

Chloramphenicol, food safety and precautionary thinking in Europe

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The authors evaluate the precautionary zero-tolerance level approach to toxins in food from different perspectives, contending that as part of insuring food safety the precautionary principle is highly paradoxical and counterproductive. The chloramphenicol case is here examined: availability biases, probability and system neglect in the application of the principle together with the regulatory 'moral free rider' dilemma are discussed. The authors conclude that the precautionary principle needs to be discarded from food safety regulations as it dramatically compounds the issue of risk and could moreover result in unlawful food safety regulations.

Introduction

The detection in 2001 of chloramphenicol, a broad-spectrum antibiotic ('CAP'), in shrimp imported into Europe from Asian countries was presented as yet another food-scandal. 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 the antibiotic destroyed. This regulatory response spilt over to other major seafood-importing countries such as the United States.

The legislative background to their response is to be found in Council Regulation EEC No. 2377/90, which was implemented to establish maximum residue limits of veterinary medicinal products in foodstuffs of animal

origin.³ This so-called 'MRL Regulation' (maximum residue limit) introduced Community procedures to evaluate the safety of residues of pharmacologically active substances according to human food safety requirements. A pharmacologically active substance may be used in food-producing animals only if it receives a favourable evaluation. If it is considered necessary for the protection of human health, maximum residue limits ('MRLs') are established. They are the points of reference for setting withdrawal periods in marketing authorisations as well as for the control of residues in the Member States and at border inspection posts.

Additionally, Directive 96/23/EC ('the Residue Control Directive') contains specific requirements, in particular for the control of pharmacologically active substances that may be used as veterinary medicinal products in food-producing animals.⁴ This includes primarily sampling and investigation procedures, requirements as to the documentation for their use, indication for sanctions in case of non-compliance, requirements for targeted investigations and for the setting up and reporting of monitoring programmes.

Zero tolerance

It has been noted that existing legislation on pharmacologically active substances used in veterinary medicinal products significantly contributed to the decreased availability of medicines for uses in food

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2 Postbus 20, 6710 BA ede, The Netherlands (www.nizo.com). Professor Dr A Bast, Professor Dr P Borst, Professor Dr V J Feron, Professor Dr R H Meloen, Dr S Notermans, and Dr R Wijnands are gratefully acknowledged for their contributions to the thinking behind this article.

3 Council Regulation (EEC) No. 2377/90 of 26 June 1990 laying down a Community procedure to set up maximum residue limits of veterinary medicinal products in foodstuffs of animal origin, Official Journal L224 18 August 1990, at 1 to 8.

4 Directive 96/23/EC on Measures to Monitor Certain Substances and Residues thereof in Live Animals and Animal Products, Official Journal L125, 23 May 1996, at 10.

producing animals in the European Community.⁵ One of the aspects *not* discussed in the EC reflection paper is the issue of zero tolerance, which has created a problematic situation in the international market. Council Regulation EEC No. 2377/90 contains an Annex IV listing pharmacologically active substances for which no maximum toxicological levels can be fixed. From a regulatory point of view any exposure to these compounds is deemed a hazard to human health. These substances are consequently not allowed in the animal food-production chain. So-called zero tolerance levels are in force for Annex IV. The reasons for this are obvious:

- The absence of an acceptable daily intake ('ADI'), and therefore an MRL, was understood as 'dangerous at any dose' which 'required' zero tolerance regulation;
- With the introduction of zero tolerance, a veterinary ban on Annex IV compounds (such as CAP) is effective in order for, it was believed, the listed compounds to disappear from the food chain as only veterinary use was given as a source;
- Earlier analytical equipment was not adequate to perform current tasks (limits of detection ('LODs') developed from ppm (parts per million) to ppb (parts per billion) and ppt (parts per trillion)).

CAP – and other Annex IV substances – should not be detected in food products at all, regardless of concentrations. The presence of CAP in food products, which can be detected by any type of analytical apparatus, is a violation of European law and moreover deemed to be a threat to public health. In consequence, food containing the smallest amount of these residues is considered unfit for human consumption. For all intents and purposes, zero tolerance is best understood as zero concentration. Food is only risk free when Annex IV substances are found to be completely absent (at zero concentration). The presence of CAP in food products is solely related to illicit veterinary use; other sources are not taken into account, or indeed considered, as they are not included in the legislation. Chloroform, chlorpromazine, colchicine, dapsone, dimetridazole, metronidazole, nitrofurans (including furazolidone) and ronidazole are the other compounds in Annex IV.

CAP is categorised by the IARC (the International

Agency for Research on Cancer) as probably carcinogenic in humans; group 2A.⁶ No ADI could be established for CAP due to the lack of scientific information to assess its carcinogenicity and effects on reproduction, and because the compound showed some genotoxic (DNA damaging) activity.⁷ Within the regulatory context, this is understood to be as 'dangerous at any dose'.

The zero tolerance approach for Annex IV compounds applies the precautionary principle to food safety issues: 'when in doubt, keep it out'. The explicit goal of zero-tolerance is not *risk*-based but *precaution*-based, as the absence of an MRL is from a regulatory point of view again translated as 'dangerous at any dose'. Indeed, the European Community tries to uphold a high level of food standards to protect public health and safety. To that end the White Paper on Food Safety has been published.⁸ In this paper the Commission presents a number of principles in ensuring a high level of human health and consumer protection, one of which is the precautionary principle. Although scientific knowledge is the buttress of European policy on food safety, the precautionary principle may be invoked where considered appropriate by the European regulators in view of the high level of protection deemed necessary. Zero tolerance is an example of invoking a precautionary measure.

Despite a ban on animal food production, CAP is still used in human medicine. It has a wide spectrum of activity against gram-positive and gram-negative bacteria. CAP therapy is usually restricted to serious infections when other drugs are not as effective. In the Netherlands for instance a number of registered pharmaceutical products are on the market that are mainly used to treat eye infections.

Objectives

In this article, we want to evaluate the zero tolerance approach from different perspectives. As scientific knowledge on the exposure risks of CAP is limited, the precautionary principle, in the form of zero tolerance, is invoked. The regulatory attitude towards scientific data is typical of a precautionary culture in which a very high level

⁵ 'Reflection Paper on Residues in foodstuffs of animal origin.' (2004) European Commission, DG Enterprise, DG Health and Consumer Protection.

