UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 16, 2009

MEMORANDUM

SUBJECT: Ethics Review of Fipronil Pet Groomer Exposure Study

TO: Wade Britton
Health Effects Division

FROM: Kelly Sherman
Human Research Ethics Reviewer
Office of Pesticide Programs

REF: Meo, N.J., Gonzalez, C.M, Belcher, T.I. (1997) Dermal Exposure of Commercial Pet Groomers During Application of Frontline Top Spot. Unpublished study prepared by ABC Laboratories under Study No. SAFXT047. 924 p. (MRID 44433303)

I have reviewed the referenced document and found no barrier in law or regulation to its being relied upon in actions under FIFRA or §408 of FFDCA.

Summary Assessment of Ethical Conduct of the Research

In this study, sixteen human subjects were monitored for dermal exposure while they applied Frontline Top Spot to eight dogs each. Researchers measured the subjects' dermal exposure by analysis of whole body dosimeters, cotton gloves, and ethanol facial swabs. The research was conducted at a pet grooming shop in Savannah, Georgia.

1. **Value of the Research to Society:** The objective of this study was to determine potential dermal exposure of commercial pet groomers to fipronil, the active ingredient in Frontline Top Spot. The study was funded by Merial Limited, the Frontline registrant. It

contributes to the assessment of commercial pet groomers' exposure while applying Frontline Top Spot (and possibly other similar products).

2. **Subject Selection**: The sixteen subjects (four men and twelve women) were employees of the pet grooming shop where the research was conducted. They ranged in age from 20 to 49 years old, with between 1.5 and 35 years of experience working as commercial pet groomers. The pregnancy and nursing status of the female subjects is not reported. The Principal Investigator conducted the recruitment by identifying employees of the grooming shop whose responsibilities included treating animals for flea control and asking them about their interest in participating in the research. The report does not indicate whether the employer played a role in the recruitment process. If the employer did take part in recruiting, the subjects may have been vulnerable to undue influence over their decision about whether to participate in the study. The report does not indicate whether any steps were taken to protect the subjects from undue influence.

3. **Risks and Benefits**: The study report and consent form characterize the potential risks and discomforts associated with participating in the study ("Frontline Top Spot is harmful if swallowed by humans and may cause eye injury… Ethanol, used in the facial wipes, is a dermal sensitizer, and it is possible a skin rash may develop as a result of its use…Some discomfort is encountered when wearing long underwear, especially on warm days.") and describes the procedures used to minimize those risks. The report also characterizes the societal benefits of the research as helping the sponsor and EPA to assess the risks to professional pet groomers associated with applying Frontline Top Spot and other similar products. It does not discuss how the investigators weighed likely benefits of the research against the risks to individual subjects, but the research appears to be justified because the potential risks were low and therefore outweighed by the benefits.

4. **Independent Ethics Review**: The study does not report any independent ethics oversight or review of the protocol or of the conduct of the research.

5. **Informed Consent**: The principal investigator informed potential participants about the nature and purpose of the study, reviewed key information from the pesticide product label, and provided potential subjects with an opportunity to ask questions. Before participating in the research, each subject signed an informed consent form containing the elements of informed consent required by the Common Rule (40 CFR 26.116).

6. **Respect for Potential and Enrolled Subjects**: The report contains photographs from which it is possible to determine the identity of some of the subjects, thus compromising their privacy. During the consent process, subjects were informed that they could withdraw from the study at any time without prejudice.

Applicable Standards

This research was initiated in July 1997, before the effective date of EPA's amended Rule for the Protection of Human Subjects of Research on April 7, 2006. It meets the definition of "research involving intentional exposure of a human subject" in the rule at 40 CFR §26.1102(i) because this research involved application of product provided by the sponsors at rates and under conditions specified by the investigators.

The report of this research was submitted to EPA in November 1997, before the effective date of EPA's Amended Rule for the Protection of Human Subjects of Research, and thus it was not subject to the requirement of 40 CFR §26.1303 for submitters to document the ethical conduct of the research.

The Agency's rule defines standards for EPA to apply in deciding whether to rely on research—like this study—involving intentional exposure of human subjects. (See 40 CFR §26 subpart Q.) The applicable acceptance standards from 40 CFR §26 are these:

> **§26.1703. Prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children.** Except as provided in §26.1706, in actions within the scope of §26.1701 EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
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> **§26.1704. Prohibition of reliance on unethical human research with nonpregnant adults conducted before April 7, 2006.** Except as provided in §26.1706, in actions within the scope of §26.1701, EPA shall not rely on data from any research initiated before April 7, 2006, if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. This prohibition is in addition to the prohibition in §26.1703.

FIFRA §12(a)(2)(P) also applied to this research. This provision reads:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

Compliance with Applicable Standards

The sixteen subjects in the study were all adults. The study is silent with respect to the pregnancy status of the twelve female subjects, but there is no indication that any were pregnant or nursing women. In the absence of any information suggesting that pregnant or nursing women were among the subjects, the Agency's interpretation is that reliance on the study is not prohibited by 40 CFR 26.1703.

40 CFR §26.1704 forbids EPA to rely on data from pre-rule research—such as this study—if there is "clear and convincing evidence that the conduct of the research was fundamentally unethical…, or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted." Although there are significant gaps in the documentation of the ethical conduct of this research, such gaps were common in similar studies from this period, and gaps do not amount to "clear and convincing evidence." I found no evidence that this research was fundamentally unethical, or that its conduct was significantly deficient relative to standards prevailing when it was conducted. Therefore, 40 CFR §26.1704 does not prohibit EPA reliance on this research.

FIFRA §12(a)(2)(P) requires that human subjects of research with pesticides be "fully informed of . . . any physical and mental health consequences which are reasonably foreseeable" from their participation in research. In this study, researchers informed potential subjects of the risks before they were asked to provide consent. The reported description of the consent process appears to meet the substantive requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary participation.

Conclusion

I find no barrier in law or regulation to reliance on MRID 44433303 in actions taken under FIFRA or §408 of FFDCA. I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.