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CHLORAMPHENICOL, EUROPEAN LEGISLATION AND HORMESIS - COMMENTARY

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The detection of chloramphenicol (CAP)—a broad-spectrum antibiotic—in shrimp imported into Europe from Asian countries in 2002 was regarded as yet another food-scandal by governments, albeit hardly noticed by the media and the public. The European reaction was closing down of the borders for fish products and making laboratories work overtime to analyse numerous batches of imported goods. Some European countries went so far as to have antibiotic-containing food-products destroyed, as these goods were presented as detrimental to human health.

Any presence of CAP in food, which can be detected by several analytical methods, was a violation of European law, deemed a human health threat and followed by an immediate regulatory sanction of zero-tolerance (Hanekamp *et al.* 2003). Because CAP is regarded as probably carcinogenic (2A) and could be weakly genotoxic, the zero-tolerance approach reflects the traditional use of the Linear Non-Threshold (LNT) model so deeply embedded in toxicological and regulatory thinking, especially concerning genotoxic carcinogens. This regulatory position and human health perspective, however, proved to be untenable in the case of CAP but also for other antibiotics not allowed in the food chain, such as nitrofurans.

Because of blatant misuses, zero-tolerance had been deemed an opportune method to ban the use of certain veterinary products, residues of which may show up in foods. However, the unfeasibility of zero-tolerance came to the fore as a result of the analytical progress made in the last two decades of the twentieth century. CAP (and also nitrofurans) proved to be more ubiquitous in food—albeit at extremely low levels—than mere abuse probably could account for (Hanekamp *et al.* 2003).

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However, one of the present authors (JCH) recognized that zero-tolerance and the LNT model (IPCS-INCHEM 2006) are regulatory conveniences infused with a precautionary human health perspective. Moreover, it was clear that medicinal products such as CAP are rarely in use as human medicine and are banned for veterinary use not because of inherent risks at low-level exposures, but because JECFA (Joint Expert Committee on Food Additives, FAO) could not establish an ADI for lack of scientific data (IPCS-INCHEM 2006). In Europe this was expediently translated as ‘dangerous at any dose’ and officially regarded as such.

Confronted with such intransigence, Hanekamp embraced the case for hormesis presented by Calabrese in numerous papers (Calabrese *et al.* 1999; Calabrese and Baldwin 2001a; Calabrese and Baldwin 2001b; Calabrese and Baldwin 1997; Calabrese and Baldwin 2003a; Calabrese and Baldwin 2003b), as a means to advance a rational approach of low-level exposures of chemicals in food, which need not be zero according to hormesis (Hanekamp and Kwakman 2004). In doing so, the concept of a Toxicological Insignificant Exposure level (TIE) (Kroes *et al.* 2004) was introduced, whereby the hormetic part of the dose-response curve was ‘translated’ into a toxicological threshold. We then evaluated the TIE within the framework of hormesis, where insignificance was understood not as a regulatory evaluation based on a MTR (Maximum Tolerable Risk) level of say 1:1,000,000, as is done within the threshold of toxicological concern (TTC) concept, but as a direct toxicological dose response bioassay and assessment (Calabrese and Cook 2005).

As a result, a regulatory shift away from zero tolerance came to be when the European Commission published a decision on 11 January 2005 (Commission Decision 2005), according to which CAP no longer is regulated at zero level but at the MRPL (Minimum Required Performance Limit) level. For CAP the MRPL is set at 0.3 ppb (for nitrofurans metabolites the MRPLs are set at 1 ppb). Prior to this decision, MRPLs were whatever low concentration levels that regulatory laboratories in the European Community could detect and confirm. With this decision MRPLs have now been given legal status in terms of explicit levels of concern.

The CAP case here described is the first policy example in which a regulatory shift is observed from zero tolerance to a threshold approach on the basis of hormetic considerations, which it is hoped could pave the way for incorporation of the hormetic perspective into not only food safety regulation but also into environmental regulation. In our view, this is clearly needed to improve pharmaceutical and industrial chemical regulation (European Commission 2004), especially in light of the recent EC decision (Commission Decision 2005) and the overwhelming evidence of hormesis in relation to many low-level exposures (Calabrese and Baldwin 2001a; Calabrese and Baldwin 2003a; Hanekamp and Wijnands 2004; Wiener 2001).

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