Beyond Zero-tolerance: A Novel and Global Outlook on Food-safety and Residues of Pharmacological Active Substances in Foodstuffs of Animal Origin

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Abstract
In this follow-up article on the issue of zero-tolerance published in the previous issue of Environmental Liability, the authors here propose a new approach of food-safety regulations for residues of pharmacological active substances in foodstuffs of animal origin. Key aspects of their proposal are a risk-based approach instead of a precautionary approach as to preclude trade barriers, and a prohibition classification based on proof of toxicity of low-level food-residues exposure. This is to preclude a *probatio diabolica* resulting from proof of absence of food-residues such as is now the case with Annex IV of Council Regulation 2377/90.[3] Regulation based on these two principals would genuinely address food-safety as its focus is on risk. This is highly desirable in view of an international level playing field of trade, as it would by definition rule out trade-barriers masqueraded as food-safety regulation, and would harness the inevitably advancing analytical field into the proper context whereby all residue sources –such as environmental ones- would be taken into account.

Introduction

With our previous paper on chloramphenicol ('CAP') and food-safety in Europe we have showed that current legislation on banned veterinary substances does not properly address food-safety as such.[4] The opening remark of the Reflection Paper –as part of an internet consultation by the EU on veterinary residues- that 'residues of pharmacologically active substances in food of animal origin are essentially a side-effect of the use of medicines in food-producing animals' has been falsified for CAP and has proven false for other veterinary substances as well.[5] Semicarbazide (SEM) is the most recent example: this supposed marker molecule for nitrofurans –a banned group of veterinary substances listed in the so-called Annex IV of Council Regulation 2377/90-[6] proved to have other sources than the banned substances whereby it has lost its legal status for demonstrating illicit use of this group of antibiotics.[7]

It was shown by the response of the European Food Safety Authority (EFSA) on the issue of SEM in packaged food that a risk-based approach of the presence of 'added' carcinogens adds considerably to reasoned and logical risk assessment, management and communication strategies on

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[3] Advice of the ad hoc expert group set up to advise the European Food Safety Authority (EFSA) on the possible occurrence of semicarbazide in packaged foods. (2003) European Food Safety Authority, Brussels.
[4] J.C. Hanekamp, G. Frapporti and K. Olieman, 'Chloramphenicol, food safety and precautionary thinking in Europe' (2003) 6 *Environmental Liability* at 209 to 221.
[5] Reflection Paper on Residues in foodstuffs of animal origin. (2004) European Commission, DG Enterprise, DG Health and Consumer Protection, at 4.
[6] 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.
[7] M. Mandix, letter dated 11 November 2003 from Dr Wiertz-Dipl.Chem. Eggert-Dr JörissenGmbH, Laboratory for Trade and Environment.

food-safety.[8] This response stands in stark contrast with the precautionary legal and political response as a result of the detection of Annex IV substances in food-products, which was discussed and critically commented on by Hanekamp *et al.*.[9] In the broadest sense it has been shown by Hanekamp *et al.* that the human and natural environment proves to be a multiple source for residues, which usually, but incorrectly, are marked as the result of veterinary intervention only.[10] Additionally it is remarked by the Reflection Paper that:[11]

> 'Existing legislation on pharmacologically active substances used in veterinary medicinal products … significantly contributed to the decreased availability of medicines for uses in food producing animals in the European Community. Moreover its construction has lead to various problems related to the implementation and enforcement of legislation related to the control of residues in foods of animal origin. These have also lead to difficulties in the functioning of the Single Market and in international trade.'

This part of the reflection paper displays only part of the present problematical state of affairs within the European Trade Zone concerning residues of pharmacological active compounds and its impact on other trade relations outside the EU. The zero-tolerance issue remains out of focus in this document, despite the fact that the matter is of overarching concern in the international trade of food. In this paper the issue of zero-tolerance will be fully addressed. A number of innovative legislative tools will subsequently be introduced that will tackle banned substances rationally. The basis for these tools is as follows:

- Focussed on food-safety to measurably warrant human health
- Enhance an international economic and regulatory level playing field
- Responsive to innovation in the pharmaceutical and food/feed industry

Food for thought: recapitulating the zero-tolerance issue

The detection in 2001 of 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. Some European countries went so far as to have food products containing the antibiotic destroyed.

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 (MRLs) of veterinary medicinal products in foodstuffs of animal origin.[12] This so-called 'MRL Regulation' 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.

