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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

December 15, 2015

MEMORANDUM

SUBJECT: Ethics Review of Davis et al Research on Flea Collars with TCVP

FROM: Maureen Lydon, Human Studies Ethics Review Officer
Office of the Director
Office of Pesticide Programs

TO: Dana Vogel, Director
Wade Britton, Environmental Health Scientist
Health Effects Division
Office of Pesticide Programs

REF: M. Keith Davis, J. Scott Boone, John E. Moran, John W. Tyler, Janice E. Chambers, Assessing intermittent pesticide exposure from flea control collars containing the organophosphorous insecticide tetrachlorvinphos, *Journal of Exposure Science and Environmental Epidemiology* (2008) 18, 564-570.

I have reviewed the referenced article on two studies which assess intermittent pesticide exposure from flea control collars containing the organophosphorous insecticide tetrachlorvinphos (TCVP).

As described in the article, "Because TCVP has been used in flea collars, the amount of exposure to TCVP that could occur in children and adults from the use of a TCVP-containing collar on a pet dog was assessed. A long study (about 4 months) was conducted first to determine the time course of transferable residue peak and dissipation as assessed by transferable residues of TCVP from the fur of dogs to white cotton gloves used to rub the dogs." Study 1, conducted in 1998, included dog plasma cholinesterase measurements as well. "This was followed by a shorter study conducted over 3 weeks to include human biomonitoring of the TCVP metabolite 2,4,5-trichloromandelic acid (TCMA) in urine of children and adults. TCVP residues transferred to tee shirts worn by children by contact with the dog were also quantified to determine whether tee shirts might serve as a surrogate of exposure." As with the first study, study 2, conducted in 2002, also assessed transferable residues of TCVP from the fur of dogs to white cotton gloves used to rub the dogs. In summary, four types of data were collected addressing: 1) transferable residues of TCVP from the fur of dogs to white cotton gloves: 2) TCVP residues on tee shirts worn by children; 3) the levels of the metabolite TCMA in urine from children and adults; and 4) dog plasma cholinesterase activity

Studies 1 and 2 are systematic investigations designed to develop or contribute to generalizable knowledge and so meet the regulatory definition of *research.* Through collection of urine and tee shirt samples, study 2 obtained data about individuals and so meets the regulatory definition of *human subject research.* Although the families involved in the studies already used flea collars, the researchers bought and provided specific flea collars to the participating families and asked that their dogs wear the flea collars during the studies. As a result, the research constitutes intentional exposure.

EPA's Office of Pesticide Programs (OPP) wants to rely only on one sub-set of the data generated from this research, specifically the data on transferable residues of TCVP from the fur of dogs to white cotton gloves used to rub the dogs. The generation of this data did not involve children. However, the data was collected as part of broader research which involved children as study participants when they wore tee shirts and provided urine samples. As a result, specific federal regulations come into play before EPA can potentially rely on the TCVP glove residue data.

40 CFR Subpart Q, §26.1703, prohibits EPA from relying on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, **or a child**. §26.1706 provides an exception. Under 40 CFR §26.1706, EPA can only rely on this research if it is crucial to making a decision to impose a more stringent regulatory restriction than could be justified without the data. If EPA's Office of Pesticide Programs (OPP) decides to rely on the TCVP glove residue data, under 40 CFR §26.1706, OPP must first complete three required steps. EPA must obtain the views of the Human Studies Review Board, provide an opportunity for public comment, and publish a full explanation of its decision to rely on the data, including a thorough discussion of the ethical deficiencies of the underlying research and the full rationale for finding that EPA met the standard in 40 CFR §26.1706 (c) (i.e., that the research is essential to a more stringent regulatory action to improve protection of public health).

I defer to others for a full review of the scientific validity of the TCVP glove residue data on which EPA wishes to rely. If the data were determined not to have scientific validity, it would also not be ethically acceptable and EPA could not use it. If EPA decides to rely on the TCVP residue data on gloves, and completes the required activities noted above, I find that there is no regulatory barrier to EPA relying on this research in actions taken under FIFRA or §408 of FFDCA. The rest of this memorandum and attachment(s) provide OPP's ethics review of the research.

I. Summary Characteristics of the Research

A. Summary of Studies Described in Article

The published research article is entitled "Assessing intermittent pesticide exposure from flea control collars containing the organophosphorous insecticide tetrachlorvinphos" by M. Keith Davis, J. Scott Boone, John E. Moran, John W. Tyler, and Janice E. Chambers. The Davis et al article discusses two studies which collected data useful for assessing the amount of exposure to tetrachlorvinphos (TCVP) that could occur in children and adults from the use of a TCVP-containing collar on a pet dog. The studies were conducted in Oktibbeha County, Mississippi,

with 55 volunteer households who routinely used flea control products on their pet dogs. In each study, Hartz Control Ultimate Flea Collars F 14.55% TCVP were purchased from a local department store.

