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Publication status and date:

Published: 01/01/2011

Document Version

Publisher's PDF, also known as Version of record

Citation for the published version (APA):

Pieterman, R., Hanekamp, J.C., & Kwakman, J. (2011). Food Safety at The Molecular Level: Crossing the Ecological Threshold. *Global Aquaculture Advocate*, 2011(March/April), 41-43. <http://hdl.handle.net/1765/32922>

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Food Safety At The Molecular Level: Crossing The Ecological Threshold



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Technology-driven assessments of the safety of food can lead to misleading results.

concerns, at the consumer level heightened awareness and anxiety of the presence of chemicals in food.

Summary:

The zero-tolerance precautionary approach to ban certain antibiotics from food has proven unworkable as a result of continuing analytical progress. New regulatory standards on chemical residues do not adequately address the situation, leaving technical progress, not toxicological relevance, to determine undesirable levels. As new chemical substances are identified in nature, detection must identify toxicity in terms of actual levels of exposure, but also whether a causal link between chemical and illegal conduct can be established.

In the view of European regulators, to ensure a high level of health protection with respect to food safety, public exposure to antibiotics used in animal rearing and aquaculture needs to be forestalled in the European Union. Lack of knowledge concerning the toxicity and sources of these antibiotics is no argument to refrain from regulatory action to eliminate any presence of banned antibiotics. This is the approved precautionary food safety approach.

The chloramphenicol episodes of late 2002 and 2003, however, launched a global debate about the limits of science and technology, the risks and uncertainties of low-level antibiotics exposure through food consumption, the effectiveness of precaution and the sources of the measured compounds: manmade and/or natural. Nevertheless, measurements of low-level concentrations in food, irrespective of toxicological and pharmacological

The zero-tolerance precautionary approach as a means to ban from food certain antibiotics for which no maximum toxicological levels can be determined – either from a lack of toxicological or pharmacological data or because of genotoxic characteristics of the compound in question – has proven unworkable as a result of the analytical progress made in the last three decades.

Chloramphenicol proved to be more ubiquitous in food – albeit at extremely low levels – than could be accounted for by mere abuse. The authors had tentatively shown that chloramphenicol, a natural product from the soil-bacterium *Streptomyces venezuelae*, can be detected in non-animal food at extremely low levels. So the detection of low levels of chloramphenicol could not be directly linked, causally and legally, to abuse of the antibiotic in food production.

E.U. Regulation

European Regulation E.C. No. 470/2009, the new regulatory standard for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, did not fundamentally amend the regulatory situation that arose from the chloramphenicol situation.

Although this new regulation points at the scientific and technical progress by which the presence of residues of veterinary medicinal products in foodstuffs is detected at ever-lower levels, a fundamental solution is not given.

A short-term alternative given for zero tolerance uses some existing minimum required performance limits (MRPLs) of forbidden antibiotics as targets for regulatory action levels of concern. The MRPL is easiest explained as the lowest concentration level regulatory laboratories in the European Community can

detect and confirm. Again, scientific and technical progress, instead of toxicological relevance, is the determining factor in detecting chemical compounds deemed undesirable in foods.

Detection Issues

Problems with regard to the detection of low-level concentrations of antibiotics and their markers persist, as shown by the 2009 semicarbazide case. In Belgium, there was an increased incidence in the detection of semicarbazide (SEM), a marker molecule for the banned antibiotic nitrofurazone that degrades rapidly and cannot be detected directly, in freshwater prawns, *Macrobrachium rosenbergii*.

This contrasted with all other European countries, where no significant increase in SEM-positive samples was detected. A possible explanation for this phenomenon was that at the request of the Belgian Federal Agency for the Safety of the Food Chain, all approved laboratories were asked to analyze complete prawns (meat and shell) for the presence of tissue-bound metabolites of nitrofurans from December 17, 2004, onward. This procedure is not common in other countries and became apparent only after publication of E.C. regulation 630/2008 on July 24, 2008, which required mandatory testing of shrimp from Bangladesh imported to the European Union.

The Directorate-General for Health and Consumers (European Commission) regards the presence of SEM as solely indicative of the illegal administration of nitrofurazone to live animals when it is found as a bound residue in food. Nitrofurazone belongs to the nitrofuran group of antibiotics that, because of their potentially carcinogenic and mutagenic effects on human health, are prohibited within the European Union as therapeutic or prophylactic medicines in food-producing animals.

It has been pointed out that SEM seems a poor marker for nitrofurazone in light of the discovery that under certain conditions, SEM in food arises from sources other than this illegal antibiotic. These sources, until now, have been found to be man-made. However, indications for a natural source were reported, as well.

A Belgian research group found that *Macrobrachium rosenbergii* cultivated under controlled lab conditions in the absence of nitrofurazone had SEM present in their shells. The 0.5 µg/kg concentration in the meat was measurable, but below the current MRPL of 1.0 µg/kg. The presence of SEM, albeit at lower concentrations, could also be shown in the shells of black tiger shrimp, *Penaeus monodon*, signifying that crustaceans might produce SEM at varying concentrations.

