

## PRACTICAL APPLICATION OF ANTIBACTERIAL DRUGS FOR THE CONTROL OF HONEY BEE DISEASES

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### Summary

The beekeeper must recognize that EU laws on residues in animal-origin food now in effect apply to honey as well as all other foods. The large purchasers of honey are requesting suppliers to certify that the honey offered for sale is pure and free of contaminants. Honey, like any food product offered for sale, can be condemned if it contains even traces of antibiotic for which no legal tolerance has been established. One publicized condemned shipment could do great harm to the entire honey market. This situation need not cause a panic in the beekeeping industry, but it does require caution and good judgement in how chemicals and medicaments are used. Many beekeepers think the food-contamination problem centres on the use of sulphonamides and antibiotics for the control of bee diseases. These are important, but they have to consider together with residues derived from *Varroa* mites control as well as from beekeeping operations and environmental pollution. Most of the materials in question are needed for profitable beekeeping management. Experience has shown that they can be used safely for the purpose intended provided they are employed at the right time, by the right method, and at the correct dosage. However, meeting the legal requirements with respect to residues is a matter of special importance. A summary of the main protocols for sulfathiazole and antibiotics application to the beehive as well as precautionary recommendations are presented here as a guide in the use of the principal chemicals and medicaments employed in beekeeping practices.

### American foulbrood

In most countries official apiary inspectors are required to burn all colonies infected with American foulbrood. The state laws are designed for the protection of the beekeeping industry. Beekeepers employing therapeutic medicaments should encourage full enforcement of their state inspection and disease-control laws. The presence of disease in any apiary is a menace to other beekeepers and an indication that the owner is not using proper control measures.

Homogeneous and populated colonies inspected on a regular basis, combs replacement approximately 2/year, early diagnosis, elimination of affected colonies, elimination of affected combs, sanitization of the hive (when appropriate) and tools are recommended for a correct management of the apiaries.

Antibiotics such as oxytetracycline HCl, streptomycin and tylosin are currently used for the prevention and control of American foulbrood (Table I), even if these substances have a transient effectiveness and are totally ineffective against the spores of *Paenibacillus larvae* sp. *larvae*.

### European foulbrood (EFB)

There is evidence that it was far more prevalent during the past decades than beekeepers realized. For many years it attracted little attention because diseased larvae were seldom seen. We now know that considerable brood was lost, but it was cleaned out by the bees before the symptoms of European foulbrood could be recognized. Colonies with low-quality brood that is not due to poor queens, pollen deficiency, or similar factors respond to medicaments that are effective against the virulent form of European foulbrood (Table II).

Routine prophylactic with the antibiotic oxytetracycline (Terramycin) is effective for preventing of EFB, but even if effective, the treatment is really not necessary. Furthermore its use can cause residues in honey.

### Nosema Disease

This disease of adult bees probably takes a greater toll of the productive capacity of honeybees than do the brood diseases. Nosema is so wide-spread we must presume that every colony has some infected bees. The infection level may range from less than 1 to 100 percent. Nosema shortens the life of bees by about one-half. The most important means of control is good colony management, which provides conditions that are favourable for brood rearing to add young bees to the colony faster than the infection spreads within the population. Losses from Nosema are most conspicuous in colonies started with package bees, in nuclei, and other weak colonies. The antibiotic fumagillin is effective in preventing Nosema from spreading within a population and in reducing queen turnover due to the infection of the queen (Table III).

The treatment with Fumagillin is effective and it is needed at least in some areas. Also residues does not seem a problems to honeybee products. Unfortunately, fumagillin is no longer available on the EU market since January 1<sup>st</sup>, 2000. In fact, no MRL has been established.