⁶ IARC (International Agency for Research on Cancer) (1997), webpage <http://www-cie.iarc.fr/htdocs/monographs/vol50/08-chloramphenicol.htm> (last visited on 15 January 2004).

⁷ IPCS-INCHEM (Chemical Safety Information from Intergovernmental Organisations), webpage <http://www.inchem.org/documents/jecfa/jecmono/v33je03.htm> (last visited on 15 January 2004).

⁸ Commission of the European Communities (2000) White Paper on Food Safety, Brussels.

of scepticism with regard to what science cannot do goes hand in hand with a very high level of confidence as to what science is supposed to deliver.⁹ It also shows the detrimental consequences of the European reluctance to bring together assessment and management in food safety issues; as will be seen at the end of this article.

Our main argument here is that the precautionary zero tolerance approach, as part of insuring food safety, is highly paradoxical and counterproductive. Availability biases, probability and system neglect in the application of the principle together with the regulatory 'moral free rider' dilemma will be discussed here. Moreover, proof of non-presence and therefore proof of the absence of harm (zero risk) is implied in zero tolerance. This could well constitute a *probatio diabolica*, which will be discussed in relation to a recent Court of First Instance ruling.

The narrow focus on potential exposure risks, which are erroneously deemed to arise only from the illicit veterinary use of CAP, leaves a number of essential issues untouched. Firstly, CAP is a natural chemical, produced by the micro-organism *Streptomyces venezuelae*. *Streptomyces* are a group of gram-positive filamentous bacteria belonging to the *Actinomycetes*, which are ubiquitous soil-bacteria found worldwide. The biomass per hectare of the *Actinomycetes* in 15 cm of topsoil is between 400 and 5,000 kilograms.¹⁰ Particularly members of the genus *Streptomyces* are well known antibiotic-producers.¹¹ The first question that comes to mind is whether CAP could in trace amounts be present biologically in all kinds of different food products, thereby opening up a multi-source perspective not incorporated in present regulations? Might there be an ecological background for such antibiotics? As zero tolerance consequently translates into a best-available-techniques approach for analytical machinery (see below), this question is all the more pertinent, as increasing analytical capabilities could result in crossing this potential ecological boundary. We therefore embarked on a small survey, in which a number of European products, not typically related to the illicit use of CAP, were analysed for the presence of CAP. Below we will discuss the results and the related intricacies of analytical techniques and their progress.

Secondly, as already has been mentioned, CAP is still

used in human medicine. Therefore, the environmental presence of CAP due to human clinical use needs to be looked at carefully. In particular, surface and waste water are targets of investigation, as they can become a source of CAP in food production other than direct medication, adding to the multi-source issue. We will summarise the data that have been generated this far and will discuss their implications in relation to a zero tolerance approach to food safety.

Thirdly, the legal concept of 'zero' does not exist in the real world; zero tolerance effectively means a best-available-techniques ('BAT') approach in the quest for analytical limits of detection. Until the mid-1960s the general idea of food safety meant that food should not contain any potentially harmful residues of veterinary medicinal products. This was a more or less realistic goal because at that time residues could only be determined in concentrations of around 1 mg/kg (parts per million: ppm). Since then the availability and sensitivity of methods of analysis have continuously improved and the detection of concentrations as low as 1 ng/kg is common today. These improvements mean that ever lower amounts of residues are detected, which would previously have gone undetected. Efforts to enforce zero tolerance for CAP, but also nitrofurans and other antibiotics, have evoked international concerns for reliable analytical methods, regulatory harmony, practical modes of prevention and useful risk assessments. The sensitivity of analytical methods determines the operational definitions for 'zero', and as the analytical sensitivities reach ppb (microgram/kg product) and ppt levels (nanogram/kg product), the cost of equipment and tests limit surveillance and furthermore increase the probability of detection. Below we will discuss intricacies of analytical techniques and their progress in relation to zero tolerance.

Fourthly, the risks of exposure to CAP through the food chain are regarded as dose-independent, meaning that any dose might give rise to disease. Indeed, protecting the general public specifically from toxic chemicals, particularly carcinogens, has been a principal goal of public policy. The REACH programme (Registration, Evaluation, and Authorization of Chemical Substances) is Europe's latest regulatory development in this field.¹² In the absence of knowledge as to how a toxicant may harm individuals, regulatory toxicology assumes that even tiny doses can cause injury. This, however, is based on toxicological extrapolation

9 R. Pieterman and J.C. Hanekamp, 'The Cautious Society? An Essay on the Rise of the Precautionary Culture' (2002)

Zoetermeer: Heidelberg Appeal Netherlands.

10 N.C. Brady and R.R. Weil (2002) *The Nature and Properties of Soils* (13th edn), New Jersey: Prentice Hall.

11 D.M. Sylvia, J.J. Fuhrmann, P.G. Hartel and D.A. Zuberer, *Principles and Applications of Soil Microbiology* (1999), New York: Prentice Hall.

12 L. Bergkamp and J.C. Hanekamp, 'The draft REACH regime: costs and benefits of precautionary chemical regulation' (2003) 5 *Environmental Liability* at 1 to 14.

models, which cannot be verified but serve as an axiom. There is in other words no proof whatsoever of the risks at low-level exposures; these risks are inferred through the linear non-threshold model (see below). Risk aversion has led legislation and regulation to seek to ban toxic chemicals or, if that is unattainable, to minimise exposure, for instance, to analytical limits of detection levels as is the case with zero tolerance. From a precautionary regulatory viewpoint the scientific impossibility of arriving at an acceptable daily intake, in the case of CAP for lack of data, is translated into 'dangerous at any dose' or 'no dose no cancer'. The precautionary zero tolerance approach therefore is a regulatory interpretation of the linear axiom.

Two models to determine the dose-response relationship have traditionally been used in toxicology in the assessment and regulation of risks of toxicants: the threshold model (B) is used in the assessment of risks for non-carcinogens, and the linear non-threshold (LNT) model (A) is used to extrapolate risks to very low doses of carcinogens. The risks associated with low-level exposures to CAP are singularly inferred from the linear non-threshold axiom.

