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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

August 10, 2009

MEMORANDUM

SUBJECT: Ethics Review of Fipronil Pet Treatment Post-Application Exposure Study

TO: Wade Britton
Health Effects Division

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

REF: Fontenay, G., Campagna, J.F., Suberville, S., Birckel, P. and Weil, A. (1997) Dislodgeable Residues of Fipronil Following a Topical Application of Frontline Spot-on Treatment to Dogs. Unpublished study conducted by Merial under Study No. MET416. 68 p. (MRID 44531203)

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

Summary Assessment of Ethical Conduct of the Research

In this study, a human subject wore a cotton glove dosimeter and stroked dogs treated with Frontline Spray in order to provide estimates of fipronil residues which dislodged from the fur. Six dogs were used in the research, and the petting procedure took place at ten time points following treatment. The scripted petting procedure involved the subject stroking each dog with the palmar surface of his gloved hand, "the whole body surface of the animal using motions that run with the lay of the haircoat, beginning from the head and ending at the tail base." The research was conducted at Chrysalis Pre-Clinical Services Europe, a research facility in L'Arbresle, France.

1. **Value of the Research to Society:** The objective of this study was to "provide estimates of the dislodgeable residues of Frontline spot-on (fipronil) following one cutaneous application according to label directions to the hair coat of dogs." The study was funded by Merial, the Frontline registrant. It contributes to the assessment of exposure while applying Frontline spot-on (and possibly other similar pet flea and tick products).

2. **Subject Selection**: The individual who wore the glove dosimeters and performed the scripted petting procedure is considered a human subject of this research. The subject is referred to as the "sampler" in the report, and the protocol states that the "same person will be used as the "sampler" at all time points for all animals." It appears that the sampler was a Chrysalis employee, and therefore also an adult. The subject is referred to using male pronouns (e.g., "the person conducting the sampling (the "sampler") stroked with his dominant hand"), which suggests that the subject was a male. There is nothing in the report to suggest that the subject was a child or a pregnant or nursing woman. If the subject was indeed a Chrysalis employee, there is no information about whether protections were in place to shield him from undue influence over his decision to participate in the research.

3. **Risks and Benefits**: Neither risks to the subject/sampler nor actions taken to minimize those risks are reported. The report does not identify societal benefits of the research or how they would be distributed. The report does not discuss how the investigators weighed likely benefits of the research against the risks to the subject/sampler, but the research appears to have been justified: an EPA-registered product was used according to its label directions, and the low potential risks were likely to have been outweighed by the benefits of the knowledge gained.

4. **Independent Ethics Review**: The study does not mention independent ethics oversight or review of the protocol or of the conduct of the research, but that was typical for similar studies at the time this one was conducted. At the time of this research, this type of study was not generally considered "research with human subjects" subject to a requirement for ethics oversight.

5. **Informed Consent**: The report is silent about whether informed consent was obtained from the subject/sampler. This was typical for similar studies at the time this one was conducted.

6. **Respect for Potential and Enrolled Subjects**: The subject/sampler is not identified in the report. The subject/sampler's freedom to withdraw is not addressed.

Applicable Standards

This research meets the regulatory definition of "research with human subjects" because the residue data were collected by an individual wearing a clothing dosimeter—i.e., a glove. The data are therefore considered a measure of exposure to that individual. This study also meets the definition of "research involving intentional exposure of a human subject" at 40 CFR §26.1102(i) because it involved application of product provided by the sponsors at rates and under conditions specified by the investigators.

But this research was initiated in March 1997 and submitted to EPA in April 1998, many years before the effective date of EPA's Amended Rule for the Protection of Human Subjects of Research, and thus the requirements of 40 CFR §26 Subparts K, L, and M concerning the conduct of third party research involving intentional exposure of human subjects and to document the ethical conduct of the research are inapplicable.

The Agency's rule (40 CFR §26 Subpart Q) defines standards for EPA to apply in deciding whether to rely on research—like this study—involving intentional exposure of human subjects. 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

This research was conducted in 1997. At that time, fur-stroking studies like this one were not generally considered "research with human subjects" either by EPA or by the human research ethics community. It is therefore not disqualifying that there is no information in the report about whether the research was conducted in compliance with ethical standards applying to research with human subjects.

Though it is not stated explicitly, there is information suggesting that the subject/sampler was an adult male. Moreover, there is no evidence suggesting that the subject was a child or a pregnant or nursing woman. In these circumstances 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." I found no evidence that this research was intended to harm the participating subject/sampler, 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 the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom" and "freely volunteer to participate in the test." In this study, the subject appears to have been an employee of the research laboratory. As such, he would have been aware that the sampling procedure he performed was part of a study involving a pesticide, and likely would have been knowledgeable about the nature and purpose of the study as a whole. He also likely filled multiple roles in the conduct of the research, in addition to performing the petting procedure, and therefore probably would have been knowledgeable about the Frontline product and familiar with the risk information conveyed on the product label. There is no information about whether protections were in place to protect the subject from undue influence over his decision to participate, but it is reasonable to infer that at a large research facility like Chrysalis Pre-Clinical Services Europe, there would not have been a shortage of employees willing to participate in this relatively innocuous study by wearing a glove dosimeter and petting dogs that had been treated with an EPA-registered flea and tick product.

Conclusion

I find no barrier in law or regulation to reliance on MRID 44531203 in EPA 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.