

## Residue avoidance after topical application of veterinary drugs and parasiticides

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The use of topical veterinary drugs is of concern to veterinarians because of their over-the-counter availability to laypersons. Extralabel use of topical drugs has the potential to cause violative residues. Parasiticides are the most frequently used topical veterinary products (prescription or over-the-counter). Other classes of topical drugs (eg, antibiotics and antiseptics) do not depend on dermal absorption to achieve therapeutic efficacy and are, therefore, unlikely to cause food animal residues. During the past 15 years, the Food Animal Residue Avoidance Databank (FARAD) has compiled a comprehensive database<sup>1,2</sup> of information derived from published animal studies (Appendix). Some of these data provide the only means to assess whether dermal absorption of drugs and pesticides will result in violative residues. It must be stressed that the Animal Medicinal Drug Use Clarification Act (AMDUCA) only allows extralabel use of approved drugs.

### Organophosphates

Few organophosphates are approved for topical application in lactating dairy cattle. The prudent practitioner would administer drugs orally or select a different class of pesticides for topical use. Topical administration of these moderately lipophilic pesticides may result in depot formation in the skin at the site of application as well as prolonged residue depletion profiles. Although the pesticides are not registered for use in lactating cattle, FARAD has fielded calls pertaining to extralabel use in lactating animals. The FARAD has, therefore, relied on a limited database from which to derive adequate withdrawal intervals for such products.

Fenthion pour-on products, such as Spotton (20% fenthion) and Triguvon (3% fenthion), are FDA approved for use in beef and nonlactating dairy cattle. Approved meat withdrawal times are 35 days after 1 treatment and 45 days after 2 treatments with the 3% formulation. Treatment with the 20% formulation also requires a 45-day meat withdrawal time. To avoid residues in milk, dairy cattle should not be treated with the 3% formulation within 28 days of initiation of lactation. Although < 2% of the absorbed drug may be eliminated in milk, limited data suggest that topical application of fenthion to lactating cattle can result in substantial residues in milk within 24 hours. The FARAD discourages use of organophosphates

in lactating ruminants. However, if a fenthion product has been used in a lactating animal, milk should be withheld for a minimum of 10 days.

Famphur pour-on products, such as Warbex, are FDA approved for use in nonlactating dairy cattle and beef cattle to treat cattle grubs. The approved meat withdrawal time is 35 days, and again, milk withdrawal times have not been established by the FDA. Limited data suggest that for topical doses < 23 mg/kg (10 mg/lb) of body weight, residue levels in milk are < 0.03 ppm at 7 days and 0 ppm at 21 days. If a famphur product has been used in a lactating animal, milk should be withheld for a minimum of 10 days.

Coumaphos products, such as CORAL, are EPA registered for use as contact and pour-on insecticides in nonlactating cattle. The meat withdrawal time is 10 days, and nonlactating dairy cattle should not be treated < 14 days before lactation begins. Data from several studies suggest that < 6% of the applied dose of coumaphos pour-on or spray formulations is absorbed; residues may be detected in milk up to 14 days after treatment. In almost all literature and case reports, coumaphos concentrations were generally less than the milk and tissue tolerance levels within 7 to 14 days, despite the many dosage forms and formulations used to treat dairy cattle. If a coumaphos product has been used in a lactating animal, milk should be withheld for a minimum of 10 days.

Chlorpyrifos is EPA registered for use in ear tags for cattle and to treat screw worms (eg, Screw Worm & Ear Tick Spray) in cattle, swine, sheep, and goats. Ear tags are slow release devices with chlorpyrifos impregnated in the plastic (polyvinyl chloride) and should be of minimum residue concern. Meat and milk withdrawal times are 0 days for this pesticide. Data from several studies demonstrated that topical application may result in more residues in fat than in meat, although tissue residues were generally less than the tolerance level of 2 ppm for the entire experimental period.

### Organochlorines

Methoxychlor products, such as Purina Cattle Dust, are EPA registered for use in dairy and beef cattle. Meat and milk withdrawal times are 0 days. Most of the data in the literature indicate small or negligible residue levels in milk or body fat after topical exposure following various dosage regimens and formulations. Although several methoxychlor formulations contained mixtures of butoxy polypropylene glycol, diethyl-m-toluamide (DEET), pyrethrins, and/or piperonyl butoxide, milk residues again remained less than the tolerance levels.

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References for determinations are available on written request.

Lindane products, such as Screw Worm Aerosol-L, are EPA registered for use in beef cattle, sheep, swine, goats, and horses, and the meat withdrawal time is 0 days for these species. Lindane is not registered for use in dairy cattle, dairy barns, or milk rooms. Milk withdrawal times have not been established. Dermal absorption is slow and to a limited extent because of slow release from the stratum corneum. Lindane residue concentrations were considerably less than the tolerance levels in adipose tissue 30 days after pigs were sprayed with amounts ranging from the normal recommended dose (0.35 g/pig) to 16 times the normal dose (5.6 g/pig). For goats and sheep dipped with 0.025% lindane solution, higher residues were found in sheep fat than in goat fat, but 2 weeks after dipping, residue concentrations were less than the tolerance levels. Because residues can be detected in meat and fat, there should be concern about milk residues if this product is administered topically to lactating dairy cattle.