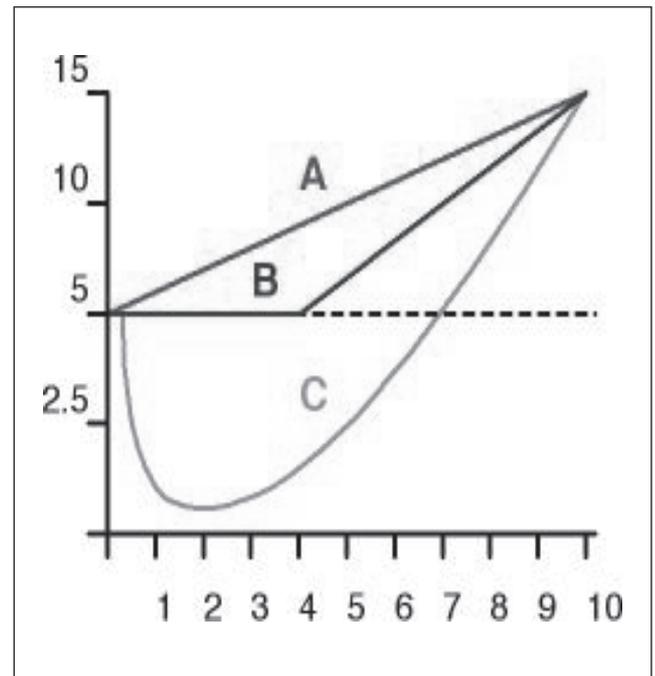
Calabrese and Baldwin, however, argue that the most fundamental shape of the dose-response is neither threshold nor linear, but U-shaped (C), and hence both current models provide less reliable estimates of low-dose risk.¹³ This U-shape is usually referred to as hormesis: a moderate stimulation of response at low doses and an inhibitory response at higher doses.¹⁴ It is to be regarded as an adaptive response of an organism towards toxicological perturbations. Acceptance of hormesis suggests that low doses of toxic/carcinogenic agents may reduce the incidence of adverse effects.

In Figure 1 tumours per animal are depicted on the y axis, with the related dose on the x axis. The animal control group (not exposed to the carcinogen) is depicted by the black horizontal broken line at the 5-level on the y axis. The hormetic model C predicts a lower amount of tumours than the control group when exposure levels of the carcinogen are below 7 (on hormesis see the BELLE website (biological effects of low level exposures)).¹⁵ The hormesis concept challenges the axiom and use of low-dose linearity in estimating cancer risks, and emphasizes that there are thresholds for carcinogens. The particular choice of the LNT dose-response model in the assessment of the exposure risks of CAP and the role of the precautionary principle will be considered in the final section of this article.

The risks of CAP exposure

Aplastic anaemia (a form of anaemia when the bone marrow ceases to produce sufficient red and white blood cells) is

Figure 1: Three toxicological dose-response models



the most dangerous effect produced by CAP. Its occurrence is extremely rare, albeit fatal and is only observed as a result of therapeutic treatment courses with CAP.¹⁶ The minimum dose of CAP associated with the development of aplastic anaemia is not known. Therefore it is unfeasible to determine a dose-response relationship for the occurrence of aplastic anaemia.¹⁷ Limited evidence exists for the carcinogenicity of CAP in humans exposed to therapeutic doses.¹⁸

Nowadays CAP is only occasionally used for internal infections. Ophthalmic infections, however, are still treated

13 E.J. Calabrese and L.A. Baldwin, 'Toxicology Rethinks its Central Belief. Hormesis Demands a Reappraisal of the Way Risks are Assessed' (2003), 421 *Nature* at 691 to 692; 'Hormesis: the dose-response revolution' (2003), 43 *Annual Review of Pharmacology and Toxicology* at 175 to 197.

14 T.D. Luckey, *Radiation Hormesis* (1991) Boca Raton: CRC Press.

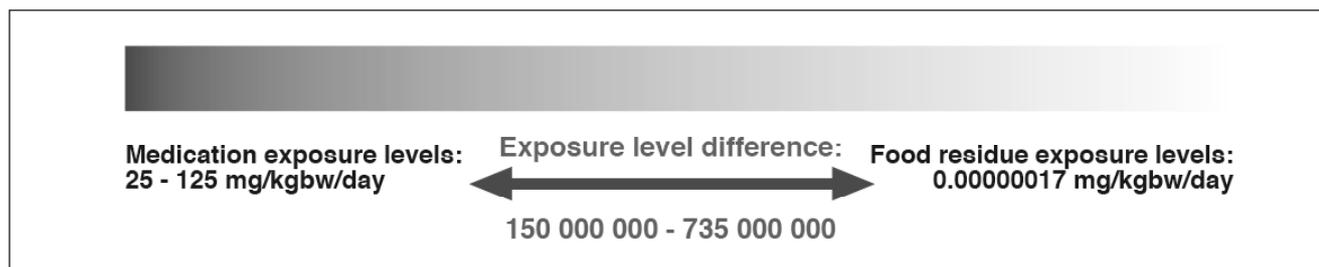
15 BELLE (Biological Effects of Low Level Exposure) www.belleonline.com (last visited 15 January 2004).

16 H.B. Benestad, 'Drug mechanism in marrow aplasia', in C.G. Geary (ed.), *Aplastic Anaemia* (1979), London: Balliere Tindall, at 26 to 42.

17 IPCS-INCHEM (Chemical Safety Information from Intergovernmental Organizations), webpage <http://www.inchem.org/documents/jecfa/jecmono/v23je02.htm> (last visited on 15 January 2003).

18 M.M. Doody, M.S. Linet, A.G. Glass, R.E. Curtis, L.M. Pottern, B.B. Rush, J.D. Boice, Jr., J.F. Fraumeni, Jr. and G.D. Friedman, 'Risks of non-Hodgkin's lymphoma, multiple myeloma, and leukemia associated with common medications' (1996) 7 *Epidemiology* at 131 to 139.

