Veterinary drugs and food safety: a toxicological approach

A.G. RICO* and V. BURGAT-SACAZE**

Summary: To eat is to take a risk. Numerous natural toxic substances occur in foods, and such substances have not yet been examined in detail. Some are known, others not, and they may be very harmful (aflatoxins). Under these conditions, natural and synthetic compounds are not different from the toxicological aspect.

The use of veterinary drugs is no doubt beneficial, but it creates the probability of residues. Ten years ago the simple idea of zero tolerance was accepted, but the development of analytical techniques led to its rejection. Residues exist, but always in small amounts and not necessarily toxic. From the aspect of toxicity, there must be no confusion between the toxicity of residual amounts and the toxicity of the actual drug for human or veterinary use: the doses acquired by ingestion or by administration are very different.

The toxicological dimension of residues can be provided solely by scientific appreciation of their toxicity: this is their toxicological significance. Any danger has to be assessed by testing for chronic toxicity, where repetition of intake is the important factor (concept of regular ingestion). As a result of such assessment it is possible to define the tolerance which will guarantee the protection of the health of consumers. Of course, such tolerances have to be treated with caution. They merely serve to guide the correct and rational utilisation of medicaments of high quality, with adequate controls.

KEY-WORDS: Drug residues - Toxicity - Public health - Veterinary medicine.

INTRODUCTION

Human health is related directly to the environment, and in particular the nature and quality of the food. Veterinary drugs are of public health importance if they gain access to foods of animal origin in the form of residues derived from treated animals. In the opinion of many consumers "natural food = safety", and any residue, which will probably be composed of the molecules of a synthetic chemical, constitutes a major risk. Consequently the following points will be discussed:

— Are there any risks associated with "natural" foods?
— What are the residues of veterinary drugs, qualitatively and quantitatively?
— What is their toxicological significance?

RISKS ASSOCIATED WITH NATURAL FOODS

This topic has been discussed by Ames (1) in a recent review. Numerous toxic compounds may occur in foods. Thus coffee contains, among other compounds,
chlorogenic acid (formed by hydrolysis of caffeic acid), a phenolic compound having mutagenic properties, and caffeine which has proved to have teratogenic and carcinogenic properties when tested under experimental conditions. A cup of coffee contains an average of 200 mg chlorogenic acid and 100 mg caffeine. This risk associated with drinking coffee has given rise to numerous publications, one of the more recent of which is that of Snowdon et al. (10).

Among the compounds present in potatoes are two alkaloids (solanine and chaconine) which are powerful cholinesterase inhibitors and may be teratogenic. Their concentration is about 15 mg per 200 g of tuber. Black pepper contains small amounts of safrole (a substance known to be carcinogenic for laboratory rodents) and almost 10% piperine, a compound similar to safrole. Extracts of black pepper can induce tumours in various organs of mice in doses about 10 times higher than those consumed daily by numerous human beings.

Turning to possible contamination, numerous moulds are capable of growing on foods (peanuts, bread, cheese, fruit), and some of the moulds are capable of synthetising very harmful mycotoxins, such as the aflatoxins and sterigmatocystin, powerful carcinogens.

Concerning the method of preparing food, it is known that types of cooking (barbecue), smoking and salting may give rise to products extremely mutagenic and carcinogenic (pyrolysates of amino acids, caramels, nitrates and nitrites).

Finally, certain feeding habits may present risks. It is now known that there is a direct relationship between cancer of the colon and a diet poor in vegetable fibre but rich in meat, and between breast cancer in women and the content of animal fat in the diet (6). The above information is summarised in Table I.

| TABLE I |
| Dietary risks (Ames N.B., 1983) |

<table>
<thead>
<tr>
<th>FOODS</th>
<th>coffee (chlorogenic acid, caffeine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>potatoes (solane, chaconine)</td>
</tr>
<tr>
<td></td>
<td>black pepper (piperine)</td>
</tr>
<tr>
<td>MOULD CONTAMINATIONS</td>
<td>nuts, peanuts butter, bread, cheese, fruit, apple juice (aflatoxins, sterigmatocystin)</td>
</tr>
<tr>
<td>PREPARATION OF FOOD</td>
<td>pyrolysates A.A., caramelisation</td>
</tr>
<tr>
<td>(cooking, smoking, salting...)</td>
<td>(nitrites, nitrates)</td>
</tr>
<tr>
<td>DIETARY CUSTOMS</td>
<td>animal fats, meat, low vegetable diet, lack of fiber</td>
</tr>
</tbody>
</table>

In summary, it seems that:

— The notion that “nature cannot be harmful” is not sustainable.

— From the general toxicological aspect, it is nonsense to claim that naturally occurring xenobiotics are safer than those of synthetic origin.

— It is clear that “to eat is to take a risk”, and the problem which remains is whether veterinary medicaments can increase this risk.
SIGNIFICANCE OF RESIDUES OF VETERINARY DRUGS

After administration of a drug to an animal, most drugs are metabolised in order to facilitate elimination, and to a large extent detoxification as well. In general, most of the parent product and its metabolites are excreted in urine and faeces. However, these substances may also be found in milk and eggs, and also (after slaughter) in the meat and offal. Note that the drug is given to an animal in a therapeutic dose, which is a priori not toxic, or of very low toxicity. In consequence any residual amount must be small in the vast majority of cases.