"Study 1 was a longer term, 112-day study conducted from September to December 1998 because the collar was recommended by the manufacturer for 6-month use. Twenty-three dogs from different households were used, and petting samples from fur and dog plasma cholinesterase (ChE) measurements were obtained." Study 1 "was conducted first to determine the time course of transferable residue peak and dissipation as assessed by transferable residues of TCVP from the fur of dogs to white cotton gloves used to rub the dogs" at three locations: near the base of the tail, at the neck with the collar removed, and at the neck with the collar in place. "Dogs were petted in a marked 10 x 4 inch area with clean, white, cotton gloves for a continuous 5-minute period." Samplers were students enrolled at the College of Veterinary Medicine, Mississippi State University. For study 1, rubbing samples were obtained prior to collar placement and at 4 hours, and 3, 7, 14, 28, 56, 84, and 112 days post-collar application.

Study 2 was a shorter, 21-day study conducted in September and October 2002 which included human biomonitoring of the TCVP metabolite 2, 4, 5-trichloromandelic acid (TCMA) in urine of children and adults. Study 2 involved 44 volunteer human subjects including one child and one adult who were selected from each of the 22 families who participated in study 2. Study 2 involved 22 pet dogs from different households and quantified the residues of TCVP from: 1) glove/rubbing samples; 2) tee shirt samples; and 3) levels of the metabolite TCMA in the urine of children and adults.

1. Glove/Rubbing Samples: Under one component of the study, "dogs were petted in a marked 10 x 4 inch area with clean, white, cotton gloves for a continuous 5-minute period." For study 2, rubbing samples were obtained prior to collar placement (day 0) and again at 5 and 12 days following collar placement.

   "Samplers utilized during both studies were students enrolled in the veterinary medicine curriculum at the College of Veterinary Medicine, Mississippi State University."

2. Tee Shirt Samples: Under the second component of the study, child participants were supplied with a new, laundered, white cotton tee shirt to wear on the day before the treatment and on each of days 7–11 after the collars were placed on the dogs; the tee shirts were worn by children for about 4 hours at selected times after pesticide application.

3. Urine Samples: The first morning urine samples were collected from the child wearing the tee shirt and from one adult in the same household on the day prior to the treatment and then again on each of days 8–12 post-collar placement.

B. EPA Reliance on Glove Residue Data and Reason for Presentation to HSRB

In order to improve the protection of public health, EPA would like to rely **only on the TCVP glove residue data from study 1 and study 2** in its risk assessment and to potentially

impose a more stringent regulatory restriction than the Agency could do otherwise without the data. Study 2 also involved the collection of data based on tee shirts worn by children and urine samples from children and adults participating in the study. With the exception of the dog plasma cholinesterase measurement, all of the data collected constitutes exposure assessment research and EPA cannot reasonably separate the different types of data in these studies as different types of human research. Because study 2 encompassed more than TCVP glove residue data and involved children wearing tee shirts and providing urine samples, study 2 constitutes research involving intentional exposure of children. For that reason, even though OPP does not wish to rely on the data involving children, OPP is submitting the research to the Human Studies Review Board for their review.

From a science perspective, OPP is interested in the Board's perspective on the scientific validity of the TCVP glove residue data, which is the only data on which EPA intends to rely. From an ethics standpoint, OPP is interested in the HSRB's perspective on two topics:

1) Does the HSRB have any comments on EPA's determination that the samplers were not human subjects?
2) Does the HSRB have any comments on the ethical conduct of the research?