### Pyrethrins

Data from the literature suggest that pyrethrins and, to some extent, pyrethroids (synthetic pyrethrins) are least likely to be absorbed through the skin of most domestic animals. For this reason, many of the most commonly used pyrethroids, such as permethrin, are EPA registered for use in most food animal species including lactating cattle and are, therefore, least likely to be a residue concern.

Permethrin products, such as Ectiban EC, are EPA registered for use in lactating and beef cattle as well as small ruminants and swine. The meat withdrawal time is 5 days in swine and 0 days in approved species.

### Antimicrobials and Other Topical Drugs

There are limited data regarding dermal absorption of topical antibiotics in domestic animals; however, their action is local, because absorption into the bloodstream is not required for efficacy. Systemic exposure is minimal, making residue problems unlikely. Many of the topical antibiotics used in veterinary medicine contain mixtures of 2 or more antibiotics or active ingredients. Nitrofurazone is approved for topical use, but not parenteral administration, in food animals. Provided there is no oral ingestion of nitrofurazones and tetracyclines, a meat or milk withdrawal interval of 0 days is adequate for topical exposure. Copper sulfate, which often is used as a footbath to treat hairy warts in cattle, has a meat or milk withdrawal interval of 0 days.

Kopertox (copper naphthenate), which is used to treat foot rot and ringworm, usually will not require a milk withdrawal interval as long as it is used topically and the chemical is not applied to the teats of lactating animals.

Formaldehyde has been used to treat hairy warts, and dermal absorption is unlikely to cause residues; thus, FARAD has recommended that a withdrawal interval is unnecessary. The FARAD does caution practitioners about use of formaldehyde, because it is considered a probable human carcinogen.

Dimethyl sulfoxide (DMSO) is rapidly absorbed

through intact skin and may substantially alter absorption characteristics of other simultaneously applied compounds. This topically applied drug is not approved in any food animal species. Under AMDUCA, licensed veterinarians may use approved DMSO products in food animals as long as all requirements for extralabel use in food animals are fulfilled. Again, it should be noted that AMDUCA does not apply to unapproved drug products or other sources of medicinal ingredients (eg, technical grade DMSO, products whose impurities may also be absorbed). If DMSO is used in food animals, FARAD recommends extended withdrawal intervals of 96 hours for milk and 4 days for meat.

### Summary

Deriving adequate withdrawal intervals for extralabel use of veterinary topical products is difficult because there are limited published data, and data for approved drugs and pesticides are usually proprietary. Where possible, approved products and doses labeled for the specific indication at hand should be used and label withdrawal times should be adhered to. When determining whether topical application of these chemicals may violate tolerance levels in meat and milk, the veterinarian often is limited to empirical data. In the decision-making process, factors, such as type of drug and pesticide formulations used, method of topical application, presence of hair or wool, environmental conditions, and animal species treated, should be considered. In many cases, a conservative estimate for the slaughter withdrawal interval can be derived, despite the data gaps. Such recommendations should not be used for routine extralabel use, but are meant to apply to situations in which the drug or pesticide has been used, and human food safety concerns must be addressed.

### Appendix

Withdrawal times (days) for several topical insecticides

| Active ingredient  | Product name                | Tissue                  | Milk               |
|--------------------|-----------------------------|-------------------------|--------------------|
| Fenthion           | Spoton                      | 35-45                   | 10*                |
| Famphur            | Warbex                      | 35                      | 10*                |
| Phosmet            | Prolate                     | 1                       | 0                  |
| Chlorpyrifos       | Screw Worm & Ear Tick Spray | 0                       | 0                  |
| Trichlorfon        | Neguvon                     | 21                      | 7-10               |
| Coumaphos          | CORAL                       | 10                      | 10*                |
| Lindane            | Screw Worm Aerosol-L        | 0                       | Data not available |
| Methoxychlor       | Purina Cattle Dust          | 0                       | 0                  |
| Permethrin         | Ectiban EC                  | 0 (cattle)<br>5 (swine) | 0                  |
| Nitrofurazone      | Furacin                     | 0                       | 0                  |
| Tetracyclines      |                             | 0                       | 0                  |
| Copper sulfate     | Proudoff                    | 0                       | 0                  |
| Copper naphthenate | Kopertox                    | 0                       | 0                  |
| Formaldehyde       |                             | 0                       | 0                  |

\*FARAD suggested withdrawal intervals.

### References

1. Sundlof SF, Riviere JE, Craigmill AL. *Handbook of comparative veterinary pharmacokinetics and residues of pesticides and environmental contaminants*. Boca Raton, Fla: CRC Press Inc, 1996.
2. Crosier KK, Riviere JE, Craigmill AL. *A comprehensive compendium of food animal drugs*. Gainesville, Fla: University of Florida Cooperative Extension Service, 1996.