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Special Article

Human Health Aspects of Use of Chemicals in Aquaculture

with Special Emphasis on Food Safety and Regulations on the Use of Chemicals

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ABSTRACT: Safe and wholesome food are essential for good health. Therefore, when one considers health issues related to unsafe foods, recorded morbidity and mortality as well as economic loss in population must be included. Risks to human health arising from micro-organisms are generally considered as major risk due to unsafe food. Chemicals in aquaculture are mainly used for treatment and prophylactic measures for disease problems which constitute the largest single cause of economic losses in aquaculture (1). However, the increasing use of chemicals in aquaculture leads to a wide public concern. The concerned issues related to human health due to chemical used in aquaculture repeatedly found in published literature include allergic reaction in a previously sensitized person triggered by chemical residue and the issue of impacts on human health from the emergence of drug-resistant bacteria in animals caused by the use of sub-therapeutic level antibiotics and by antibiotic residues persisted in sediment of the aquaculture environment. This paper discusses the risk evaluation principles, data requirements and the concept of maximum residue limit (2-6). The uncertainties inherent in the process include, but are not limited to the state of the art of toxicological evaluation, understanding the environmental transport process of chemicals, exposure data, assumptions and extrapolations.

KEY WORDS: Aquaculture, Food safety, Regulations on use of chemicals, Human health.

Note: 1. This paper was presented at the Meetings on the Use of Chemicals in Aquaculture in Asia organized by SEAFDEC, FAO and CIDA, 20-22 May 1996, Tigbauan, Iloilo, Philipines.

2. This paper expresses viewpoints of the authors and does not represent any organizations mentioned in text.

INTRODUCTION

Risk Evaluation / Risk Assessment

A major objective of risk evaluation / risk assessment of chemicals is to provide a reliable basis for sound management of toxic chemicals.

The Joint FAO/WHO Expert Consultation on application of risk analysis to food standards issues which was held in Geneva, Switzerland 13-17 March 1995 supports the use of science based risk assessment process (7).

The concept of maximum residue limits of veterinary drugs adopted in 1989 by the Commission of the Codex Alimentarius was discussed as an approach, aimed at guaranteeing the absence of chemical residues that might present a risk to the consumer's health (8).

Decision Process for Establishing Recommended Maximum Residue Limits

"In recommending a Maximum Residue Limit (MRL) for a specific compound, several factors are taken into account by the Committee. Among them are the results of toxicological and radiolabel residue studies, the bioavailability of bound residues, the identification of target tissue(s), the existence of a residue marker for determining compliance with safe residue limits, residue data from use of the veterinary drug according to good practice in the use of veterinary drugs, withdrawal periods for adequate residue depletion, and practical analytical methods for residue analysis.

The first step in establishing a recommended MRL is the determination of an Acceptable Daily Intake (ADI) based on the available toxicological data. If the use of the veterinary drug according to good practice yields concentrations of residues lower than those corresponding to the ADI, the MRL will be reduced accordingly. However, if the residues cannot be measured using a practical analytical method under these conditions of use, the MRL will be raised so that compliance with the MRL may be checked analytically. In no instances, however, will an MRL be recommended at concentrations that significantly exceed the MRL based on toxicological considerations.

An important factor to be considered in the establishment of MRLs in various edible tissues and other products of animal origin is the amount of the food item consumed. In order to protect all segments of the population, it is reasonable to use intake data at the upper limit of the range for individual edible tissues and animal products. The Committee based its recommendations on the following daily intake values : 300 g of meat (as muscle tissue), 100 g of liver, 50 g of kidney, 50 g of tissue fat, 100 g of egg and 1.5 L of milk" (3).

"The human consumption of farmed fish and prawns, for example, seems to vary considerably and accurate food intake data are difficult to obtain at the international level. In order to protect all segments of the population, MRLs for these food commodities should be based on the food intake values noted in the thirty-fourth report of the committee" (6).