C. Support from EPA Grants

The acknowledgements at the end of the research article note that the research was supported by grants from the US EPA's Science to Achieve Results (STAR) grant program (specifically grant numbers R825170 and R828017). I contacted EPA's Office of Research and Development (ORD), the Office of the Science Advisor (OSA) to determine if ORD had documentation associated with either or both grants. ORD provided the documentation in Attachment 1 related to ORD's review of grant proposal R828017. (ORD reviewed the grant proposal at the time because it was proposed for partial funding by EPA and involved human research. Documentation for the other grant, R825170, is not available because it did not require ORD review.) The ORD file presents several documents, including the abstract of the proposed research entitled, "Assessing Levels of Intermittent Exposure of Children to Flea Control Insecticides from the Fur of Dogs." Page 11 of the abstract cites the research objectives and describes "3 specific aims, each of which will involve a correlation of residues from the rubbing procedure with cotton gloves (the technique we are using at present), residues from tee shirts worn by a child in the household, and urinary metabolites of this child and an adult in the household: 1. To determine the exposure of children to permethrin resulting from residues from the fur of dogs from a permethrin spot treatment; 2. To determine the exposure of children to TCVP resulting from residues from the fur of dogs treated with a TCVP flea collar; and 3. To determine the exposure of children to chlorpyrifos resulting from residues from the fur of dogs treated with a chlorpyrifos flea collar." The published article by Davis et al describes the two studies which support aim #2, noted above, related to the TCVP flea collars. The primary investigator for the two studies, Dr. Janice Chambers from Mississippi State University, confirmed that the TCVP research described in the ORD file relates to the two studies discussed in the Davis et al article. For that reason, pertinent information from the ORD file is referenced throughout this ethics review. The ORD documentation in Attachment 1 includes:

1) The Mississippi State University (MSU) Statement of "Assurance of Compliance with EPA Regulations for Protection of Human Research Subjects";

2) Institutional Review Board (IRB) statement of institution and investigator compliance with 40 CFR 26;
3) Certification of IRB Approval and Institutional Endorsement signed by MSU's Vice President for Research, the MSU IRB Chairman at the time and the MSU project investigator Janice Chambers;
4) List of MSU IRB members at the time of the research;
5) Draft minor's assent form;
6) Draft consent form for adult human subjects (also referred to as the authorization for participation in the research project on flea collars);
7) 16-page abstract describing the research along with 3.5 pages of additional references; and
8) ORD's comments on the draft consent forms.

The file and Attachment 1 also includes an email from ORD's then Assistant Director for EPA's National Center for Environmental Research (NCER) identifying ORD's comments on the consent forms. The primary investigator (PI) agreed to the changes requested by ORD. The final versions of the consent forms are not included in the file. Both the PI and EPA agree that the changes to the consent forms must have been made because receipt of grant funding was contingent on addressing EPA comments. Given that the grants were awarded, EPA reasonably assumes that comments were addressed. This ethics review takes into account, when appropriate, the 16-page description of the research project, the draft consent forms and the IRB correspondence included in the ORD file.

D. Contact with IRB and Primary Investigator

To supplement the ethics information provided in the journal article, I contacted the relevant institutional review board, the Institutional Review Board for Research on Human Subjects at Mississippi State University, and requested copies of the available records about the two studies profiled in the Davis et al article. Because study 2 was conducted in 2002, the IRB did not maintain documentation past the required retention time. As a result, the IRB did not have copies of their reviews. However, the ORD file included IRB-related documents listed on page 4 of this memo.

After speaking with the IRB, I contacted the Primary Investigator for the Research, Dr. Janice E. Chambers, Professor and Director of the College of Veterinary Medicine Faculty at MSU. Dr. Chambers confirmed relevant background information from the ORD file on how the study was conducted; that background information is incorporated into this ethics review. My interview with Dr. Chambers is documented in Attachment 2. Dr. Chambers was a member of the Human Studies Review Board (HSRB) for 8 years, from March 27, 2006 until August 31, 2014.

E. Role of Veterinary Students in Rubbing Dogs and EPA's Position

As discussed on page 566 of the Davis et al article, "Samplers utilized during both studies were students enrolled in the veterinary medicine curriculum at the College of Veterinary Medicine, Mississippi State University." Primary investigator Dr. Chambers confirmed that both the researchers and IRB viewed the samplers as technicians in the study and not as human

subjects. EPA considers the view of the researchers' and IRB on this pre-rule research to be a reasonable one.

Looking at the information in the research article and ORD file, the primary investigator did not obtain data **about the technicians**, nor did they ever intend to do so. Human subject means a living individual about whom an investigator conducting research obtains data. The researchers were not focusing on the technicians in this study. Instead, the researchers were collecting data only about the residues on the gloves.

The researchers did not question the technicians about how they rubbed the animals. If it were a situation where the dog owners were petting their own animals throughout the day and the researchers had to interview and interact with the dog owners to collect data about how long they interacted with their pets, where they petted their dogs, and in what manner, the researchers would be collecting data about the human subjects, not just about the residues. This was not the case in this situation. As stated in the research article, the samplers/technicians rubbed the dogs "in a marked 10 x 4 inch area with clean, white, cotton gloves for a continuous 5-min period." The dogs were rubbed in three specific locations (near the base of the tail, at the neck with the collar removed, and at the neck with the collar in place). In the ORD file, page 14 of the research abstract further states that "the samplers will be trained so that consistency in the sample collection is maintained among dogs and among samplers." The samplers/technicians were wearing gloves and stroking the animals in a standardized and prescribed way. The researchers did not collect information or data about the samplers. EPA agrees with the primary investigator and IRB that the samplers were not human subjects in these studies.