Taking the above information into account, it can be concluded that:

— Residues are composed of the parent compound and its metabolites, the latter being less toxic than the parent compound in most cases.
— The concentration of such residues is low or very low, and the following units are used to express these concentrations:
  . ppm (parts per million) = 1 mg/kg
  . ppb (parts per billion) = 1 µg/kg,
  . ppt (parts per trillion) = 1 ng/kg

When it is stated that a substance contains 0.1 ppb of residue X, this means that 1 kg contains 0.1 µg of X, while 100 ppt is equivalent to 100 ng/kg

These data may seem to be too abstract for the layman, and too difficult to comprehend their significance, so here are some more concrete alternatives.

Parts per million expressed in units of time is equivalent to one minute in a million minutes = 2 years.

Parts per billion expressed in volume is one drop in 50 m³ or 50,000 litres.

Parts per trillion expressed in surface area is equivalent to a coin of 0.50 F (or 1 penny) lost in the city of Paris. This symbolism is shown in Figure 1.

These examples serve to place residual amounts in the context of their content in the products of treated animals.

One idea which has been advanced and defended frequently, and which at first sight seems to be wise and satisfactory, is that no product coming from a treated animal should be consumed unless all of the drug administered has been eliminated completely. This is called zero tolerance.

The concept of zero tolerance is in fact equivalent to the idea of total absence of residual amounts. This idea remained in force for about 15 years, after which it had to be abandoned because of the refinement of analytical techniques, which meant that the value for zero became smaller and smaller. This is demonstrated in the falling curve of Figure 2, which depicts the limits corresponding to sensitivities of ppm, ppb and ppt.

Taking into account the high efficacy of the analytical methods now available, it can be concluded that there are nearly always detectable residues, but that such residues are at an extremely low concentration and they are not inevitably toxic.

Bearing in mind this last comment, there is a need to analyse the risks that such residues pose for the consumer, and to place such small amounts in toxicological perspectives, taking into account the scientific appreciation of their toxic potential.
Symbiotic presentation of drug residues in food products

<table>
<thead>
<tr>
<th>ppt</th>
<th>a coin</th>
<th>lost in Paris</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppb</td>
<td>a drop</td>
<td>in 50 m³</td>
</tr>
<tr>
<td>ppm</td>
<td>1 minute</td>
<td>in 2 years</td>
</tr>
</tbody>
</table>

**Fig. 1**
0-tolerance = No residues, acceptable 15 years ago. 0 has become lower and lower.

Residues always exist, but they:
— have very low concentrations
— are not compulsorily toxic.

TOXICOLOGICAL SIGNIFICANCE OF RESIDUES

The first question to be answered is: What risks are attached to the ingestion of residues?

Given that residual amounts of drugs are present in foods of animal origin in very low concentrations, it is evident that there is no risk of acute toxicity. No one has ever been poisoned, or ever will be poisoned, by consuming one or more times during a lifetime, in a non-repetitive manner, a food containing residues.

On the other hand, it could be envisaged that regular ingestion of small amounts of the same substance may in the long term have a cumulative effect, leading to toxic manifestations: insidious and diverse organic disorders, allergy (2) and, at the extreme, cancer.

This is the sole possible danger of residues. It has led scientists engaged in this problem to divide veterinary drugs into two major groups:
— Those used to a limited extent for treating individual animals or only a small number of animals at any one time. They are called occasional drugs, and present practically no risk to the consumer.
— Those administered to large groups of animals, on a regular basis, in the course of therapy, prophylaxis or intensive husbandry: anabolics (8), antiparasitic agents, antibiotics, etc. Such mass medicaments must be controlled strictly, and closely supervised in distribution and application, for they can raise public health problems.

An important point to make when referring to the toxicity of residual amounts of veterinary drugs is that a clear distinction must be made between the relative danger of a drug used in considerable dosage in human medicine and residual amounts of the same substance present in low concentration in a food. A striking
example is that of diethylstilbestrol (DES), once used legally, but now used solely fraudulently in numerous countries as an anabolic. DES has been found to be carcinogenic in human beings, inducing vaginal cancer in the daughters of women treated during pregnancy.

However, when a comparison is made between the doses used in this type of accident with the amounts present in the meat of treated animals, the following is found.

An epidemiological survey in the USA cited by Pitot (7) showed that vaginal cancer occurred in 0.2% of the daughters of treated women. The total dosage used ranged from 0.5 to 300 mg/kg, which is enormous. If the smallest dose rate of 0.5 mg/kg is taken, calculations based on the residual amounts found in implanted animals show that a woman would have to eat 750 g of calf liver once daily for 100 years to reach this dose rate.

Such a finding is at least reassuring, but the toxicological profile of DES must not be disregarded. It is active by the oral route, not undergoing metabolism, and is potentially carcinogenic, so that prohibition of DES is a good thing to the extent that the prohibition can be effectively enforced.

