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Review or Mini-review

Antibiotics exposure and health risks: Chloramphenicol

Jaap C. Hanekamp[a,b,c,*], *Aalt Bast*[d,1]

[a] *Science Department, University College Roosevelt, P.O. Box 94, 4330 AB Middelburg, the Netherlands*
[b] *Environmental Health Sciences, University of Massachusetts, Amherst, USA*
[c] *Chair Working Group Chemical Food Safety of the Global Harmonization Initiative (GHI)*
[d] *Department of Toxicology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands*

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ABSTRACT

The antibiotic chloramphenicol (CAP) is banned from food production. Besides being a medicinal product, CAP is also a natural product, produced by *Streptomyces Venezuelae*. The lack of scientific data hampers setting of an Acceptable Daily Intake (ADI). Consequently, a maximum residue limit (MRL) in food could not be established. This was then translated into a zero tolerance using the so-called Minimum Required Performance Limit (MRPL) level, *viz.* the achievable detection limit in food, to guide the zero tolerance policy. The MRPL is clearly not relevant to food safety and human health but is solely related to analytical technological capabilities. The increase in the latter enables detection at ever-lower levels and ignores toxicological relevance. We here provide arguments to use a Threshold of Toxicological Concern (TTC) for CAP that can accommodate developing toxicological insights.

Contents

* *Corresponding author*. Tel.: +31 0 625002373.
E-mail addresses: j.hanekamp@ucr.nl, hjaap@xs4all.nl (J.C. Hanekamp), a.bast@maastrichtuniversity.nl (A. Bast).
[1] Tel.: +31 0 433881418.

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1. Introduction

Setting scientific and policy standards that benchmark the benefits and risks of products intended to be consumed is of great consequence for industry, policymakers and, consumers. The safety of products consumed is more often than not defined as *chemical* product-safety, meaning that the product consumed is regarded as 'safe' when man-made chemicals such as antibiotics and/or pesticides are absent or only present at very low levels.

One such much-debated chemical is the antibiotic chloramphenicol (CAP). This particular antibiotic is banned from food production because of toxicological deliberations we will discuss below, yet is still used as human medication.

In this paper, we will propose a sensible toxicological approach with respect to the inevitable presence of CAP in food-products that goes beyond the oversimplified ban-policies now in place. For that reason, we will elucidate CAP's origin, drug-medicinal and food-exposure levels, risks and the manner in which such risks are derived and regulated. Presence and sources of CAP are discussed in general terms with respect to the state-of-art scientific knowledge available in the literature.

The CAP-case discussed here, however, goes beyond this specific item, as in food we are potentially dealing with innumerable chemicals at low-dose for which no regulation is designed. We propose a route beyond the problematic 'assessment paradigm' Cramer, Ford and Hall already coined in 1978: 'Safety evaluation is caught in a frustrating circle. It is neither possible nor sensible to try to obtain the information needed to assess every imaginable toxic risk associated with every substance, and pursuit of greater safety therefore demands the setting of priorities as well as sensible limits for investigation. To do this with confidence requires possessing the very information that is lacking and that can be won only slowly on a few substances at a time, with significant uncertainty and at considerable cost. This requires priorities, and completes the circle of frustration' (Cramer et al., 1978).

2. CAP—origins and use

CAP (2,2-dichloro-N-((1R,2R)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl)acetamide) is a natural product, as most antibiotics are. It has two asymmetric carbon centres that theoretically would result in four stereoisomers. However, the natural component, which is also the only one with bacteriostatic properties, is the R,R stereoisomer (Pongs, 1979; Berendsen et al., 2011).

The majority of antibiotics we now know today are derived from nature's topmost antibiotic producers, the *Actinomycetes*. These soil-bacteria are ubiquitously found worldwide. To give an impression, the biomass per hectare (100 × 100 m) of the *Actinomycetes* in topsoil can be as high as 5000 kg (Brady and Weil, 2002).

Streptomyces, genus of filamentous bacteria of the family *Streptomycetaceae* (order *Actinomycetes*), account for well over two thirds of these commercially and therapeutically significant antibiotics. The *Streptomyces* therefore are the most important source of antibiotics for medical, veterinary and agricultural use (Hopwood, 2007). CAP is produced by the *Streptomyces venezuelae* (Chater, 2006).

CAP was the first mass-produced antibiotic (Ehrlich et al., 1947) and was shown to be effective against typhoid (Patel and Banker, 1949). It was widely used in the world as a human antibiotic and was also used as a veterinary drug. Nowadays, CAP is banned from food-production, specifically in the animal food-production chain, and is hardly used as human medication, for reasons discussed below, although in Asian countries CAP is still used as a human therapeutic. Ophthalmic infections, however, are still treated extensively with CAP (Hanekamp and Kwakman, 2009).

3. The European focus on CAP

The detection of CAP in shrimp in 2001, imported into Europe from Asian countries, was branded as a food scandal and triggered the focus on CAP, and other banned antibiotics such as nitrofurans, in foods since then. The initial European response was to close European borders to fish products, mainly shrimp, from these countries and make laboratories work overtime to analyse numerous batches of imported goods for the presence of this antibiotic. Some European countries went so far as to have food products containing this antibiotic destroyed as public health was deemed to be at risk. This regulatory response spilled over to other major seafood-importing countries, including the USA. Imported shrimp was found to contain between 1 and 10 ppb (μg/kg product) of CAP (Hanekamp et al., 2003).

The legislative background to European response then was found in Council Regulation 2377/90, which was implemented to establish maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (Council Regulation 2377/90). This so-called 'MRL Regulation' (maximum residue limit) introduced Community procedures to