F. Ethical Considerations

1. Value of the Research to Society:

The objective of this research was to assess the amount of exposure to TCVP that could occur in children and adults from the use of a TCVP-containing collar on a pet dog. According to the authors, one research area that had not been adequately explored is the possibility that residues of insecticides remaining on pet fur from flea control collars could be a significant source of pesticide exposure in children who pet or hug treated animals. EPA is considering some of the data from this research in its risk assessment for tetrachlorvinphos and to potentially take a more stringent regulatory action than could be taken without the data.

2. Subject Selection:

a. Demographics. The studies were conducted in Oktibbeha County, Mississippi, with volunteer households whose pet dogs routinely wore flea collars. For study 1, the dogs from 23 families were used. For study 2, one child and one adult participated from each of the 22 volunteer households, which equates to 44 human subjects for study 2. The participating children ranged in age from 3 to 13. Approximately half of the participating children and adults were male and half were female.

b. Pregnancy and Nursing Status and Participation of Children. There is no indication in the research article or ORD file that pregnant or nursing women participated in the

studies. However, 22 children, ranging in age from 3 to 13, participated in study 2. EPA can only rely on research involving children if the criteria and procedures in 40 CFR §26.1706 are met.

c. ***Recruitment.*** The article states that, "the studies were conducted in Oktibbeha County, Mississippi (USA), with volunteer households having pet dogs" and that "participating families were volunteers who routinely used flea control products on their pet dogs." The article states that, "One child and one adult were selected from each participating family (study 2 only) as previously described by Chambers et al (2007)." However, the 2007 article to which this citation refers does not include additional information regarding recruitment or subject selection.

The ORD file includes the following pertinent information. As stated on page 13 of the research abstract, "Dogs selected for this study will be owned by professional (DVM) or graduate students enrolled in the College of Veterinary Medicine, or staff/faculty members of Mississippi State University with a child aged 4-10 years in the household who routinely plays with this dog. Students or staff should be the most reliable group of owners (in contrast to the general public) in that they are accessible daily, their dogs can readily be treated and sampled when the students are in class or the staff members are at work, and as members of the academic community, the compliance and appreciation of the value of research should be high. Dogs participating in this study must be enrolled in the Small Animal Community Practice Health Maintenance Program, so that their health status and vaccination history are known..". Primary Investigator Janice Chambers confirmed that MSU's College of Veterinary Medicine is located in Oktibbeha County, Mississippi.

Page 14 of the research abstract includes a section entitled, "Selection of human test subjects" which reads as follows: "The human subjects will be residents in the same household as the canine test subject. The household must have a child (either sex) in the age range of 4-l 0 years who regularly plays with the dog, and an adult (probably a parent; either sex); both subjects must be willing to provide the samples required by the study protocol. The samples will be tee shirts from the child and first morning urine samples from the child and the adult. The age, sex, height and weight of both child and adult test subjects will be recorded, and the adult will be asked to give an estimate of the amount of time and degree of contact that the child and the adult had with the dog on the day of the tee shirt sample; these data will be available for later correlations with residue/metabolite data. A description of the protocol and an informed consent form will be developed, and the subjects will be assured of anonymity. These protocols and approval forms will be approved by the Institutional Review Board for Research on Human Subjects."

3. Risks and Benefits:

a. ***Risks.*** The Davis et al article is silent about risks to subjects **from their participation in the study.** The article states that, "Because TCVP is an organophosphate insecticide, its primary mechanism of toxicity is the inhibition of the nervous system enzyme, acetylcholinesterase (Ecobichon, 1996)." However, only families who

routinely used flea control products on their pet dogs participated in the studies. The researchers purchased, for use in the studies, over-the-counter flea collars that were already registered with the U.S. EPA.

b. Benefits. There were no benefits to the subjects and none were noted in the research article.

c. ***Risk-Benefit Balance.*** The research article does not explicitly discuss the risk-benefit balance. However, the stated objective of this research was to assess the amount of exposure to TCVP that could occur in children and adults from the use of a TCVP-containing collar on a pet dog. According to the authors, one research area that does not seem to have been explored is the possibility that residues of insecticides remaining on pet fur from flea control collars could be a significant source of pesticide exposure in children who pet or hug treated animals. The article provides study results in this area of research.