Figure 2: CAP exposure level differences between therapy and food residues



with CAP. Documentation on the ophthalmic use of CAP provides no evidence that this route of administration is associated with the same toxicity risk as therapeutic CAP administered parenterally.¹⁹

The available data on the genotoxicity of CAP show mainly negative results in bacterial systems and mixed results in mammalian systems. It was concluded that CAP must be considered genotoxic, but only at concentrations about 25 times higher than those occurring in patients treated with the highest therapeutic dose.²⁰ Moreover, no adequate studies are available to evaluate the carcinogenicity of CAP in animals used for experimentation.

The total aplastic anaemia incidence estimated by the JECFA (Joint FAO/WHO Expert Committee on Food Additives) is in the order of 1.5 cases per million people per year.²¹ Only about 15 per cent of the total number of cases was associated with drug treatment and among these CAP was not a major contributor. These data gave an overall incidence of therapeutic CAP-associated aplastic anaemia in humans of less than one case per 10 million per year. In considering epidemiological data derived from the ophthalmic use of CAP, systemic exposure to this form of treatment was not associated with the induction of aplastic anaemia. All in all, there seems to be no evidence whatsoever that low-level exposure to CAP, either as a result of ophthalmic use or of residues in animal food, is related to aplastic anaemia.²²

When considering the difference between therapeutic exposure – as a result of which aplastic anaemia has been observed, albeit rarely – and exposure as a result of food residues – as a result of which aplastic anaemia has *never*

been observed – it is clear that CAP does not present any hazard. The food residue exposure levels shown in Figure 2 are taken from the RIVM study (Rijksinstituut voor Volksgezondheid en Milieu; Dutch National Institute for Public Health and Environment) on CAP in shrimp.²³

The RIVM in their above-mentioned study estimated the cancer risk as a result of the consumption of shrimp containing CAP.²⁴ The concentrations in imported shrimp varied roughly between 1 and 10 ppb (parts per billion; 1 and 10 µg/kg product). The estimated reasonable worst-case risk as a result of eating shrimp containing CAP is lower than the MTR-level by at least a factor of 5,000 (being a 1:1,000,000 added cancer risk in the human population).

The ecology of CAP and its potential presence in foodstuff

Of approximately 12,000 known antibiotics, it is estimated that some 160 are or have been used as human medication. The *Streptomyces* account for well over half of these commercially and therapeutically significant antibiotics, which are produced by means of complex 'secondary metabolic' pathways. Many other pharmaceuticals such as anti-tumour agents and immuno-suppressants²⁵ are also

19 D. Kairys and M.B. Smith, 'Topical ocular chloramphenicol: clinical pharmacology and toxicity in optometric practice' (1990) 61 *Journal of American Optometric Association* at 14 to 17.

20 A. Martelli, F. Mattioli, G. Pastorino, L. Robbiano, A. Allavena and G. Brambilla, 'Genotoxicity testing of chloramphenicol in rodent and human cells' (1991) 260 *Mutation Research* at 65 to 72.

21 Note 7 above.

22 *Ibid.*

23 P.A.H. Janssen, A.J. Baars and M.N. Pieters, 'Advies met betrekking tot chlooramfenicol in garnalen' (2001) RIVM/CSR, Bilthoven, The Netherlands. [Recommendations on chloramphenicol in shrimp.] Kgbw stands for kilogram bodyweight. Toxicological data are usually related to this unit.

24 Note 23 above.

25 W.C. Champness, *Prokaryotic Development*, (2000) Washington D.C.: ASM Press; J. Mann, *Secondary Metabolism*, (2001) New York: Oxford University Press; S.D. Bentley, K.F. Chater, A.-M. Cerdeño-Tárraga, G.L. Challis, N.R. Thomson, K.D. James, D.E. Harris, M.A. Quail, H. Kieser, D. Harper, A. Bateman, S. Brown, G. Chandra, C.W. Chen, M. Collins, A. Cronin, A. Fraser, A. Goble, J. Hidalgo, T. Hornsby, S. Howarth, C.-H. Huang, T. Kieser, L. Larke, L. Murphy, K. Oliver, S. O'Neil, E. Rabinowitsch, M.-A. Rajandream, K. Rutherford, S. Rutter, K. Seeger, D. Saunders, S. Sharp, R. Squares, S. Squares, K. Taylor, T. Warren, A. Wietzorrek, J. Woodward, B.G. Barrell, J. Parkhill and D.A. Hopwood, 'Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3(2)', (2002) 417 *Nature* at 141 to 147.

derived from the *Streptomyces*. A small sample of these *Streptomyces* derived antibiotics are presented in Table 1.²⁶

Table 1: Some Streptomyces antibiotics

Antibiotic	Organism
Avermectin	<i>Streptomyces avermitilis</i>
Chloramphenicol	<i>Streptomyces venezuelae</i>
Clavulanic acid	<i>Streptomyces clavuligerus</i>
Kanamycin	<i>Streptomyces kanamyceticus</i>
Tetracycline	<i>Streptomyces aureofaciens</i>
Tylosin	<i>Streptomyces fradiae</i>
Virginiamycin	<i>Streptomyces virginiae</i>

The overall natural production of antibiotics by *Streptomyces* under natural conditions is unknown. Nonetheless, it is possible to isolate CAP from *Streptomyces venezuelae* present in the soil.²⁷ Considering the ubiquitous occurrence of antibiotic-producing *Streptomyces*, it seemed interesting to investigate the potential natural presence of CAP in different kinds of food products not associated with the illicit use of the antibiotic. To that end the 'Instituto Tecnológico Agroalimentario' (Agri-food Technology Institute: AINIA), an accredited Spanish, non-profit organisation created by, among others, companies in the food-manufacturing sector, was asked to sample ready-to-sell products acquired from retailers for the presence of CAP. A commercial ELISA (enzyme-linked immunosorbent assay) kit for detecting the presence of CAP was used. A number of samples that presented a high value in the ELISA test were confirmed by HPLC-MS (High Performance Liquid Chromatography-Mass Spectrometry) technique.²⁸ Of the total amount of food products tested (83 in total):

- 40 per cent were below the ELISA LOD (limit of detection: 0.05 ppb (parts per billion));
- 44 per cent of the tested products gave a response between the 0.05 and 0.5 ppb;
- 16 per cent responded above the 0.5 ppb;
- One of the ELISA positives was confirmed by HPLC-MS as containing CAP (the other HPLC-MS tested samples were below the LOD of 1 ppb).