"MRLs for veterinary drugs are established based on the daily food intake values considered, namely 300 g of meat as muscle tissue, 100 g of liver, 50 g of kidney, 50 g tissue fat, 100 g of egg and 1.5 L of milk which protect the vast majority of the population of the world" (2).

"It is recommended that governments should consider whether local diets may result in intakes that exceed the ADI" (5).

Relevant Data for Assessing the Human Food Safety of Residues of Veterinary Drugs (5).

"When investigating the safety of the consumption of residues of veterinary drug in food, the Committee required detailed reports (including individual animal data) of the following types of studies relevant to the toxicological evaluation:

- Pharmacokinetic, metabolic and pharmacodynamic studies in experimental and food-producing animal, and in humans, when available.
- Short-term, long-term / carcinogenicity, reproduction and developmental studies in experimental animals, and genotoxicity studies.
- Special studies designed to investigate specific effects, such as those on mechanisms of toxicity, no-hormonal-effect levels, immune responses or macro-molecular binding.
- For compounds with antimicrobial activity, studies by the manufacturer designed to evaluate the possibility that the compound might have an adverse effect on the microbial ecology of the human intestinal tract.

-Studies providing relevant data on the use of, and exposure to, the drug in humans, including studies of effects observed after occupational exposure and epidemiological data following clinical use in humans."

"Detailed reports of studies relevant to the evaluation of drug residues in food-producing animals that are required for evaluation include information on:

-The chemical identify and properties of the drug.

-Its use and dose range.

-As for the toxicological evaluation, pharmacokinetic and metabolic studies in experimental animals, target animals and humans, when available.

-Residue-depletion studies with radiolabelled drug in target animals from zero withdrawal time to periods extending beyond the recommended withdrawal time. These studies should provide information on total residues, including free and bound residues, and major residue components to permit selection of a marker residue and target tissue.

-Residue-depleting studies with unlabelled drug for the analysis of marker residue in target animals and in eggs, milk and honey. These should include studies with appropriate formulations, routes of application, and species, at doses up to the maximum recommended.

-A review of routine analytical methods that may be used by regulatory authorities for the detection of residues in target tissue.

-A description of the analytical procedures used by the sponsor for the detection and determination of parent drug residues. The sponsor is also required to describe a method that may be used by regulatory authorities for the specific determination of the marker residue with a sensitivity equal to or less than the MRL" (5).

Some Issues of Public Concerns and The Safety Evaluation Process.

1. Issue of risk due to allergic reactions due to chemical residues in foods.

Allergic reactions caused by antibiotic residues in food are of great public concern, but generally, it is found that the incidence of allergic reaction following ingesting of antibiotic residues in food animal is very low (9-10). Many drugs are considered to have a high potential for sensitizing susceptible individuals such as penicillins, tetracyclines, sulfonamides and some aminoglycosides. Penicillins have the greatest potential and cause allergic response characterized by dermatitis in most reports. It is implied that the amount of penicillin required to induce the primary sensitization may be greater than the quantities eliciting an allergic response (about 1-10 units or less) (10) and the dairy products which test negative by microbiological assay may contain sufficient penicillin or its metabolites to maintain urticaria (11). According the these studies, it is indicated that very minute of penicillin in food can cause allergic reactions.

Report (3) stated that "Although there is no evidence from which threshold doses for such effects can be determined, the Committee concluded that hypersensitivity reactions due to the ingestion of food of animal origin containing allergic drug residues were unlikely to be of major health significance. This view was supported by the small numbers of reports in the published literature. Nevertheless, the Committee recognized that reactions could occur in highly sensitized individuals and therefore recommended that residues of drugs with known or suspected allergenic properties be kept as low as practicable, particularly penicillin and other β-lactam antibiotics such as the cephalosporins."

Difficulty still exists concerning the strategy and approach to be used for evaluating this risk especially when chemical residue may trigger an allergic reaction in previously sensitized person or to undermine the immune system.