4. Independent Ethics Review: The Institutional Review Board for Research on Human Subjects at Mississippi State University reviewed and approved the sampling protocols and informed consent forms. Furthermore, EPA's Office of Research and Development (ORD), the National Center for Environmental Research and Quality Assurance (NCERQA) reviewed the STAR grant proposal focusing on this research because it involved the use of human subjects and requested funding by EPA. ORD supported the research dependent on incorporation of NCERQA comments on the consent forms.

5. Informed Consent: The article states that "A copy of the protocol was distributed to each participating household, and informed consent was obtained from the adults. Children were informed verbally of the procedures and oral or written assent was obtained from them. The Institutional Review Board for Research on Human Subjects at Mississippi State University approved all sampling protocols and informed consent forms."

The ORD file contains a draft consent form for adult human subjects entitled, "Authorization for Participation in Research Project (collar)" and a draft "Minor's Assent Form," both provided in Attachment 2. The "authorization for participation" form states that the study involves research and identifies its purpose, the expected duration, number of urine and tee shirt samples to be provided, that research results will be coded, participants are free to withdraw, provides a contact for information and identifies compensation of $150 for each participating household. The consent form also states that, "no risks are anticipated to the participants" as a result of participating in the study. The implication is that since the families already used flea collars on their dogs, there was no added risk from participating in the study. However, the researchers proposed the following hypothesis on the bottom of page 10 and top of page 11 of the research abstract submitted to ORD: "The residues of insecticides available for intermittent transfer to children from the fur of dogs treated by either a spot treatment or a collar for flea control will be appreciable and of a magnitude necessitating inclusion in cumulative risk assessments of pesticides to children; secondly, that the fur rubbing procedure developed to quantify dislodgeable residues provides a useful estimate of insecticide residues which could be transferred from the fur of dogs to children." Although the families involved already used flea collars which were

registered by EPA, in the interest of transparency, the researchers should have shared their hypothesis with the parents of the participating children and included it in the consent form. This information may have been stated in the protocol provided to the families but we do not know.

The minors' assent form states that researchers "will specifically obtain assent from the children recruited to our project 'Assessing levels of intermittent exposures of children to flea control insecticides from fur of dogs' for their participation in the project…We will explain that the child's parent or guardian has given us permission to request his/her help participation in the research project. We will then explain the urine collection protocol and the tee shirt protocol to the children in language appropriate to the age of the child and obtain his/her assent to participate. We will not explain the connection to the pesticide residues on the dog so as not to alter the behavior of the child with the dog. We will obtain the children's assent orally because of the age range of the children involved."

6. **Respect for Subjects:** The article does not reveal the subjects' identifies. The article states that, "A copy of the protocol was distributed to each participating household, and informed consent was obtained from the adults. Children were informed verbally of the procedures and oral or written assent was obtained from them. The Institutional Review Board for Research on Human Subjects at Mississippi State University approved all sampling protocols and informed consent forms." The tee shirts worn by the children as part of study 2 were provided by the researchers. The ORD file includes the following additional information relevant to respect for subjects.

   Researchers demonstrated respect for subjects by providing light-weight, short-sleeve (as opposed to long-sleeve) tee shirts to the children participating in study 2. Page 15 of the research abstract in the ORD file states that, "The child will wear the tee shirt during the afternoon and evening of the sampling day for a 5 hour period. (While long sleeve shirts might give a better estimate of exposure, long sleeves would not be tolerable and could be a health risk because of the heat during 6-8 months of the year in this region.) The child will not be instructed to alter his/her normal behavior with respect to the dog." Page 12 of the abstract states that the tee shirt "is a piece of clothing which the child would readily wear without embarrassment in front of his/her peers and siblings." These statements illustrate that the researchers took into account the feelings and comfort of the children participating in study 2.

   Furthermore, page 20 of the abstract in the ORD file states that, "The protocols do not require any invasive procedures and are not expected to cause any physical or mental distress to the individuals involved. The test subjects will be asked to continue their routine activities and to not modify their activities in any way. They will be asked to provide urine samples on a set schedule; we will give them written assurance that the urine sample will be used only for quantitation of insecticide urinary metabolites and will not be used for any other purposes, and that all data will remain anonymous."