In general, it can be claimed that there are potential risks for the consumer who eats foods of animal origin coming from animals which have been treated with veterinary drugs. The problem now is to assess this risk or, in other words, to place these residues in their toxicological context.

From the general point of view, various types of toxicity tests on laboratory animals (rats, mice, dogs, hamsters, etc.), and particularly the regular ingestion of the product in question over a long period, can lead to a definition of the acceptable daily intake (ADI) for man. This dose is expressed in mg/kg of body weight, and is calculated as follows:

The dose which has no toxic effect on the most sensitive species of animal is divided by a safety factor, which varies from 100 to 1,000, depending on the nature of the effects observed. This safety factor particularly takes into account the possibility that human beings may be more sensitive than the animal species under test. This concept is important for calculating and understanding the notion of tolerance which will now be discussed. There are three types of tolerance, toxicological, practical and analytical.

**Toxicological tolerance:** this is calculated from the acceptable daily intake. By multiplying this figure by mean body weight of a human being (70 kg), one obtains the daily amount which a person can ingest without harm. Division of this figure by the amount of food consumed daily, for example 500 g of meat, provides the maximum concentration which can be tolerated in that food. Below this concentration (or toxicological tolerance), the health of the consumer is no longer at risk.

**Practical tolerance:** it is often found that when a veterinary drug is used under the correct conditions (of dosage, route of administration, adequate withdrawal period) the residual amount is less than the calculated toxicological tolerance. This practical tolerance is retained in legislation, because it indicates that the product has been used correctly. This mode of operation introduces an additional safety factor.

**Analytical tolerance:** there has to be a way of checking the practical tolerance, and this is done by an analytical method having a limit of sensitivity lower than the practical tolerance which has to be measured.

Table II illustrates these theoretical findings.
If medicament X has a no-effect dosage for mice of 1 mg/kg, a safety coefficient of 100 would give an ADI for man of 0.01 mg/kg. This means that the toxicological tolerance for daily consumption of a "contaminated" food would be 1.4 mg/kg, or 1.4 ppm. Under normal conditions of use, the residual concentrations never exceed 0.5 ppm, so 0.5 ppm becomes the practical tolerance for regulatory purposes. The analytical method required to check such concentrations, such as thin-layer chromatography, must have an analytical sensitivity (or analytical tolerance) of 0.1 ppm.

We now have all the toxicological data required to guarantee the protection of the health of the consumer.

The analysis given above is very similar to the terminology applied by the *Codex alimentarius* in the case of pesticides (4).

In any toxicological evaluation, it is obvious that the chemical nature of the residues is also important. Seen from this point of view, a food product derived from a treated animal may contain the unchanged parent drug, and various free or conjugated metabolites, mostly structurally similar to the parent molecule, as well as in forms having covalent bonds with macromolecules. We have noted elsewhere (3, 9) that residues attached by covalent bonds are certainly practically non-toxic for the consumer. Various theoretical and practical arguments support such an absence of toxicity, which is partly because of a generally poor biological availability. Such availability is an important factor to be considered when assessing the toxicology of residues (4).

To conclude this section we can state that although the presence of drug residues in foods theoretically poses a risk for the health of the consumer, this risk should not be exaggerated. Various factors operate in favour of a very limited danger.

Passage of a drug through an animal provides a major element of protection, since the biological transformation which the drug undergoes in the animal amounts to detoxification. The animal acts as a beneficial filter for man.
It has been amply demonstrated that the biological availability of residues is often limited or very weak, even when biotransformation (which augments their polarity) is taken into account.

The residual concentrations are invariably low, and often they can be detected solely by developments in analytical procedures which have taken place during the past 15 years.

Finally, any residues ingested in such small amounts and not readily available are certainly subjected to the detoxifying action of the human metabolism.

All these elements confirm our opinion on the question of residues, that their existence should not be systematically linked to danger. The actual risk can be estimated only by a serious toxicological appraisal.

We have the means for evaluating this risk by defining the tolerances indispensable for guaranteeing the protection of the health of consumers. It is, of course, essential to ensure that such tolerances are correctly established and observed, and a certain number of conditions have to be fulfilled, as follows:

— The drugs used must be of high quality. This means that they have to be made correctly, and must pass the necessary tests for ensuring efficacy and safety. The requirements are in any case stipulated before they can be licensed for sale.

— The drugs must be administered under the normal conditions of use (dosage, administration route, withdrawal period, correct therapeutic indication). Veterinarians and farmers are responsible for ensuring that this is done.

— The need for effective supervision should be obvious. The government should fulfil its obligations in this sphere.

— An absolutely vital requirement is that consumers be fully and honestly informed, or one could say educated, for any danger which is poorly understood and poorly explained can give rise to irrational fear. Only this can avert conflict, passion and irrational opposition to science. Such an educational programme is under way in the USA, and it is surprising that it has not yet been developed in the same way in Europe.

However, it must always be borne in mind that it is necessary to risk one's life in order to live, and by way of conclusion an appropriate phrase is that of Judge Warren Burger at the US Supreme Court: "Perfect safety is a chimera, regulation must not strangle human activity in a search for the impossible".

* * *

REFERENCES