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

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[8] See note 3 above; P. Slovic, *The Perception of Risk* (2001), London: Earthscan Publications Ltd; J. Flynn, P. Slovic and H. Kunreuther (eds), *Risk, Media and Stigma. Understanding Public Challenge to Modern Science and Technology* (2001), London: Earthscan Publications Ltd.
[9] See note 4 above.
[10] See note 9 above.
[11] See note 5 above at 1.
[12] 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.

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 maximum residue limit (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. Only when Annex IV substances are completely absent from food (at zero concentration) the risks are deemed completely absent.

Although a ban might legally translate logically in a zero-tolerance paradigm, reality has shown that such a translation is laden with complications. As we have shown in our previous article, presence of CAP in food could be traced to multiple sources not included in current legislation. Both natural and environmental sources of the banned substance could be identified. Other multi sources examples emerged during our research on CAP, such as the semicarbazide case. These examples seriously challenged the effectiveness of MRL legislation, especially when considering banned substances. Food-safety regulation on veterinary residues degenerated into fraud prevention and gave rise to trade barriers masqueraded as precautionary food-safety measures.

The recent 62nd JECFA (Joint FAO/WHO Expert Committee on Food Additives) meeting on food additives addresses the CAP issue whereby it implicitly refers to the article of Hanekamp *et al.*.[13] The committee drew the following conclusions:[14]

> 'There was no evidence supporting the hypothesis that chloramphenicol is synthesized naturally in detectable amounts in soil. Although this possibility is highly unlikely, data generated with modern analytical methods would be required to confirm this; There was evidence that low concentrations of chloramphenicol found in food monitoring programs in the year 2002 could not originate from residues of chloramphenicol persisting in the environment after historical veterinary uses of the drug in food producing animals. However, due to the high variability of the half-life of chloramphenicol under different environmental conditions, such a mechanism might occasionally cause low-level contamination in food; Valid analytical methods are available to monitor low levels of chloramphenicol in foods. However confirmatory methods require sophisticated and expensive equipment.'

It is remarkable that the committee does not address a number of crucial issues raised by Hanekamp *et al.* such as the human use of CAP, which could result in traceable amounts in surface waters, as Hirsch *et al.* discussed for German surface waters.[15] For the United Kingdom for instance, Webb calculated the predicted environmental concentration (PEC) for human clinical use of CAP. The clinical CAP use in the UK was estimated to be 377 kg/year. This annual consumption of CAP

[13] See note 4 above.
[14] Joint FAO/WHO Expert Committee on Food Additives. (2004) Sixty-second meeting Rome, 4 – 12 February 2004.
[15] 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.

resulted in a PEC of 0.07 μg/l.[16] It is a gross omission that the JECFA did not address the human medicinal use of CAP and its potential environmental impact.

That historical veterinary CAP use would not constitute an overall sustained environmental source for food contamination is a trivial observation made by the JECFA committee. Astoundingly though, the committee does surmise –divergent from their initial statement- that historical veterinary CAP use might yet on occasion be an environmental source of food contamination; the multi-source aspect we introduced surfaces here unmistakably. However, if historical veterinary CAP use would on occasion constitute an environmental source for food contamination, than it would be inherently logical to assign present-day human medicinal use as an equally valid source for food contamination. Even more so, contemporary human medicinal use of CAP is a much more plausible environmental source for food contamination than historical veterinary use. Environmentally present CAP as a result of historical veterinary use would under environmental conditions decrease over time despite the varying half-life in diverse environmental circumstances. Human medicinal use conversely is an invariable contemporary source of contamination of especially the aquatic environment, contrary to the terminated veterinary application. For the Asian countries this is all the more pertinent, as the human CAP consumption in this global region is manifestly higher than in Western countries.[17] For no apparent reason the JECFA committee limits the multi-source issue to the historical veterinary context and thereby does not take the argument to its logical conclusion, which we have done here.