   With regard to compensation, the consent form states that each participating household will receive $150. The ORD file, page 20 of the abstract, states that, "Dogs participating in this study will be required to be enrolled in MSU's Small Animal Community Practice Health

Maintenance Program whereby the dog's health will be known by physical examination and vaccination history. If the dog was not previously enrolled in the program, the cost of the initial physical will be borne within the $100 incentive offered to each participant." Page 19 of the abstract has a section on incentives for dog owners which states, "In order to provide incentives for the cooperative participation of the dog owners in this study, we propose to offer $100 equivalent of veterinary care provided by the Animal Health Center of the College of Veterinary Medicine for each dog participating in the study. In addition, the spot treatments, shampoos, and collars constituting the study will be provided to the owners without additional charge. An additional $150 cash incentive will also be given to each participating household because of the shirt and urine samples. We predict that these incentives will lead to more than an adequate number of households to participate in this study. We currently estimate that there will be at least 500 dogs owned by veterinary and graduate students and faculty and staff at the College of Veterinary Medicine at any given time, and many of these households would have a child of the appropriate age. In the unlikely event that insufficient numbers of households can be enrolled for the study, we will open the participation to students, faculty, and staff members of Mississippi State University outside the College of Veterinary Medicine; these individuals would be offered the same incentives."

II. Applicable Standards

A. Definition of Research

The relevant definitions are discussed below:

- In order to meet the regulatory definition of *research involving human subjects*, the regulatory definition of both *research* and *human subject* must be met.
- Studies 1 and 2 described in the Davis et al article are systematic investigations designed to develop or contribute to generalizable knowledge and so meet the regulatory definition of *research.*
- Through collection of urine and tee shirt samples, study 2 obtained data about individuals and so meets the regulatory definition of *human subject research.*
- Although the families involved already used flea collars, the researchers bought and provided specific flea collars to the participating families and asked that their dogs wear the flea collars during the studies. As a result, study 2 constitutes intentional exposure.
- These studies determined, in part, the amount of transferable TCVP residues and the urinary TCMA concentration. The purpose of these studies was not to identify or measure a toxic effect in humans. The research was conducted prior to the effective date of the human research rule.

As a result, the only reason that EPA is bringing this pre-rule research to the HSRB for review is because study 2 involved children as participants in providing tee shirt and urine samples.

B. Standards Applicable to the Conduct of the Research

The research article was published in 2008 and focuses on two studies. Study 1 was conducted in 1998 and study 2 was conducted in 2002, both before EPA's Rule for Protection of Human Subjects of Research became effective in 2006. Thus, 40 CFR part 26 did not apply

when this research was conducted. However, the Common Rule was in place and applies to the underlying research which received EPA STAR grant funding.

Key elements of the Common Rule are IRB oversight and prior approval, an acceptable informed consent process and consent form, risk minimization, a favorable risk-benefit balance, equitable subject selection, and fully informed, fully voluntary participation by subjects.

In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) existed at the time of these studies and 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.

C. Standards Applicable to EPA's Reliance on the Research

The Agency's rule (40 CFR part 26 subpart Q) defines standards for EPA to apply in deciding whether to rely on research—like study 1 and 2—involving intentional exposure of human subjects. The applicable acceptance standards from 40 CFR part 26 subpart Q are these:

> **§26.1703:** Except as provided in §26.1706, EPA must not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> **§26.1704**: 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: (1) 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 (2) the conduct of the research was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.
>
> **§26.1706:** This section establishes the exclusive criteria and procedure by which EPA may decide to rely on data from research that is not acceptable under the standards in §§26.1703 through 26.1705. EPA may rely on such data only if all the conditions in paragraphs (a) through (d) of this section are satisfied:
>
> (a) EPA has obtained the views of the Human Studies Review Board concerning the proposal to rely on the otherwise unacceptable data,
>
> (b) EPA has provided an opportunity for public comment on the proposal to rely on the otherwise unacceptable data,

(c) EPA has determined that relying on the data is crucial to a decision that would impose a more stringent regulatory restriction that would improve protection of public health, such as a limitation on the use of a pesticide, than could be justified without relying on the data, and

(d) EPA has published a full explanation of its decision to rely on the otherwise unacceptable data, including a thorough discussion of the ethical deficiencies of the underlying research and the full rationale for finding that the standard in paragraph (c) of this section was met.

FIFRA §12(a)(2)(P): In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) applies. This passage 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.

D. Completeness of Ethics Information

EPA ensured compliance with §26.1303 as demonstrated by the checklist in Attachment 3; the checklist summarizes the completeness of available information pertaining to the ethical conduct of the completed research.

E. Compliance with Applicable Standards

§26.1703. Except as provided in §26.1706, prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children.