2. Issue of microbial resistance due to the use of subtherapeutic antibiotics

The predominant public concerns on microbial resistance due to the use of subtherapeutic antibiotics are the impacts on human health from the emergence of drug-resistant bacteria in animals caused by prolonged use of low-level antibiotics in animal feed (12-13) and antibiotic residues (i.e. oxytetracycline, oxolinic acid) persisted in sediment for a long time (14). These situations actually bring human to new medical dilemma.

Recently published studies implied that the transmission of antibiotic resistant pathogenic bacteria from animal origin to man may be possible and apparently related to subtherapeutic use of the drugs in animal production. Furthermore, the resistant strains in the environment may also transfer R plasmid to human intestinal flora (15-19).

Therefore, such pathogenic resistant bacteria may be direct or indirect causes of human illness and induction a

significant loss of antibiotic efficacy in bacterial infection treatment, for example, Salmonella outbreak in the United States between 1971-1983 (20).

Nevertheless, this topic is still controversial and there is no direct evidence by reason of the difficulties to trace the resistant strains from animal-to-man and complexity of antibiotic use in human (9).

In assessing the microbiological risk due to residues of antimicrobial drugs in food, WHO (3) stated that "In evaluating the safety of residues of antimicrobial drugs, the specific risks associated with their antimicrobial activity should be considered in addition to their pharmacological properties. The antimicrobial activity could become the determining factor for this safety evaluation if the toxicity of the substance to be considered is such that higher levels of residues could be tolerated in food on a toxicological basis.

In this respect, the Codex Committee on Residues of Veterinary Drugs in Foods has adopted a definition of Maximum Residue Limit or Veterinary Drugs taking into account "other relevant public health risks (that may refer to allergic and microbiological risks) as well as food technological aspects".

In assessing the microbiological risk, two biological systems need to be considered:

- The intestinal flora of the consumer
- Bacteria used in the food processing industry.

The risk being considered by the Committee does not deal with the potential health effects associated with ingesting of food of animal origin that contains resistant bacteria selected under the pressure of antimicrobial therapy, because the Committee's terms of reference include only the safety assessment of drug residues" (3).

Inherent Uncertainties in The Safety Evaluation Process

The uncertainties inherent in the risk assessment process include, but are limited to the state of the art of toxicological evaluation, understanding the environmental transport process of chemicals, exposure data, assumptions and extrapolations.

The pharmacokinetic studies are also become more complicated when there is the possibility of repeated exposure due to environmental transport processes in the aquatic environment. The limited understanding of environmental fate of chemicals will contribute to uncertainty in risk evaluation.

CONCLUSION

Scientific principles are the most important for maintaining consistency in assessments of health risk although there are differing pharmacological and toxicological properties of chemicals used in aquaculture and the widely varying amounts of information available on them.

An approach, aimed at guaranteeing the absence of chemical residues that might present a risk to the consumer's health which is the concept of maximum residue limits of veterinary drugs in foods is used by the Commission of the Codex Alimentarius (8).

Risk evaluation / assessment process is generally accepted to provide a reliable basis for identifying and managing health risks. However, in some area of public concerns such as allergic reactions due to chemical residue which may trigger reactions in previously sensitized person and the issue of microbial resistance due to the use of subtherapeutic antibiotics, difficulties exist concerning the strategy and approach for evaluating these risks (9).

The uncertainties are due to lack of knowledge of the impact of chemical use on multiple species and multiple routes of exposure in an ecosystem. The uncertainties are also due to limited knowledge of environmental transport of chemicals which will affect exposure of chemicals to aquatic organisms, which, in turn, will affect pharmacokinetics and metabolism of such chemicals resulting in changing of the chemical residue profile within the organism.

The complexity of these issues and often lack of data as well as lack of monitoring and surveillance system are the limiting factor to the risk analysis process. These insufficiency of data are even more pronounced in developing countries where resources are more limited or less available. Therefore, only the policy of safe and effective use of chemicals must be developed. Strategies chosen should be appropriate according to individual country's and region's needs. Strengthening of research efforts and human deve-

lopment as well as information exchange may be encouraged through international collaboration.

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