Indeed, other wild-caught crustacean species tested by the research group, such as *Scylla serrata*, *Portunus pelagicus* and *Nephrops norvegicus*, were shown to have bound SEM in their shells at varying concentrations up to 12.6 µg/kg. The exact source of the SEM, now identified as a natural metabolite, is unknown as of yet.

It seems clear then that SEM can not be used as a marker molecule for the illegal use of nitrofurazone. The legal causal link between the presence of SEM and the illegal use of nitrofurazone, and the corollary that if SEM is found in reported wild-caught produce, then this produce must by implication have been cultured in the presence of nitrofurazone, seems to be broken.

The fact that SEM is likely to be a natural metabolite in crustaceans rules out the possibility of tracking illegal nitrofurazone use through the use of SEM as a marker. The notion the authors put forward in 2002 that ever-lower analytical detection levels will result in the crossing of some ecological threshold in the food matrix has been conclusively illustrated by the SEM case.

Natural Counterparts

But there is another more pressing problem, namely that the biochemistry of animals, plants or even entire biogeochemical cycles is immeasurably more intricate than the mere allocation of marker molecules for the ostensible legal control of certain pharmaceuticals implicitly or explicitly suggests. In the view of the authors, it is preposterous that our immense complex biogeochemical reality, which includes animals, plants, bacteria and fungi, as well as geochemical processes, is forced into a highly reductionist legal construct put in place to ostensibly protect the public against “toxic” chemicals of man-made origin in food. It is not an exaggeration to state that most, if not all, molecules that can be identified as man-made or man-induced have natural counterparts.

A famous example is the group of chemicals known as halogenated hydrocarbons, of which the chlorinated chemical compounds are the most “notorious.” Chlorine is one of the most abundant elements on the surface of the earth. It was widely believed that all chlorinated organic molecules are xenobiotic, man-made chemicals; that chlorine does not participate in biological processes at all; and that it is present in the environment only as the relatively benign chloride anion Cl⁻, the anion of table salt.

Ubiquitous In Nature

In the 1990s, a controversy arose in the United States regarding an environmentalist call to ban or phase out the production and use of chlorinated organic chemicals, inorganic chlorine bleaches and elemental chlorine. The argument for a chlorine ban was carried by the notion that the vast majority of organochlorine compounds are mostly foreign to nature.

However, it has become increasingly clear that organohalogenes are ubiquitously produced in nature. Some of these compounds are produced in amounts that dwarf human production, and other compounds are produced at low levels. More than 5,000 different natural organic halogen compounds, from the very simple to the very complex, have been identified so far. They come from widely diverging sources: marine, terrestrial biogenic, terrestrial abiotic, biomass combustion (natural and anthropogenic) and volcanoes.

As an example of man-made organohalogenes that were later shown to be natural components of the biosphere, consider the benzodiazepines (such as temazepam and diazepam) first introduced into clinical practice in 1960 and nowadays the most widely used psychotropic drugs that affect the central nervous system.

Natural benzodiazepines are found in soil, plants, and animal and human tissues, and are chemically identical to their pharmaceutical counterparts. Other examples of industrial-like chemicals are single- or multiple-chlorinated, brominated and iodated methanes; halogenated alkanes, alkenes and alkynes; halogenated terpenes; dioxins and dibenzofurans.

So, detecting certain chemicals not only requires the still not properly addressed question of toxicity in terms of actual levels of exposure, but also whether an unambiguous causal link between

Detecting certain chemicals not only requires the still not properly addressed question of toxicity in terms of actual levels of exposure, but also whether an unambiguous causal link between chemical and illegal conduct can be established.

chemical and illegal conduct can be established. The efforts to lower the levels of detection of sought-after compounds in food matrices paradoxically have increased the uncertainty with regards to the source.

Background Concentrations

Ecological background concentrations are present in food at low levels. As remarked in relation to the chloramphenicol issue in 2003: “The first question that comes to mind is whether (chloramphenicol) 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, this question is all the more pertinent, as increasing analytical capabilities could result in crossing this potential ecological boundary.”

Recently this has been shown in herbs and grass. Samples of the *Artemisia* family retrieved from Mongolia and Utah, USA, and a therapeutic herb mixture obtained from local stores in the Netherlands proved to contain chloramphenicol at levels ranging from 0.1 to 450.0 µg/kg. These findings firmly underline the authors’ findings from 2003.

Perspectives

As stated in 2003, as the analytical detection limit is set lower, the probability that some ecological background is detected in the food matrix becomes higher. SEM and chloramphenicol are unambiguous examples thereof.

Precaution as a means to forestall exposure to chemicals with a certain toxicological profile is a flawed and unsustainable approach when considering chemical food safety in light of the increasing capabilities of science and technology.

Precaution is no substitute for knowledge. Quite the contrary. It augments uncertainty with regards to the presence and sources of increasing numbers of detectable chemicals of all sorts. Clearly, more examples will come to the fore in the future, when analytical capabilities have again raised the bar in detecting ever-lower amounts of certain chemicals.