Study 1 did not involve children or pregnant or nursing women. As part of study 2, conducted in 2002, researchers collected three types of data: TCVP glove residue data, tee shirt samples, and urine samples. Children participated in study 2 by wearing the tee shirts and providing urine samples. As such, EPA is prohibited from relying on study 2 unless the conditions of §26.1706 are met.

§26.1704. Prohibition of reliance on unethical human research with nonpregnant adults conducted before April 7, 2006.

There is no clear and convincing evidence that this pre-rule research was fundamentally unethical; that is, the research was not intended to harm the participants and did not fail to obtain informed consent. Similarly, the conduct of the research was not deficient relative to the ethical standards prevailing at the time the research was conducted; the studies did not place participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impair their informed consent. As a result, EPA is not prohibited from relying on this research under §26.1704.

§26.1706: Criteria and procedures for decisions to protect public health by relying on otherwise unacceptable data.

As of the date of this memo, OPP wishes to rely on the TCVP glove residue data generated in study 1 and 2. The data may be crucial to a potential EPA decision to improve public health protection by imposing a more stringent regulatory restriction than could be justified without the data. If EPA proceeds under §26.1706, EPA needs to obtain the views of the Human Studies Review Board, provide an opportunity for public comment, and publish a full explanation of its decision to rely on the data, including a thorough discussion of the ethical deficiencies of the underlying research and the full rationale for finding that EPA met the standard in 40 CFR §26.1706 (c) (i.e., that the research is essential to a more stringent regulatory action to improve protection of public health).

FIFRA §12(a)(2)(P):

The researchers complied with FIFRA §12(a)(2)(P). The human subjects were informed of the nature and purposes of the research and volunteered to participate in the studies.

III. Conclusion

I defer to others for a full review of the scientific validity of the TCVP glove residue data on which EPA wishes to rely. If the data were determined not to have scientific validity, it would also not be ethically acceptable and EPA could not use it.

The TCVP glove residue data was one component of broader research that also included tee shirt and urine samples. Children and adults were participants in study 2 and provided tee shirt and urine samples. Because of this, EPA can only rely on this research if EPA determines that reliance on the data may be crucial to EPA's decision to improve public health protection by imposing a more stringent regulatory restriction than could be justified without the data. If OPP determines this, under 40 CFR §26.1706, EPA must first complete three required steps. EPA must obtain the views of the Human Studies Review Board, provide an opportunity for public comment, and publish a full explanation of its decision to rely on the data, including a thorough discussion of the ethical deficiencies of the underlying research and the full rationale for finding that EPA met the standard in 40 CFR §26.1706 (c) (i.e., that the research is essential to a more stringent regulatory action to improve protection of public health).

The conduct of studies 1 and 2 was not deficient relative to the ethical standards prevailing at the time the research was conducted. If EPA's Office of Pesticide Programs makes the aforementioned determination and implements the required steps identified above, there is no regulatory barrier to EPA relying on this research in actions taken under FIFRA or §408 of FFDCA.

Attachment 1: ORD file with relevant information *(Note: Please see separate ORD file.)*
Attachment 2: OPP Interview with Primary Investigator
Attachment 3: Completeness Checklist for Ethics Documentation

Attachment 2

Questions for Principal Investigator Dr. Chambers – November, 2015

This attachment provides responses to questions posed to Dr. Janet Chambers regarding Study1 and 2 referenced in the Davis et al research article.

Background:
The EPA supported the research described in the published article through the STAR grant program and issuance of two grants (R8251770 and R828017). The Office of Research and Development (ORD) had a copy of ORD's review of the proposed research entitled, "Assessing Levels of Intermittent Exposures to Children to Flea Control Insecticides from the Fur of Dogs," funded under R8251770. This ORD file of research is referenced in some of the questions.

1) Were you the primary investigator for study 1 and 2 referenced in the Davis article?

Response: I was the principal investigator.

2) The research related to TCVP described in the ORD file appears to relate to the two studies discussed in the Davis article. Do you agree that this is the case?

Response: Yes, I agree.

3) A) Were the consent forms included in the ORD file the same as the consent forms used in Study 2 referenced in the *Davis et al* article? These consent forms include the minor's assent form and the adult's authorization for participation in the research involving flea collars.

Response: The consent forms would have been updated based on the comments from ORD on the draft.

B) Do you recall if the families received signed copies of the consent forms?

Response: I do not recall.

C) Do you recall if you addressed ORD's comments on the consent forms before using them?
Response: We would have had to address ORD comments in order to receive the STAR grant funding. Given that we received the STAR grant funding, I'm assuming we addressed their comments before finalizing the consent forms.

