Residues of antibacterial drugs in foodstuff of fish origin: risk assessment

H. POULIQUEN and H. LE BRIS

SUMMARY
A large number of antibacterial drugs, both licenced and non licenced, are available for use in fish. The purpose of this article is to outline the current state of knowledge about residues of antibacterial drugs licenced in France (oxytetracycline, oxolinic acid, flumequine, sulfadiazine and trimethoprim) in foodstuff of fish origin. The risk assessment of these residues was explained with special focus on maximum residue limits and withdrawal times. Many factors influence withdrawal times of antibacterial drugs residues in foodstuff of fish origin, thus explaining the need for expansion and rationalization of scientific informations on residues in fish.

KEY-WORDS: residues - antibacterial drugs - fish - oxytetracycline - oxolinic acid - flumequine - sulfadiazine - trimethoprim.

RÉSUMÉ
Résidus de substances antibactériennes dans la chair des poissons: estimation du risque. Par H. POULIQUEN et H. LE BRIS.

De nombreux antibactériens, commercialisés ou non sous la forme de spécialités pharmaceutiques destinées aux poissons, sont utilisés en pisciculture. L’objectif de cet article est de faire le point sur les résidus dans la chair de poissons des antibactériens commercialisés en France (oxytetracycline, acide oxolinique, fluméquine, sulfadiazine et triméthoprime). L’estimation du risque de ces résidus est expliquée en portant une attention particulière aux limites maximales de résidus et aux temps d’attente. De nombreux facteurs influencent les temps d’attente des résidus d’antibactériens dans la chair de poissons, expliquant le besoin d’accroissement et de rationalisation des informations scientifiques sur les résidus chez le poisson.

A large number of antibacterial drugs, both licenced and non licenced, are available for use in fish. These antibacterial drugs may return to humans as residues via the fish food. The purpose of this article is to outline the current state of knowledge about residues of the major antibacterial drugs in food-stuff of fish origin. It is not possible to review all the antibacterial drugs in a communication of this nature, therefore, we shall focus attention on those licenced in France: oxytetracycline, oxolinic acid, flumequine, sulfadiazine and trimethoprim.

**Definition of antibacterial drugs residues**

Residues of antibacterial drugs in fish means « all the pharmacologically active substances, whether active principles, excipients or degradation products, and their metabolites which remain in foodstuffs obtained from fish to which the antibacterial veterinary medicinal product in question has been administered » (Article 1 - 1 of the regulation 2377/90/CEE).

It is important to underline that the residues are identified and quantified in fish muscle with a naturally-occurring amount of skin.

**Toxicity of antibacterial drugs residues**

Potential antibacterial residues in foodstuff of fish origin depends on:

- intrinsic toxic properties of the residues,
- residues concentrations in fish muscle and skin in natural proportions,
- residues bioavailability and distribution in humans.

Antibacterial residues in foodstuff of fish origin may cause problems for several reasons: direct toxicity of the residues, possible involvement in allergic reactions, involvement in the development of antibacterial-resistant strains of bacteria.

**Risk assessment of antibacterial drugs residues**

For each antibacterial drug « pharmacologically active substance », a MRL (Maximum Residue Limit) is established by the CVMP (Committee for Medicinal Veterinary Products) in fish muscle with a naturally-occurring amount of skin. The MRL means « the maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg or µg/kg on a fresh weight basis) which may accepted by the Community to be legally permitted or recognized as acceptable in or on a food » (Article 1 - 1 of the regulation 2377/90/CEE). The MRL is established in order to guarantee food safety and facilities for free trade of foodstuff of fish origin.

The MRL is based on the ADI (Acceptable Daily Intake), which is an extrapolation in humans from the lowest NOEL (No Observable Effect Level) in animals.

Firstly, NOELs are established by performing toxicological assays in vitro or in vivo in animals per os. An example is given in table I.
Secondly, the ADI was established in humans by dividing the lowest NOEL by a safety factor whose value is often 100 or 1000. In our example, the ADI is 0.01 mg/kg/d (10 : 1000) or 0.6 mg/d for a man weighing 60 kg.

