and manufacturers would need to institute alternative procedures to mitigate microbiological growth.

While there is an absence of data in the published scientific literature on the selection and/or development of microorganisms resistant to ethyl lauroyl arginate, resistance to other cationic surfactants, such as quaternary ammonium compounds, has been reported. The Applicant provided unpublished data from a laboratory study investigating the potential for *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans* to develop resistance to ethyl lauroyl arginate. Microorganisms were cultured in a series of media containing increasing concentrations of ethyl lauroyl arginate, starting with levels below the minimum inhibitory concentration. The results showed that microorganisms increased their resistance to ethyl lauroyl arginate over time, however, this response was considered to be a physiological adaption of the microbial population to the stress from the presence of the antimicrobial. This adaption was temporary, as resistant cultures quickly became susceptible following growth in ethyl lauroyl arginate-free media.

It has been suggested that resistance of microorganisms to cationic surfactants and other biocides, may also confer resistance with certain antibiotics, although results from studies are inconclusive (McDonnell and Russell, 1999; Ishikawa *et al*., 2002; Joynson *et al*., 2002). For cross-resistance to occur, the organism must possess a common mechanism of resistance to both types of antimicrobial agents, for example up-regulation of efflux pumps or changes in membrane permeability (Poole, 2002). Evidence suggesting exposure of microorganisms to biocides at sub-lethal concentrations leads to increased antibiotic resistance is based primarily on results from *in-vitro* studies, with very few studies being undertaken *in situ*.

This raises questions around the complex interaction of biocides with microorganisms in various matrices, and the survival of resistant microorganisms in the environment compared with wild-type strains. There is also a lack of epidemiological data to indicate the public health significance of cross-resistance (Fraise, 2002).

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) – an independent committee that provides scientific advice to the European Commission – recently reviewed the literature in relation to the antibiotic resistance effects of biocides (SCENIHR, 2009).

It concluded that current scientific evidence does indicate that the use of certain active substances in biocidal products in the health care, consumer, animal and food settings, may contribute to the increased occurrence of antibiotic resistant bacteria.

The committee also acknowledged that there was a lack of data and methodologies to clearly indentify the risks arising from the use, or misuse, of biocides.

In summary, while there is a potential for resistance of microorganisms to antimicrobial agents, such as ethyl lauroyl arginate and other preservatives used in food production, this can be minimised through proper management and monitoring of their use. These measures include the setting of appropriate maximum limits and following the principles of GMP – i.e. the quantity of additive added to food shall be limited to the lowest possible level necessary to accomplish its desired effect.

References

Capita, R. (2007) Variation in Salmonella resistance to poultry chemical decontaminants, based on serotype, phage type, and antibiotic resistance patterns. *J Food Prot* 70(8):1835-1843.

Fraise, A.P. (2002) Biocide abuse and antimicrobial resistance--a cause for concern? *J Antimicrob.Chemother.* 49(1):11-12.

Heir, E., Sundheim, G. and Holck, A.L. (1995) Resistance to quaternary ammonium compounds in Staphylococcus spp. isolated from the food industry and nucleotide sequence of the resistance plasmid pST827. *J Appl Bacteriol.* 79(2):149-156.

Heir, E., Sundheim, G. and Holck, A.L. (1998) The Staphylococcus qacH gene product: a new member of the SMR family encoding multidrug resistance. *FEMS Microbiol Lett* 163(1):49-56.

Ishikawa, S., Matsumura, Y., Yoshizako, F. and Tsuchido, T. (2002) Characterization of a cationic surfactant-resistant mutant isolated spontaneously from Escherichia coli. *J Appl Microbiol* 92(2):261-268.

Joynson, J.A., Forbes, B. and Lambert, R.J. (2002) Adaptive resistance to benzalkonium chloride, amikacin and tobramycin: the effect on susceptibility to other antimicrobials. *J Appl Microbiol* 93(1):96-107.

Kramer, N.E., van Hijum, S.A., Knol, J., Kok, J. and Kuipers, O.P. (2006) Transcriptome analysis reveals mechanisms by which Lactococcus lactis acquires nisin resistance. *Antimicrob.Agents Chemother.* 50(5):1753-1761.

McDonnell, G. and Russell, A.D. (1999) Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev* 12(1):147-179.

Paulsen, I.T., Brown, M.H. and Skurray, R.A. (1996) Proton-dependent multidrug efflux systems. *Microbiol Rev* 60(4):575-608.

Plumridge, A., Stratford, M., Lowe, K.C. and Archer, D.B. (2008) The weak-acid preservative sorbic acid is decarboxylated and detoxified by a phenylacrylic acid decarboxylase, PadA1, in the spoilage mold Aspergillus niger. *Appl Environ Microbiol* 74(2):550-552.

Poole, K. (2002) Mechanisms of bacterial biocide and antibiotic resistance. *Symp.Ser Soc.Appl Microbiol* (31):55S-64S.

Potenski, C.J., Gandhi, M. and Matthews, K.R. (2003) Exposure of Salmonella Enteritidis to chlorine or food preservatives decreases susceptibility to antibiotics. *FEMS Microbiol Lett* 220(2):181-186.

SCENIHR (2009) *Assessment of the antibiotic resistance effects of biocides*. European Commission and Directorate-General for Health & Consumers. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_021.pdf. Accessed on 2 February 2009.