26 C. Walsh, *Antibiotics. Actions, Origins, Resistance* (2003), Washington D.C.: ASM Press.

27 Hazardous Substances Data Bank <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> (last visited 15 January 2004).

28 AINIA, *Presence of chloramphenicol in foods* (2003). (This report can be obtained through the authors.)

The HPLC-MS confirmed sample concerned Spanish white wine with an estimated CAP concentration of 2.7 ppb. We will further discuss these results below.

Presence of CAP in the aquatic environment

Pharmaceuticals (both human and veterinary), personal care products and other domestic organic contaminants have been detected in the aquatic environment (rivers and lakes). These contaminants are sometimes referred to as PPCPs (Pharmaceuticals and Personal Care Products). PPCPs comprise all drugs, diagnostic agents (such as X-ray contrast media), 'nutraceuticals' (bioactive food-supplements), and other consumer chemicals, such as fragrances and sun-screen agents.²⁹

In other studies emphasis is put on their point of entry in the aquatic environment namely waste water and waste water treatment plant discharge and are referred to as organic wastewater contaminants (OWCs).³⁰ However, the veterinary use of pharmaceuticals results in a diffuse dispersion in the (aquatic) environment, comparable to for instance pesticides.

Focusing on antibiotic presence in sewage treatment plant effluent and surface waters, Hirsch *et al.* published the analysis of various water samples for 18 antibiotic substances.³¹ Interestingly, CAP was detected in the effluent of a sewage treatment plant in the south of Germany at a maximal concentration of 0.56 µg/l. In surface waters, CAP again was detected, at a maximum concentration of 0.06 µg/l.

Observations and discussion

Zero tolerance as a precautionary regulation is intended to eliminate certain risks to human health as a result of exposure to residues in animal food products. This in effect means three things in relation to food safety: (i) detection of CAP as such, irrespective of concentrations, is deemed a public health risk displaying the regulatory choice for the LNT maxim from which the risks are inferred; (ii) detection

29 K. Kummerer (ed.), *Pharmaceuticals in the Environment. Sources, Fate, Effect and Risks* (2001). Berlin: Springer Verlag. T. Terner, <http://www.epa.gov/nerlesd1/chemistry/ppcp/images/ternes-security.pdf> (last visited on 15 January 2004).

30 D.W. Kolpin, E.T. Furlong, M.T. Meyer, M.E. Thurman, S.D. Zaugg, L.B. Barber and H.T. Buxton, 'Pharmaceutical, hormones, and other organic waste water contaminants in U.S. streams, 1999-2000: a national reconnaissance', (2002) 36 *Environmental Science and Technology* at 1202 to 1211.

31 R. Hirsch, T. Ternes, K. Haberer and K.-L. Kratz, 'Occurrence of antibiotics in the aquatic environment', (1999) 225 *The Science of the Total Environment* at 109 to 118.

of CAP in food is singularly related to the illicit veterinary use in food production; (iii) a precautionary zero tolerance approach in food safety of the illicit veterinary use of CAP would 'totally' remove CAP (and its concomitant risks) from the food chain and food products. The last two aspects will be discussed here; the first will be tackled in the conclusion.

CAP's usage as a medicinal antimicrobial and antibacterial agent could result in its release into the environment through various waste streams by which food may be contaminated during the production phase. Indeed, Hirsch *et al.* did find CAP in the aquatic environment.³² It was detected in the effluent of one sewage treatment plant and in surface-water at concentrations of 0.56 µg/l and 0.06 µg/l respectively. So, through human clinical use, CAP can enter the food chain. This fact alone makes the presumption untenable that in order to ban illicit veterinary use, zero tolerance would eliminate its presence in food. In other words, with CAP we are dealing with a multi-source issue.

Hirsch *et al.* surmise that this environmental presence might also be due to the veterinary use of CAP, despite its legal status as being part of Annex IV. However, from the large number of groundwater samples that were taken from agricultural areas in Germany, on only two sites was contamination by antibiotics detected. More importantly, municipal waste water is usually not disposed of with animal manure from farms. This suggests that intake from veterinary applications to the aquatic environment is of negligible importance. As sales of CAP in Hong Kong are between about 11 times and 440 times greater than in several western countries and Australia, environmental contamination of surface waters as a result of human use is expected to be at much higher levels than in Germany and the United Kingdom.³³

The present knowledge on the spread and behaviour of PCPPs is still anecdotal, and biased towards 'finding' the contaminant in the environment. However, the detection of PCPPs warrants an unbiased review of concentration levels of CAP (and other PCPPs) in the aquatic systems to assess and quantify its distribution. In designing PCPP base surveys, experience of monitoring pesticides may be useful. Pesticides/herbicides/insecticides as a contaminant group are comparable because (i) they are also applied in small loads (although considerably higher than PCPPs); (ii) they are detected in very low concentration; (iii) in the aquatic environment they show a temporal concentration

fluctuation over the year;³⁴ and (iv) the chemical transport behaviour and the metabolites often are not very well known.

As CAP is a natural antibiotic, natural contamination of numerous food products is a definite possibility. This hypothesis was tested by means of a small survey described above. The results are difficult to interpret. They do not indicate definitive proof for a measurable ecological background of CAP, despite its ubiquitous natural producer. The presence of CAP in white wine, however, does represent an interesting, albeit inexplicable, caveat for the possibility of a natural bacteriological source of CAP in the food chain adding to the multi-source issue.

A problem with the AINIA data, as with all data produced at the edge of analytical limits of detection, is that food matrices artefacts to which the ELISA responds cannot be differentiated from a real presence of CAP. The reality of false-positives ('detection' of a non-present target-molecule) is a well-known problem in the analytical sciences.