The JECFA committee additionally does not address the issue of false-positives, which seriously interjects global trade. Compliance and non-compliance is with zero-tolerance first and foremost dependent on the state of the analytical art. We need not go into detail here, as we addressed this issue quite extensively in our previous paper.[18] Finally, the JECFA committee theorised that natural production of CAP in soil would not be detectable, whereby it could not function as a source for food contamination. This is a tenuous statement clearly at odds with the findings we produced, presented and discussed in our paper.[19]

Zero-tolerance proved to be contrary to the empirical reality and constitutes a *probatio diabolica* for industry; by definition proof of absence of Annex IV substances (or any other chemical substance for that matter) is unachievable. Legislators did not contemplate the advent of precise analytical equipage, which made zero-tolerance legislation an artefact of technological and scientific ingenuity. As the Reflection Paper remarks:[20]

> '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 realistic goal because at that time residues could only be determined in concentrations of around 1 mg/kg [*ppm; authors*]. Since then the availability and sensitivity of methods of analysis has continuously improved and the detection of concentrations as low as 1 ng/kg [*ppt, authors*] are frequently state of the art today. These improvements mean that ever lower amounts of residues are detected, which would previously have gone undetected.'

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[16] S.F. Webb, *A Data Based Perspective on the Environmental Risk Assessment of Human Pharmaceuticals II – Aquatic Risk Characterisation*, (2001) in K. Kummerer (ed) *Pharmaceuticals in the Environment. Sources, Fate, Effect and Risks* at 203-230.

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

[18] See note 4 above.

[19] Hazardous Substances Data Bank http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (last visited 15 January 2004); AINIA, *Presence of chloramphenicol in foods* (2003). (This report can be obtained through the authors.)

[20] See note 5 above at 4.

Annex IV compliance and food safety: a dichotomy

The 'vanishing zero' has become a reality. This fact has brought into view that food-products compliance –meaning that tested food-products did not show, after analysis, presence of regulated substances- is quite different than 'safe food'. In general the entire toxicological profile of food –to be regarded as a mixture of numerous chemicals amongst which natural carcinogens and anti-carcinogens, pesticides, veterinary residues-[21] is not changed measurably by the presence of veterinary residues. (We have discussed this issue with the aid of a table in which various food-safety issues in relation to their relative importance were depicted.[22]) This is particularly true for banned substances as these are usually detected –if at all- at very low concentrations usually in the ppb (parts per billion; μg/kg product) or even ppt range (parts per trillion; ng/kg product). Food-safety as such is by any standard not determined by the detectable presence of banned substances.[23]

Moreover, a ban such as is the case with CAP is often –but certainly not always- derived from risks surfacing at therapeutic concentration levels. Extrapolating high exposure risks to low levels found in food-products is fraught with impression and usually relies on linear extrapolation models, which are to be regarded as conservative.[24] It is safe to say that the risks involved are usually overestimated. Therefore is seems logical to alter legislation dealing with banned veterinary substances. Below we will propose tools of innovation within the context described in the introduction (focussed on food-safety, responsive to innovation, creating a level playing-field).

Tools of innovation

Food safety should be the main concern of any future legislation. It should not be the route through which fraud (in this case use of illegal veterinary substances) is tackled. The chloramphenicol and nitrofurans cases are illustrative for the regulatory failure to challenge fraud through food safety regulations. SEM, which primarily functions as a marker for nitrofurans (as part of Annex IV) was also found in a number of food products that are packaged in glass jars with metal lids sealed with plastic PVC gaskets. The EFSA review of SEM is an illustration of the cool headedness required to handle contamination from a food safety perspective instead of a mere legal perspective:[25]

> 'Semicarbazide is not specifically regulated by EU food packaging directives but if it were present in food packaging materials, for instance as an impurity or a reaction or degradation product, its presence in food would be covered by the Council Directive 89/109/EEC. Under Article 2 of this Directive, it could be present in food contact materials provided it did not transfer into foodstuffs in quantities which could endanger human health.'

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[21] *Carcinogens and Anticarcinogens in the Human Diet. A Comparison of Naturally Occurring and Synthetic Substances.* (1996) Committee on Comparative Toxicity of Naturally Occurring Carcinogens, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, Washington D.C.: National Academy Press.

[22] See note 9 above at 219.

[23] B.N. Ames and L.S. Gold, 'Environmental Pollution, Pesticides, and the Prevention of Cancer: Misconceptions' (1997) 11 *FASEB Journal* at 1041; B.N. Ames and L.S. Gold, 'Paracelsus to parascience: the environmental cancer distraction' (2000) 447 *Mutation Research* at 3 to 13; See the Carcinogenic Potency Project at http://potency.berkeley.edu/; see also L.S. Gold, T.H. Slone, N.B. Manley and B.N. Ames, *Misconceptions about the Causes of Cancer* (Vancouver, The Fraser Institute, 2002); available at http://potency.berkeley.edu/text/Gold_Misconceptions.pdf.