Thirdly, the MRL is calculated by the distribution of the ADI (expressed in mg/kg for a man weighing 60 kg) in foodstuffs by taking into account a daily standard food ration (0.300 kg fish + 1.5 kg milk + 0.100 kg eggs + 0.020 kg honey). In our example, the MRL in fish is established to 100 µg/kg fish by calculations.

The MRL of the antibacterial drugs which are licenced in fish in France are in the table II.

For each trade name containing the antibacterial drug, a WDT (WithDrawal Time), i.e. the minimum time between the last administration of the antibacterial drug in fish and the slaughter of fish, is established, based on a comparison between the MRL and the depletion kinetics of the antibacterial drug residues in fish muscle.

An example is given in figure 1 for which the WDT can be estimated between 6 and 8 days in order to guarantee that the antibacterial drug concentration in fish tissues is below the MRL.

The WDT of the trade names containing antibacterial drugs which are licenced in fish in France are in the table II.

Factors influencing WDT of antibacterial drugs residues

Some questions may be stated about the establishment of WDT in fish.

For example, it is clear that WDT is highly influenced by water temperature. Nevertheless, the relation between WDT of antibacterial drugs in fish tissues and temperature is not always linear. So, WDT must be perhaps expressed in days inside an interval of water temperatures rather than in degree days.

It is also clear that WDT is highly influenced by fish species. So the WDT is only valid for one fish species and not for another one.

WDT is also influenced by factors relating to fish (age, sex, ...) and to fish farming (food, ...).

Conclusion

On one hand, the problems of residues after « label » use of antibacterial drugs in fish is considered as solved both by a European regulation and an education of veterinarians and fish farmers about proper drug use and residues resulting therfrom. Nevertheless, the WDTs do not reflect genetic (tri-

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**TABLE I.** — Toxicological assays performed with an antibacterial drug

<table>
<thead>
<tr>
<th>Species</th>
<th>NOEL (mg/kg/d)</th>
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<tbody>
<tr>
<td>Oral toxicity 90 d</td>
<td>Rat 92</td>
</tr>
<tr>
<td></td>
<td>Dog 180</td>
</tr>
<tr>
<td>Reproduction in male</td>
<td>Dog 95</td>
</tr>
<tr>
<td>Embryofetal toxicity</td>
<td>Rabbit 10</td>
</tr>
<tr>
<td>Mutagenicity tests</td>
<td>Micronucleus -</td>
</tr>
<tr>
<td>Effects on bacteria</td>
<td>Bacteria -</td>
</tr>
</tbody>
</table>

**TABLE II.** — Maximum Residue Limits and WithDrawal Times of licenced antibacterial drugs in french fish farming.

<table>
<thead>
<tr>
<th>Antibacterial drug</th>
<th>MRL (µg/kg) in fish tissue</th>
<th>Trade name in France</th>
<th>WDT (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytetracycline</td>
<td>100</td>
<td>PS Oxytétracycline Aquaculture®</td>
<td>30</td>
</tr>
<tr>
<td>Oxolinic Acid</td>
<td>300</td>
<td>Oxomid 24% Salm.®</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inoxyl Acide Oxolinique 240®</td>
<td>6</td>
</tr>
<tr>
<td>Flumequine</td>
<td>600</td>
<td>Flumix Fluméquine 160 Salm.®</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flumiquil poudre 3%®</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluquick poudre 50%®</td>
<td>2</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>100</td>
<td>Tribriessen Poissons®</td>
<td>28</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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ploid fish, ...) as well as developmental (age, ...) and environmental differences (food, ...).

On another hand, antibacterials drugs may also be used by both veterinarians and fish farmers in « extra label » fashions. This « extra label » use is the administration of drugs to a fish species differently from the notice indicated in the product label i.e. from the conditions under which WDTs are established: increased dose, increased frequency of administration, increased total number of treatments, altered route of administration, use in different species, use in different conditions. In these cases, it is clear that the WDTs must be again calculated.

In conclusion, there is a need for expansion and rationalization of information on residues resulting from different treatment regimes and development of more precise mathematical and computer models to predict residues.

References