Results obtained in a recent collaborative trial on the determination of CAP in shrimp provide an illuminating illustration.³⁵ Together with a number of CAP-spiked shrimp samples in which predefined amounts of CAP, resulting in different predetermine concentrations, were added to the shrimp, blank (unspiked) samples were also tested. In the blank shrimp three laboratories of the 14 participating laboratories measured CAP levels of 0.27 (n=2), 0.42 (n=1), and 3.98 µg/kg (n=3). The last two results were marked in this collaborative trial as outliers (not deemed to be valid). However, any given real-market sample would have been judged positive by these laboratories for the presence of CAP and removed from market. In this case each of the three laboratories used a different method: ELISA, GC-MS/NCl and HPLC-UV. Four other laboratories obtained results varying from 0.03 to 0.09 µg/kg, using ELISA (2x), GC-MS/NCl (1x) and LC-MS-MS (1x). These low values could again be designated as false positives. Alternatively, they could reflect a natural background level, as indicated by us in the AINIA results. In summary, 50 per cent of the laboratories designated blank shrimp as being positive for CAP, which are worrying results in view of present political unease.

The sensitive detection of analytes has improved dramatically during the past decades, including methods

32 Note 31 above.

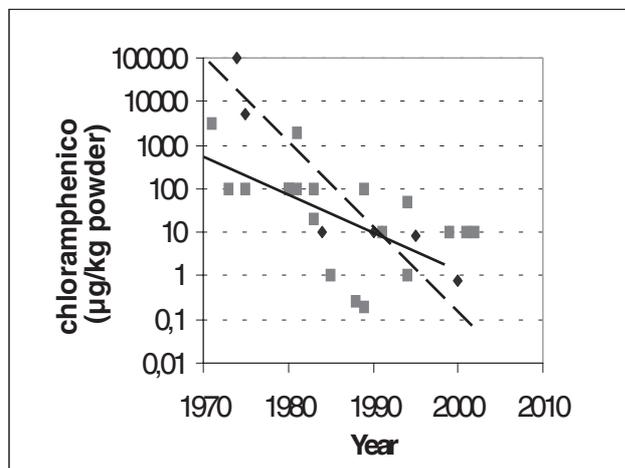
33 Note 7 above.

34 See Turner, Note 29 above.

35 U. Schröder, 'Final Report on Chloramphenicol – Laboratory Comparison Study' (2002), Bundesforschungsanstalt für Fischerei, Institut für Fischereitechnik und Fischqualität (GFR, Hamburg).

used for the detection of CAP. Screening methods based on immunochemistry showed on average a tenfold improvement of sensitivity for the detection of CAP in milk powder every seven years (Figure 3). The developments in instrumental methods, which are used for confirmation, have been less prominent. On average they needed 14 years to increase tenfold in sensitivity. However, it is not unlikely that the instrumental methods will show a more rapid evolution in the future. The sensitivity of LC-MS-MS has improved circa tenfold in the last six years and a fundamental limit has not yet been reached.

Figure 3: Development of the detection limit of CAP in milk powder. (Instrumental methods are denoted by ■ and the solid line; screening methods by ♦ and the broken line.)



Only a very tiny amount of the analyte becomes ionised in the widely used electro-spray interface and again just a tiny amount of the ions produced in the spray is actually sampled by the mass spectrometer. Therefore, one can expect that detection of CAP in ng/kg (parts per trillion) will become feasible in the next decade. In combination with the present zero tolerance policy this will lead undoubtedly to the destruction of increasing amounts of food and feed due to contamination by the natural presence of CAP or remnants of it in municipal waste water after human medical use.

There is some confusion about the Minimum Required Performance Limit ('MPRL').³⁶ MRPL is no more and no less than the concentration level that regulatory laboratories in the European Community should at least be able to detect and confirm. The MRPL should not be mistaken for a tolerance limit, or any similar terminology. EU regulatory laboratories are therefore obliged to try and find residues of banned substances, like CAP, at the lowest technically possible concentration. As a result of that, depending on the skills and equipage of the laboratories, lower than MRPL

concentration may lead to the result being positive ('non-compliant sample'). The policy of zero tolerance can and will lead to economic inequality: products designated as 'safe' by an exporting country can be designated 'non-compliant' if the importing country uses a more sophisticated method of analysis, resulting in lower detection limits. In that sense the MRPL did not produce a harmonised market that was disturbed by the zero tolerance issue.

Conclusions

The simple legal inference espoused by the Council Regulation EEC No. 2377/90 that when a compound on the Annex IV list is detected in food products this is a result of illicit use in food production is falsified in the case of CAP. The straightforward legal reasoning that detection of CAP in food can only imply illegitimate use does not hold and needs revising as we are dealing here with a multi-source issue. The mere reality of the human clinical use of CAP resulting in a measurable environmental source for contamination of food products bears witness to that. The AINIA results might even be indicative for a natural source. The presence of CAP in Annex IV of Council Regulation Council Regulation EEC No. 2377/90 therefore is superfluous. Zero tolerance will moreover become a legal artefact as a result of increasing analytical capabilities in which, however, the possibility of false positives will continue to haunt legal issues. Clearly, we do not surmise that CAP is never used illicitly in food production.

The false positives issue surfaced poignantly in the German trial discussed above. Blank samples were in 50 per cent of the labs found to contain CAP. As has been said, no distinction can be made between the possibility of false positives and the possibility of a background concentration level due either to environmental contamination through human clinical use or to a natural bacteriological source or even to illicit use. Correspondingly, the source of CAP when indeed detected will be more diverse than is covered by the Council Regulation EEC No. 2377/90.

In recent months another multi-source example surfaced concerning nitrofurans, also listed on the Annex IV. SEM (semicarbazide) has long been considered a characteristic metabolite of the antibiotic nitrofurazone. Studies have shown that the parent drugs (nitrofurans) are

³⁶ Commission Decision of the European Communities (2003), making a change to Decision 2002/657/EG concerning MRPL of certain residues in food of animal origin, Official Journal L71/17, 15 March 2003.

rapidly metabolised by animals, and are therefore undetectable. The stable metabolites are however detectable for a number of weeks after application of nitrofurans and are therefore regarded as reliable indicators for the (illegal) application of nitrofurans. Evidence for illicit use is therefore related to the detection of the metabolites such as SEM. However, recently SEM was found as a contaminant in food packaged in glass jars, which was not related to the nitrofurans at all. SEM is formed by thermal degradation of azodicarbonamide ('ADC'). ADC is used as the blowing agent in plastic gaskets of packaging material. SEM migrates from the gaskets into food products.