Table I

**Protocols for the application of antibiotics against American foulbrood**

Disease/causative agent	Active principle/commercial name	Authorization for apiculture	Time of treatment	Method of treatment	Withdrawal time	References
American foulbrood ( <i>Paenibacillus larvae larvae</i> )	Oxytetracycline HCl (Terramycin-25, TM-25, TSP=Terramycin Soluble Powder)	Yes (USA) No (EU)	early spring	200 mg in powdered sugar	at least 4 wks before the main honey flow	J Invert Pathol 67, 65-71, 1996
	Oxytetracycline HCl (Terramycin-25)	Yes (USA) No (EU)	early spring	mix 1 lb. (454 g) TM-25 to 8 lbs. Powdered sugar apply 8 tablespoons up to 3 times at 4-5 days intervals administration as dust (top bars)	at least 4 wks before the main honey flow	<a href="http://ag.udel.edu/extension/information/beekeeping">http://ag.udel.edu/extension/information/beekeeping</a> <a href="http://www.ncf.arleton.ca/Apiculture/AFB.htm">http://www.ncf.arleton.ca/Apiculture/AFB.htm</a>
	Oxytetracycline HCl (Terramycin-10)	Yes (USA) No (EU)	early spring	mix 1 lb. TM-10 to 2 lbs. Powdered sugar apply 28 g up to 3 times at 4-5 days intervals	at least 4 wks before the main honey flow	<a href="http://ag.udel.edu/extension/information/beekeeping">http://ag.udel.edu/extension/information/beekeeping</a> <a href="http://edis.ifas.ufl.edu">http://edis.ifas.ufl.edu</a>
	Oxytetracycline HCl (TAFSP)	Yes (USA) No (EU)	early spring	mix 1 teaspoon of TAFSP-terramycin animal formula soluble powder in a 5 lbs pail of 1:1 sugar syrup Feed 2 quarts up to 3 times at 4-5 days intervals	at least 4 wks before the main honey flow	<a href="http://ag.udel.edu/extension/information/beekeeping">http://ag.udel.edu/extension/information/beekeeping</a> <a href="http://edis.ifas.ufl.edu">http://edis.ifas.ufl.edu</a>
	Oxytetracycline HCl (TAFSP)	Yes (USA) No (EU)	early spring	mix 1 teaspoon of TAFSP-terramycin animal formula soluble powder to 1 oz. powdered sugar Feed 4 tablespoons up to 3 times at 4-5 days intervals	at least 4 wks before the main honey flow	<a href="http://ag.udel.edu/extension/information/beekeeping">http://ag.udel.edu/extension/information/beekeeping</a> <a href="http://edis.ifas.ufl.edu">http://edis.ifas.ufl.edu</a>
	Oxytetracycline HCl (TM, Oxytet-25-s)	Yes (USA) No (EU)	spring/fall	mix 1 part of TM to 5 parts of powdered sugar Feed tablespoon up to 3 times at 5-10 days intervals	at least 4 wks before the main honey flow	<a href="http://www.honeycouncil.ca/distable.html">http://www.honeycouncil.ca/distable.html</a>
	Oxytetracycline HCl (TM-25)	Yes (USA) No (EU)	early spring	OTC doses: 200 mg to 1240 mg/patty; 700 to 1000 mg/patty OTC concentration: 1 mg/g to 5.9 mg/kg	at least 4 wks before the main honey flow	Apidologie 31, 517-524, 2000 <a href="http://www.ncf.carleton.ca/Apiculture/AFB.htm">http://www.ncf.carleton.ca/Apiculture/AFB.htm</a>
	Streptomycin sulfate or dihydrostreptomycin sulfate	No (EU, USA)		Administration as a liquid at a concentration of 0.6 g (600 mg) per gallon (3.8 l) of 2:1 syrup (2 oz./100 gals) 3 applications during a period of 2 weeks by the gorging method	at least 4 wks before the main honey flow	<a href="http://www.beesource.com/pov/usda/abjmay1960.htm">http://www.beesource.com/pov/usda/abjmay1960.htm</a>
	Tylosin	No (EU, USA)	spring/fall	mix 100-200 mg in powdered sugar (up to 800 mg/7 g sugar) No side effects observed dust once, protection for 3 wks (100 mg), 4 wks (200 mg)	at least 4 wks before the main honey flow	J Invert Pathol 67, 65-71, 1996

