

February 28, 2002

Edited for *Typographical Errors*, March 1, 2002

## **Food and Drug Administration/Center for Veterinary Medicine Report on the risk from pentobarbital in dog food**

The low levels of exposure to sodium pentobarbital (pentobarbital) that dogs might receive through food is unlikely to cause them any adverse health effects, Food and Drug Administration scientists concluded after conducting a risk assessment.

During the 1990s, FDA's Center for Veterinary Medicine (CVM) received reports from veterinarians that pentobarbital, an anesthetizing agent used for dogs and other animals, seemed to be losing its effectiveness in dogs. Based on these reports, CVM officials decided to investigate a plausible theory that the dogs were exposed to pentobarbital through dog food, and that this exposure was making them less responsive to pentobarbital when it was used as a drug.

The investigation consisted of two parts. First, CVM had to determine if dog food could contain residues of the drug. Second, if residues were found, the Center had to determine what risk, if any, the residues posed to dogs.

In conjunction with this investigation, the Center wanted to determine if pet food contained rendered remains of dogs and cats.

### **How pentobarbital can get into dog food**

Because in addition to producing anesthesia, pentobarbital is routinely used to euthanize animals, the most likely way it could get into dog food would be in rendered animal products.

Rendered products come from a process that converts animal tissues to feed ingredients. Pentobarbital seems to be able to survive the rendering process. If animals are euthanized with pentobarbital and subsequently rendered, pentobarbital could be present in the rendered feed ingredients.

In order to determine if pentobarbital residues were present in animal feeds, CVM developed a sophisticated process to detect and quantify minute levels – down to 2 parts per billion of pentobarbital in dry dog food. To confirm that the methods they developed worked properly, CVM scientists used the methods to analyze dry commercial dog foods purchased from retail outlets near to their Laurel, MD, laboratories. The scientists purchased dog food as part of two surveys, one in 1998 and the second in 2000. They found some samples contained pentobarbital (see the attached tables).

### **Dogs, cats not found in dog food**

Because pentobarbital is used to euthanize dogs and cats at animal shelters, finding pentobarbital in rendered feed ingredients could suggest that the pets were rendered and used in pet food.

CVM scientists, as part of their investigation, developed a test to detect dog and cat DNA in the protein of the dog food. All samples from the most recent dog food survey (2000) that tested positive for pentobarbital, as well as a subset of samples that tested negative, were examined for the presence of remains derived from dogs or cats. The results demonstrated a complete absence of material that would have been derived from euthanized dogs or cats. The sensitivity of this method is 0.005% on a weight/weight basis; that is, the method can detect a minimum of 5 pounds of rendered remains in 50 tons of finished feed. Presently, it is assumed that the pentobarbital residues are entering pet foods from euthanized, rendered cattle or even horses.

### **Finding levels of pentobarbital residues in dog food**

Upon finding pentobarbital residues in dog food, the researchers undertook an assessment of the risk dogs might face. Dogs were given known quantities of pentobarbital for eight weeks to determine if consumption of small amounts of pentobarbital resulted in any physiological changes that could indicate potential effects on health. In short, the scientists wanted to find the level of pentobarbital dogs could be exposed to that would show no biological effects. The most sensitive indicator that pentobarbital had an effect is an increase in the production of certain enzymes collectively called cytochrome P450.

Virtually all animals produce enzymes as a normal response to metabolize naturally occurring and man-made chemicals in their environment. Barbituates, such as pentobarbital, are especially efficient at causing the liver to produce these enzymes. In dogs, the most sensitive biological response to pentobarbital is an increase in the production of cytochrome P450 enzymes, which is why the scientists chose that as the best indicator of biological effect. If a low level of pentobarbital did not cause a dog to produce additional cytochrome P450 enzymes, then scientists could assume that the pentobarbital at that low level had no significant effect on the dog.

In CVM's study, experimental animals were each dosed orally with either 50, 150, or 500 micrograms pentobarbital/day for eight weeks. The results were compared with control animals, which were not exposed to pentobarbital.

Several significant pentobarbital-associated effects were identified in this study:

1. Dogs that received 150 and 500 micrograms pentobarbital once daily for eight weeks had statistically higher liver weights (relative to their bodyweights) than the animals in the control groups. Increased liver weights are associated with the increased production by the liver of cytochrome P450 enzymes;
2. An analysis showed that the activity of at least three liver enzymes was statistically greater than that of the controls at doses of approximately 200 micrograms pentobarbital per day or greater.

But researchers found no statistical differences in relative liver weight or liver enzyme activity between the group receiving 50 micrograms pentobarbital per day and the controls. Based on the data from this study, CVM scientists were able to determine that the no-observable-effect level – which is the highest dose at which no effects of treatment were found – for pentobarbital was 50 micrograms of pentobarbital per day.

### **Adverse health effects unlikely**

For the purposes of CVM's assessment the scientists assumed that at most, dogs would be exposed to no more than 4 micrograms/kilogram body weight/day based on the highest level of pentobarbital found in the survey of dog foods. In reality, dogs are not likely to consume that much. The high number was based on the assumption that the smallest dogs would eat dog food containing the greatest amount of pentobarbital detected in the survey of commercial pet foods-- 32 parts per billion.

However, to get to the exposure level of 50 micrograms of pentobarbital per day, which is the highest level at which no biological response was seen, a dog would have to consume between 5 to 10 micrograms of pentobarbital per kilogram of body weight. But the most any dog would consume, based on the survey results, was 4 micrograms pentobarbital per kilogram of body weight per day.

It should be emphasized that induction of cytochrome P450 enzymes is a normal response to many substances that are naturally found in foods. It is not an indication of harm, but was selected as the most sensitive indicator to detect any biological effect due to pentobarbital.

Thus, the results of the assessment led CVM to conclude that it is highly unlikely a dog consuming dry dog food will experience any adverse effects from exposures to the low levels of pentobarbital found in CVM's dog food surveys.

### [Appendix](#)