SEM was also detected in special animal and vegetable matrices that had been concentrated using drying procedures like heating to reduce water content. A substantial formation of SEM was observed after samples were treated with hypochlorite (bleach) in accordance with common food processing methods used for disinfection or bleaching.³⁷

The examples of CAP, which has been systematically discussed in this article, and SEM open up a broad perspective on numerous other multi-source cases whereby zero tolerance policies will of necessity fail as a means to ban certain products from the animal food production chain.

The choice of the LNT maxim to underpin zero tolerance is in line with the precautionary principle, which however holds a strong availability bias.³⁸ The above-mentioned toxicological model is cognitively available to the regulators and follows in a long-standing toxicological tradition whereas other models are not, or are to a much lesser extent. Also, the one source of CAP, veterinary use, is cognitively available to the regulators and is part of Annex IV of the specific Council Regulation whereas other sources are not. Moreover, the linear model is an attractive one, as it proposes complete regulatory control over the CAP risks, whether or not these risks are relevant.

This last point brings us to another bias, namely probability neglect.³⁹ The precautionary zero tolerance approach is focused on the outcome of CAP exposure in humans – aplastic anaemia or cancer – and neglects the

probability of this outcome. Worse, the envisaged outcomes – aplastic anaemia and cancer – are merely theoretically inferred on the basis of the LNT toxicological model discussed above, and not empirically observed. The JECFA committee concluded that low-level exposure to CAP is not associated with the induction of aplastic anaemia. Realistically, the risks as a result of CAP exposure from food consumption are nil. Indeed, neglect of probability here leads to the probability of neglect.

The hormetic U-shaped model advocated by Calabrese and Baldwin openly and scientifically challenges the regulators' choice of the LNT model (from which, as said, the risks are theoretically inferred):⁴⁰

The *a priori* criteria we developed to assess whether experiments displayed evidence of hormesis based on study design, magnitude of the stimulatory response, statistical significance of the stimulatory response and reproducibility of findings, revealed up to 5,000 examples of hormetic responses independent of chemical class/physical agent, biological model and endpoint measured. Low levels of agents such as cadmium, dioxin, saccharin, various polycyclic aromatic hydrocarbons, X-rays and various gamma-ray sources reduce tumours in some species. Low doses of X-rays enhance life span in male and female mice and guinea pigs; ethanol and acetaldehyde enhance longevity in fruit flies; multiple stressor agents extend longevity in nematodes; numerous toxic substances (for example, cadmium and lead) enhance growth in various plant species. Low or modest consumption of ethanol reduces total mortality in humans, while increasing it at higher levels of consumption. The hormesis concept is thus highly generalizable and far-reaching.

Hormesis redefines our concept of 'pollution' and 'contamination'.⁴¹ It questions the premise that 'pollutants' are unreservedly bad. This is revolutionary because modern environmental and public health legislation is built in large part on the moral dichotomies of good versus evil, clean versus dirty, natural versus unnatural.⁴² Annex IV exudes

37 M. Mandix, letter dated 11 November 2003 from Dr Wiertz-Dipl.Chem. Eggert-Dr Jörissen GmbH, Laboratory for Trade and Environment.

38 D. Kahneman, P. Slovic and A. Tversky (eds), *Judgement under Uncertainty: Heuristics and Biases* (1982), Cambridge: Cambridge University Press; C.S. Sunstein, 'Beyond the Precautionary Principle' (2002), John M. Olin Law & Economics Working Paper No. 149 (2nd series), the Law School, University of Chicago; C.S. Sunstein, *Risk and Reason. Safety, Law and the Environment* (2000), Cambridge: Cambridge University Press.

39 Note 38 above.

40 Note 13 above.

41 F.B. Cross, 'Legal Implications of Hormesis', (2001) 20(3) *Humans & Experimental Toxicology* at 156 to 158 (see also <http://www.belleonline.com/n2v92.html> last visited 15 January 2004); J.B. Wiener, 'Hormesis and the Radical Moderation of Law', (2001) 20(3) *Human & Experimental Toxicology* at 162 to 164. (see also <http://www.belleonline.com/n13v92.html> last visited 15 January 2004).

42 M. Douglas and A. Wildavsky, *Risk and Culture. An Essay on the Selection of Technological and Environmental Dangers* (1982), Berkeley: University of California Press.

'badness'. Zero tolerance, and thereby zero risk, is the express goal of Annex IV and of many who advocate the precautionary principle.⁴³ Hormesis challenges the very premises of the Annex IV list: things are not either bad or good; they are both, depending on exposure levels and adaptive responses from the exposed organisms. In our view the LNT maxim needs to be reconsidered in relation to its use in food safety regulation.

This brings us to our final reflections. When a single problem is examined, it can be difficult to see the full consequences of legal interventions.⁴⁴ The precautionary principle has the appearance of being workable only because a limited subset of the relevant effects is 'on screen'. The key aspect of system neglect is the risk of trade-offs. This is especially salient in the light of international trade, as the zero tolerance approach has until now resulted in a trade-off (such as the faulty communication of risk)⁴⁵ between perceived food risks for Europeans and economic risks of the exporting countries no longer accepted by Europe as trade partners. The risk–risk trade-off translates into a health–health trade-off to the detriment of the exporting countries.⁴⁶ Moreover, with zero tolerance policies the reality of multiple-sources of the banned substances is ignored, the potentially ambiguous nature of the methods of analysis is not adequately tackled (such as in the case of SEM), and the issue of false-positives remains out of focus whereby the very basis of MRL legislation is in jeopardy. Additionally, the Second Law of Thermodynamics cancels out zero-tolerance policies, as zero-concentration – as implied by zero tolerance – is not a physico-chemical reality.

