

Human Health Aspects of the Use of Chemicals in Aquaculture, with Special Emphasis on Food Safety and Regulations¹

Palarp Sinhaseni

Pesticide Safe Use Unit and Department of Pharmacology
Faculty of Pharmaceutical Sciences
Chulalongkorn University, Bangkok 10330, Thailand

Malinee Limpoka

Department of Veterinary Pharmacology
Faculty of Veterinary Sciences
Kasetsart University, Bangkok 10900, Thailand

and

Ornrat Samatiwat

Pesticide Safe Use Unit and Department of Pharmacology
Faculty of Pharmaceutical Sciences
Chulalongkorn University, Bangkok 10330, Thailand

ABSTRACT

Safe and wholesome food is essential for good health. Therefore, when one considers health issues related to unsafe foods, recorded morbidity and mortality as well as economic losses in a population must be included. Due to their presence in unsafe food, micro-organisms are generally considered to pose a major risk to human health. In aquaculture, chemicals are used mainly in the treatment and prophylaxis of disease problems, which constitute the largest single cause of economic losses. However, the increasing use of chemicals in aquaculture has led to wide-spread public concern. The concerns related to human health due to chemical use in aquaculture are repeatedly found in the published literature. They include allergic reactions in previously sensitized persons triggered by chemical residues, and the potential impacts on human health resulting from the emergence of drug-resistant bacteria caused by the use of sub-therapeutic levels of antibiotics and by antibiotic residues persisting in the sediments of aquaculture environments. This paper discusses the risk evaluation principles, data requirements and the concept of maximum residue limit. The uncertainties inherent in the process include, but are not limited to, the state-of-the-art of toxicological evaluation, the level of understanding of the environmental transport process of chemicals, the exposure data available, and any assumptions and extrapolations.

¹ This paper expresses the views of the authors and does not represent those of any organization mentioned in the text.

INTRODUCTION

A major objective of risk evaluation/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 from 13-17 March, 1995 supports the use of a science-based risk assessment process (FAO/WHO 1995). 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 consumer health (Boisseau 1993).

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 these are the results of toxicological and radio-labelling 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 a veterinary drug according to good practice in the use of veterinary drugs 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 instance, 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 gm of meat (as muscle tissue), 100 gm of liver, 50 gm of kidney, 50 gm of tissue fat, 100 gm of egg and 1.5 L of milk (WHO 1990), figures that are believed to protect the vast majority of the population of the world (WHO 1989). "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 34th report of the committee" (WHO 1995b). It is recommended that governments consider whether local diets may result in intakes that exceed the ADI (WHO 1995a).

RELEVANT DATA FOR ASSESSING THE HUMAN FOOD SAFETY OF RESIDUES OF VETERINARY DRUGS

When investigating the safety of the consumption of residues of veterinary drugs in food, the Committee requires 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 animals, and in humans, when available.

- Short-term and 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, non-hormonal-effect levels, immune responses and 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 identity 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, are needed. These include:

- Residue-depletion studies with radio-labelled 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-depletion 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.

Also required are:

- 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 (WHO 1995a).

SOME ISSUES OF PUBLIC CONCERN AND THE SAFETY EVALUATION PROCESS

Issue of Risk Due to Allergic Reactions Due to Chemical Residues in Foods

Although allergic reactions caused by antibiotic residues in food are of great public concern, it is found that, in general, the incidence of allergic reaction following ingestion of antibiotic residues in food animals is very low (Adkinson 1980, Black 1984). Many drugs, such as penicillins, tetracyclines, sulfonamides and some aminoglycosides, are considered to have a high potential for sensitizing susceptible individuals. 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) (Adkinson 1980), and that dairy products that test negative by microbiological assay may contain sufficient penicillin or its metabolites to maintain urticaria (Boonk and Van Ketel 1982). According to these studies, it is indicated that very minute levels of penicillin in food can cause allergic reactions.

WHO (1990) 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 a chemical residue may trigger an allergic reaction in a previously sensitized person or may undermine the immune system.

Issue of Microbial Resistance Due to the Use of Sub-therapeutic Levels of Antibiotic

The predominant public concerns on microbial resistance due to the use of sub-therapeutic levels of antibiotics are the possible impacts on human health resulting from the emergence of drug-resistant bacteria in animals caused by the prolonged use of low-level antibiotics in animal feed (Gersema and Helling 1986, Sorum *et al.* 1992), and that antibiotic residues (i.e., residues of oxytetracycline and oxolinic acid) may persist in sediment for a long time (Pedersen *et al.* 1995). These situations actually bring humans to new medical dilemma.

Recently published studies have implied that the transmission of antibiotic-resistant pathogenic bacteria of animal origin to man may be possible, and is apparently related to the sub-therapeutic use of these drugs in animal production. Furthermore, the resistant strains in the environment may also transfer R plasmid to human intestinal flora (Levy *et al.* 1976a, b; Holmberg *et al.* 1984a, b). Therefore, such antibiotic-resistant bacteria may be direct or indirect causes of human illness, and the induction a significant loss of antibiotic efficacy in bacterial infection treatments, as, for example, in the case of the *Salmonella* outbreak in the United States in 1971-1983 (Cohen and Tauxe 1986). Nevertheless, this topic is still controversial, and there is no direct evidence by reason of the difficulties in tracing the resistant strains from animal to man and the complexity of antibiotic use in humans (Black 1984).

In assessing the microbiological risk due to residues of antimicrobial drugs in food, WHO (1990) 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 anti-microbial activity could become the determining factor of 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 for 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, and the bacteria used in the food processing industry. The risk being considered by the Committee does not include potential health effects associated with ingesting 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 (WHO 1990).

INHERENT UNCERTAINTIES IN THE SAFETY EVALUATION PROCESS

The uncertainties inherent in the risk assessment process include, but are not limited to, the state-of-the-art of toxicological evaluation, the level of understanding of the environmental transport process of chemicals, the exposure data available, and any assumptions and extrapolations. Pharmacokinetic studies also become more complicated when there is the possibility of repeated exposure due to environmental transport processes in the aquatic environment. This limited understanding of the environmental fate of chemicals will contribute to uncertainty in risk evaluation.

CONCLUSIONS

Adherence to scientific principles is the most important factor in maintaining consistency in assessments of health risk, although there are differing pharmacological and toxicological properties of chemicals used in aquaculture and widely varying amounts of information available on them.

An approach, aimed at guaranteeing the absence of chemical residues that might present a risk to consumer health, is the concept of maximum residue limits of veterinary drugs in foods, used by the Commission of the Codex Alimentarius (Boisseau 1993).

The risk evaluation/assessment process is generally accepted to provide a reliable basis for identifying and managing health risks. However, in some areas of public concern, such as the triggering of allergic reactions in previously sensitized persons by chemical residues and the issue of microbial resistance due to the use of sub-therapeutic levels of antibiotics, difficulties exist concerning the strategy and approach for risk evaluation (Black 1984).

Uncertainties exist due to a lack of knowledge of the impacts of chemical use on multiple species and the multiple routes of exposure in an ecosystem. They are also due to limited knowledge of the environmental transport of chemicals, which affects exposure of aquatic organisms to chemicals. This, in turn, affects the pharmacokinetics and metabolism of such chemicals, resulting in changing of the chemical residue profile within the organism.

The complexity of these issues, and often the lack of data as well as the lack of monitoring and surveillance systems, are the factors limiting the risk analysis process. This insufficiency of data is 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. Appropriate strategies must be chosen, according to individual country's and region's needs. Strengthening research efforts and programs for human training and development, as well as enhancing mechanisms for information exchange, may be encouraged through international collaboration.

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