Table II

**Protocols for the application of antibiotics and sulfathiazole against European foulbrood**

Disease/causative agent	Active principle/commercial name	Authorization for apiculture	Time of treatment	Method of treatment	Withdrawal time	References
European foulbrood ( <i>Melissococcus pluton</i> )	Oxytetracycline HCl (Terramycin-25)	Yes (USA) No (EU)	early spring	administration as a dust. Mix 1 lb. of TM-25 to 8 lbs. powdered sugar. Feed 4 tablespoons up to 3 times at 4-5 days intervals.	at least 4 wks before the main honey flow	<a href="http://ag.udel.edu/extension/information/beekeeping">http://ag.udel.edu/extension/information/beekeeping</a>
	Oxytetracycline HCl (TAFSP)	Yes (USA) No (EU)	early spring	administration as a dust. Mix 1 level teaspoon of TAFSP-terramycin animal formula soluble powder to 1 ounce of powdered sugar. Dust 4 tablespoons up to 3 times at 4-5 days intervals.	at least 4 wks before the main honey flow	<a href="http://ag.udel.edu/extension/information/beekeeping">http://ag.udel.edu/extension/information/beekeeping</a>
	Oxytetracycline HCl (TAFSP)	Yes (USA) No (EU)	early spring	administration as a liquid. Mix 1 teaspoon of TAFSP-terramycin animal formula soluble powder in a 5 lb pail of 1:1 sugar syrup Feed 2 quarts up to 3 times at 4-5 days intervals.	at least 4 wks before the main honey flow	<a href="http://ag.udel.edu/extension/information/beekeeping">http://ag.udel.edu/extension/information/beekeeping</a>
	Oxytetracycline HCl (TM, Oxytet-25-s)	Yes (USA) No (EU)	early spring	administration as a dust. Mix 1 part of TM to 5 parts of powdered sugar Feed 1 tablespoon up to 3 times at 5-10 days intervals.	at least 4 wks before the main honey flow	<a href="http://www.honeycouncil.ca/distable.html">http://www.honeycouncil.ca/distable.html</a>
	Oxytetracycline HCl (OTC)	Yes (USA) No (EU)	early spring	administration as a liquid. A single 1 g dose of OTC suspended in a small volume of sugar syrup sprinkle to the area immediately around the brood nest.	at least 4 wks before the main honey flow veterinary prescription, bee inspector application	<a href="http://www.csl.gov.uk/environment/level3/nbu.htm">http://www.csl.gov.uk/environment/level3/nbu.htm</a>
	Sodium sulfathiazole	Yes (USA) No (EU)	spring	administration as a liquid.	1 g of sodium sulfathiazole per gallon of 2:1 sugar syrup (1 oz. sulfa/30 gals. syrup) applying three gorging treatments at 4- to 5-day intervals. Incorporate the same medicated syrup in preparing any pollen supplement	<a href="http://www.beesource.com/pov/usda/abjmay1960.htm">http://www.beesource.com/pov/usda/abjmay1960.htm</a>

Table III

Protocol for the application of fumagillin against *Nosema apis*

Disease/causative agent	Active principle/commercial name	Authorization for apiculture	Time of treatment	Method of treatment	Withdrawal time	References
Nosemosis ( <i>Nosema apis</i> )	fumagillin	Yes (USA) No (EU)	early spring	mix 100 mg (and 1 teaspoon) of fumagillin to 1 gallon of sugar syrup (mix 2 parts sugar to 1 part water). Feed 2-3 gallon in the fall at least 1 gallon to newly installed spring packages	nd	<a href="http://ag.udel.edu/extension/information/beekeeping">http://ag.udel.edu/extension/information/beekeeping</a> <a href="http://www.honeycouncil.ca/distable.html">http://www.honeycouncil.ca/distable.html</a> ; <a href="http://edis.ifas.ufl.edu">http://edis.ifas.ufl.edu</a>

nd = not defined

## Mechanisms of action of antibacterial substances

### Antibiotics

#### *Oxytetracycline:*

- tetracyclines
- bacteriostatic
- protein synthesis inhibition by interference with aminoacyl-tRNA link and sub-unit 30S

#### *Streptomycin:*

- aminoglycosides
- bactericid
- interference with sub-unit 30S and membrane permeabilization

#### *Tylosin:*

- macrolides
- bacteriostatic
- protein synthesis inhibition by stable link with sub-unit 50S

#### *Fumagillin:*

- aminopeptidase inhibitor, type II
- bacteriostatic
- inhibition of RNA synthesis

#### *Sulphonamides:*

- sulfatiazole
- bacteriostatic
- inhibition of folate synthesis by competition with PABA (synthesis of folic acid, nucleic acid)

## Conclusions

Risks related to the use of antibiotics for the control of honeybee diseases are persistence of the infection, reappearance of the disease and honey contamination (Directive 96/23/CE and further amendments).

The following advices to beekeepers can thus be proposed:

- Do not use drugs or antibiotics!
- Use drugs or antibiotics only when necessary!
- Drugs should never be considered a substitute for good beekeeping;
- All drugs are toxic if used in excessive quantities;
- Do not administer any drugs or antibiotics during honey flow or into honey supers.

Furthermore, no authorized medicinal products for the treatment of bacterial and protozoan honeybee diseases are currently on the market within EU. In fact, in the European consultation conference on the availability of veterinary medicinal products "Practical and safe use of veterinary medicines" held in June 1999, it was realized that tetracyclines and sulphonamides are used in the treatment of foulbrood. However, although MRLs have been established for all-food producing species for these two classes of compounds, there are no MRLs for honey. Furthermore, there is no formulation, which is really adapted to the treatment of bees.