[24] E.J. Calabrese and L.A. Baldwin, 'Toxicology Rethinks its Central Belief. Hormesis Demands a Repraisal of the Way Risks are Assessed' (2003), 421 *Nature* at 691 to 692; E.J. Calabrese and L.A. Baldwin, 'Hormesis: the dose-response revolution' (2003), 43 *Annual Review of Pharmacology and Toxicology* at 175 to 197; ; K.K. Rozman and J. Doul, 'Scientific foundations of hormesis. Part 2. Maturation, strengths, limitations, and possible applications in toxicology, pharmacology, and epidemiology' (2003), 33 (3-4) *Critical Reviews in Toxicology* at 451 to 462.

[25] See note 3 above at 3 to 4.

On the other hand, when SEM is viewed as derived from the illicit application of nitrofurans, zero-tolerance is legislatively demanded. This is a flagrant inconsistency, which needs to be remedied. The following regulatory instruments could serve this purpose:

- An 'Annex IV' based on proof of harm of low-level exposure toxicity
- Risk assessment
- MTR (Maximum Tolerable Risk level)
- Toxicologically Insignificant Exposure Level (TIE)
- Internationally harmonised veterinary products authorisation and analysis
- (Fractional) integration of risk assessment, management and communication

In order to preclude future regulation leading to an unlawful *probatio diabolica*, it is essential that proof-of-harm of low-dose toxicity supersede the current proof-of-no-harm Annex IV regulation. When *proof-of-harm* as a result of food residue levels exposure surfaces, then the substance needs to be listed on an amended 'Annex IV'. Lack of data to establish a MRL as such is not a sufficient ground to ban certain veterinary products, even more so when those products are authorised as human medication and damaging effects surface only as a result of human therapeutic use. Indeed, with any authorised human and veterinary medication a balance is struck between toxicity and beneficial effects at the biological active dosage. Risks materialising at the human therapeutic level are not indicative for food residue level exposures.

Risk assessment and management are the tools of choice when dealing with food safety. Through these instruments the legality of food safety regulation is clearly distinguished from the question of toxicological relevance. The RIVM (Rijksinstituut voor Volksgezondheid en Milieu; Dutch National Institute for Public Health and Environment), in their study on CAP in shrimp, estimated the cancer risk as a result of the consumption of shrimp containing CAP.[26] The concentrations in imported shrimp varied roughly between 0.1 and 10 ppb (0.1 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). By introducing the MTR as a transparent human health management target, unequivocal answers can be given in relation to low-level exposures through food-products. The MTR serves best as a risk assessment and management criterion as it is internationally recognised and accepted. Moreover, from a risk communication point of view, MTR addresses the relativity of risk much more effectively, as food-safety is more dependent on other factors such as we addressed in our previous paper.[27] The message of zero-tolerance is impossible to communicate in a multi-risk world, especially when food is concerned as it confuses the issue of risk resulting from food consumption.[28]

Obviously, acute exposure such as is the case with human medication toxicologically differs markedly from chronic low-level exposure, and therefore food-residue low-level exposure requires a prudent approach. Nevertheless, with banned veterinary substances zero-tolerance proves to be unachievable and unlawful. We therefore propose a TIE –a Toxicologically Insignificant Exposure level- for banned substances as to preclude analytical progress as the sole limiting factor for the determination of regulatory compliance. Research of indirect additives in food, based on the Carcinogenic Potency Project,[29] suggests a TIE of 0.5 ppb. [30] This TIE level is all the more pertinent in

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[26] 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.

[27] See note 9 above.

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

[29] See note 23 above.

[30] A.M. Rulis, *Threshold of regulation: Options for handling minimal risk situations* (1992), in: *Food Safety Assessment*, ACS Symposium Series 484 at 132 to 139; See further note 21 above.

view on the current scientific dialogue on hormesis we considered in our previous paper.[31] On the other hand, based on our propositions on risk assessment and the MTR threshold the TIE concept leaves open a case-by-case approach of food contamination. The cases of SEM in packaged food as discussed by the EFSA and CAP in shrimp as discussed by the RIVM and Hanekamp *et al*. are the working examples here.[32]