Zero tolerance has so far resulted in the race for ever lower limits of detection. As a result analytical technology becomes a goal in itself, irrespective of toxicological relevance of the concentrations detected. Food-safety as such has been disregarded for a legal construct. Indeed, with zero tolerance, proof of absence of a banned product, and therefore proof of no harm is brought centre-stage.

43 W. Douma, 'The Precautionary Principle. Its Application in International, European and Dutch Law' (2003), PhD thesis, University of Groningen, The Netherlands.

44 D. Dorner, *The Logic of Failure* (1996), Perseus Books.

45 O. Renn, 'Implications of the hormesis hypothesis for risk perception and communication', (1998) 17 *Human & Environmental Toxicology*, at 431 to 438.

46 J.D. Graham and J.B. Wiener (eds), *Risk vs. Risk. Tradeoffs in Protecting Health and the Environment* (1995), Cambridge: Harvard University Press; R.L. Keeney, 'Estimating Fatalities Induced by the Economic Costs of Regulation', (1997) 14 *Journal of Risk and Uncertainty* at 5 to 23; T.O. Tengs, M.E. Adams, J.S. Pliskin, D.G. Safran, J.E. Siegel, M.C. Weinstein and J.D. Graham, 'Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness', (1995) 15-3 *Risk Analysis* at 369 to 389.

Zero tolerance stands in other words for zero risk. This, however, is a scientific impossibility. Indeed, in the *Pfizer* case on the antibiotic growth promoter virginiamycin, the Court of First Instance remarked:⁴⁷

130. Supported more specifically by Fedesa and Fefana, Pfizer submits that in any such risk assessment, the Community institutions must show that the risk, although it has not actually become a reality, is nevertheless probable. The existence of a 'very remote' risk should be allowed given the concrete positive elements arising from the use of the product concerned. In any event, the Community institutions cannot legitimately apply a test which Pfizer describes as a 'zero risk' test. Such a test is inappropriate since it is impossible to satisfy. It amounts essentially to requiring *probatio diabolica* from the industry, something which is recognised as unlawful in all the legal systems of the Member States (Opinion of Advocate General Mischo in the *Greenpeace* case cited at paragraph 115 above, ECR I-1651, at I-1653, point 72). It is never possible to prove conclusively that a chemical or pharmaceutical compound or anything created by modern technology represents a zero risk to public health now or that it will do so in the future. To apply such a test would quickly lead to the paralysis of technological development and innovation.

In the light of this ruling, Annex IV of Council Regulation could be considered as unlawful, as zero tolerance promulgates the explicit goal of zero risk, which is unfeasible in the real world and demands the impossible of economic parties. A way out of this predicament is that the Annex IV should list only compounds, which clearly show toxic effects at very low dosage. Proof of no harm is then rewritten in proof of harm; a much more solid base for regulation, which does not generate a *probatio diabolica* for industry.

The precautionary zero tolerance approach encourages people to think that 'safe' food actually exists, which is an impossibility and that it is, with the implementation of the precautionary principle, within reach. More importantly, with zero tolerance, chemical food safety is presented as the prime aspect of food safety as a whole, which is explicitly not the case. On a relative scale of risk, food safety issues rank as follows:⁴⁸

47 Case T13/99 *Pfizer Animal Health SA*.

48 J.P. Groten, 'Adverse effects of food contaminants', in J de Vries (ed.), *Food Safety and Toxicity* (1997), Boca Raton: CRC Press, at 133 to 146.

Table 2: Ranking of food safety issues in relation to human health

Food issues	Relative importance
1. Microbial contamination	100,000
2. Unbalanced diet	100,000
3. (Environmental) contamination	100
4. Natural toxins	100
5. Pesticides residues	1
6. Food additives	1

By scrutinising the chemical safety of food products, other aspects of food safety run the risk of receiving a lower priority in public and politics. Furthermore, such an approach to food safety carries the risk of intensifying the search for banned chemicals, as has been the case in Europe so far, tying up budgets, research efforts and personnel to the detriment of food safety as a whole.

The precautionary principle clearly belongs to the broader precautionary culture, which holds the view that society's 'systems managers' have a duty to prevent all damage, irrespective of cost and reality.⁴⁹ It encourages people therefore to become moral free riders by overlooking their own responsibilities. In that sense the European food laws contain a NIMBY (Not In My Back Yard) aspect through the precautionary principle, in which the view is propagated that potential public health risks, for instance as a result of low-level exposure to CAP, are to be averted at all cost. Cost-benefit analysis is often criticised for comparing the costs of some with the benefits of others.

The precautionary principle, however, does not seem to be doing any better. In the case of CAP, affluent European citizens avoid immeasurably small potential risks with the result that citizens in exporting countries have to forgo very real economic opportunities with ensuing risks to the quality of their lives. Indeed, the perceived, albeit absent, benefits from zero tolerance for the European population are converted into economic and public-health costs of the exporting countries.⁵⁰

In this article, we have attempted to broaden the picture on the CAP issue and have covered many issues. A rational system of food safety regulation is certainly cautious in its review of risk, but at the same time needs to be aware of and take in the width of the issues at hand. Proof of no harm cannot and never will be a guide for food safety regulations, as this requires massive research efforts focused on minute risks. And even then the gathered data might again give rise to further questions, resulting in an endless scientific quest. *A probatio diabolica* indeed.

In our view, the case of zero tolerance and its failure to add to food safety demands a reappraisal of the strict separation between risk assessment and risk management. The assessment of risk, or the lack of it, has by definition policy implications, which need to be addressed in order to avert mishaps. The absence of an ADI for CAP does not imply 'dangerous-at-any-dose' at all, as it only derives from a lack of data. A precautionary zero tolerance policy therefore is superfluous. Consequently, in our view, the precautionary principle needs to be discarded from food safety regulations as it dramatically confounds the issue of risk.⁵¹ It only applies to the perception of food safety as opposed to food safety itself.

⁵⁰ Note 46 above; J.B. Wiener, 'Precaution in a Multi-Risk World' (2001), Duke Law School Public Law and Legal Theory Working Paper Series Working Paper No. 23.

⁵¹ H. Sapolsky, 'The Politics of Risk', (1990) 119(4) *Daedalus* at 83 to 96.

⁴⁹ Note 9 above.