Global compliance –traceable to a universal banned substances list, proof of toxicity of low-level food-residues exposure, risk assessment methodologies and internationally accepted risk and exposure thresholds- requires an internationally harmonised analytical approach. This proposed framework of food-safety regulation –as founded on sound scientific principle- necessitates a move towards analytical harmonisation. Exporting and importing countries and the various internal markets are in need of general compliance rules as to preclude unwarranted trade-barriers or to put it positively to generate a truly free and open market for all food-producing countries. Tools of analysis need to be horizontally unified in order to generate international compliance and a level playing field as to preclude trade-barriers. Trade between nations will benefit from international cross-compliance, in which properly analysed goods will be accepted unreservedly by importing nations. In cases where banned substances are detected, a risk analysis of observed concentrations and potential exposure routes needs to be undertaken with food safety as the leading objective. With the aid of the TIE, endless analytical exercises will thereby become non-operational. This will in our view further add to a renewed pharmaceutical interest in applying for authorisation for innovative veterinary medication. Proof of no harm –as intrinsically espoused by zero-tolerance strategies- generates a chilly climate for innovation typical for the cautious culture one of the authors discussed elsewhere.[33]

In conclusion some thoughts on assessment, management and communication

As we argued in our previous paper, the case of zero tolerance and its failure to add to food safety demands a reappraisal of the strict separation in Europe 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. What does it mean for food-safety and human health that particular risks of certain veterinary substances have surfaced in human clinical use, or in experimental toxicological research? Is food-safety subsequently at stake? Does the impossibility to arrive at an acceptable daily intake imply that the substance under scrutiny is dangerous at any dose whereby a zero-tolerance is mandatory? What are the management and communication options when these issues surface? What are the regulatory options? What are the regulatory consequences when certain veterinary compounds are banned?

These questions show –while there are numerous other questions that can be put forward in this matter- that a scientific assessment raises numerous management, communication and regulatory issues that need to be addressed subsequently. We have shown that isolated assessments of veterinary substances and the preferred regulatory choices made on the basis of these assessments does not by definition address food-safety as such. The fact that for CAP no acceptable daily intake could be established –for lack of data- was regulatory translated in zero-tolerance. The regulatory choice of zero-tolerance is, however, not implied by the scientific assessment. It is an expression of the regulatory preference for the precautionary principle and has very little to do with food-safety or human health as such.[34] Nonetheless, it is assumed by regulatory bodies that zero-tolerance adds measurably to food-safety and human health, which, on the other hand, requires scientific inquiry.

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[31] See note 4 above.
[32] See notes 3, 4, and 26 above.
[33] R. Pieterman and J.C. Hanekamp, 'The Cautious Society? An Essay on the Rise of the Precautionary Culture' (2002) Zoetermeer: Heidelberg Appeal Netherlands.
[34] See note 33 above; I.M. Goklany, *The Precautionary Principle. A Critical Appraisal of Environmental Risk Assessment*, (2001), Washington D.C.: Cato Institute; J. Morris, (ed) *Rethinking Risk and the Precautionary Principle*, (2000) Oxford (UK): Butterworth-Heinemann; A. Wildavsky, *But is it True? A Citizen's Guide to Environmental Health and Safety Issues*, (1997) Cambridge: Harvard University Press.

However, history shows that feedback to the scientific community to assess the regulatory efficacy of zero-tolerance has not happened. This gross faux pas of both the regulatory and scientific bodies is the result of the strict separation of risk assessment and management.

We therefore propose that strict separation of risk assessment and management is –at least in part- discarded. Scientific institutes, researchers and advisors on the one hand and regulators and politicians on the other hand need to come to terms that risk assessment, management, communication and regulation are part of one and the same attempt of industry and policy to protect public health when food-safety is considered. Both a feedback to the designated scientific bodies on the implementation of food-safety regulations and the contextualisation of the residue topic in the entirety of food-safety are matters of science. Regulatory choices in matters of food-safety need to demonstrably add to human health whereby a societal cost-effectiveness can be made transparent.[35] This is important in a global market that increasingly demands for an international level playing field.

In this follow-up article on the issue of zero-tolerance we hopefully add to a discussion, which is in dire need of rationalisation. In order to generate a level playing field international agreement is needed on the issues raised in this article. The scientific approach of food-safety is the only viable option. The disorder created by the precautionary zero-tolerance episode, which unfortunately has not reached its final chapter yet, is an unequivocal signal of that to the world of trade and politics.

[35] R.W. Hahn, (ed) *Risks, Costs and Lives Saved. Getting Better Results from Regulation*, (1996) Oxford: Oxford University Press; 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.