D) Do you recall if you resubmitted the revised forms to the IRB for their approval?
Response: I don't recall. But it would have been standard procedure to resubmit the revised consent form(s) to the IRB so I'm assuming that we did that.

4) A) Regarding the *Davis et al* article and studies 1and 2, were the students enrolled in the veterinary medicine curriculum at the College of Veterinary Medicine, Mississippi State University the only "samplers" who petted the dogs?

Response: As far as I know, yes, they would have been the only samplers.

B) Did you consider these students to also be human subjects?

Response: No, we did not. We considered them to be technicians involved with the study.

C) Do you know whether the MSU IRB considered the petting element of the study to be "human research"?

Response: No, they did not.

D) Do you recall if the students were compensated for their participation?

Response: It's likely that the students would have been conducting clinical veterinary rotations. We probably compensated them in some way for their time.

5) Regarding the compensation discussed on page 19 in the ORD file, do you recall if this same compensation was used for study 2 discussed in the Davis article?

Response: Yes, this would have been the compensation. (Dr. Chambers noted that part of the compensation discussed in the ORD file only related to Study 2.)

6) Were the names of participating subjects kept confidential?

Response: Yes.

5) Here is some background information included in the ORD file: For the study "Assessing Levels of Intermittent Exposures to Children to Flea Control Insecticides from the Fur of Dogs" submitted to ORD, page 13 of the ORD file indicates that dogs involved in the study must be enrolled in the Small Animal Community Practice Health Maintenance program and would belong to professional (DVM) or graduate students enrolled in the College of Veterinary Medicine or staff/faculty members of MSU with children in the household who routinely play with their pet dog. Page 19 of the ORD file states that, "in the unlikely event that insufficient numbers of households can be enrolled for the study, we will open the participation to students, faculty, and staff members of Mississippi State University outside of the College of Veterinary Medicine; these individuals would be offered the same incentives."

The Davis article talks about 2 studies that involved families in Oktibbeha County, Mississippi and the families' pet dogs.

a) Do you recall how the families in Study 2 were recruited?

   Response: I do not. I'm assuming that we probably circulated a flyer.
   Do you recall how the adult and child from each household was selected?

   Response: I do not.

If not, the ORD file indicates that Dr. John Tyler was responsible for recruitment. Do you know how we can reach Dr. Tyler?

Response: You could try the address included in the footnote of the article.

b) Do you recall if the participating families included adults who were members of the University?

Response: Yes, they probably would have been. Oktibbeha County is where the University is located.

7) The paragraph on page14 of the ORD file that's entitled "selection of human test subjects," states in part that: The age, sex, height and weight of both child and adult test subjects will be recorded, and the adult will be asked to give an estimate of the amount of time and degree of contact that the child and adult had with the dog on the day of the tee shirt sample. Do you recall if this information recorded was also recorded during study 2?

Response: Yes, this information would have been recorded. We gave a sheet to the participating family and asked the adult to record the estimated amount of time and contact the child and adult had with the dog on the day of the tee shirt sample.

8) Are the raw data which support the exposure outcomes of the studies available for further evaluation by EPA?

Response: I don't know. I will look to see if I can access it and will get back to EPA and let you know.

Attachment 3

§ 26.1303 Checklist for Completeness of Reports of Human Research Submitted for EPA Review

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

	Requirement	Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.	Y n/a Y n/a	The Davis et al article describes the research. The ORD file provided to the HSRB contains a research proposal and draft consent forms that were reviewed by EPA.
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.	N	Mississippi State University's (MSU's) Assistant Director for Human Research Protection Program / Office of Research Compliance confirmed that the MSU IRB did not retain records beyond the required retention time. She noted that: "Per 45 CFR 46.115(b) 'the records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research'. This requirement is consistent with our Standard Operating Procedure 01-27 Records of the HRPP which states that records will be maintained for at least 3 years after the study has closed."
	§1115(a)(3): Records of continuing review (CR) activities.	N	See comment above.
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	Y	The ORD file provided to the HSRB with the ethics memo provides "certification of IRB approval and institutional endorsement."
	§1115(a)(5): • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution	Y Y	The ORD file includes a list of IRB members at the time the research proposal was submitted to EPA. It references affiliations with MSU.
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).	Y	The written procedures for the IRB are posted on the MSU IRB website.
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).	n/a	
(b) Copies of all of the	§1125(a) A discussio	(1) The potential risks to human subjects;	Y	Statement regarding primary mechanism of toxicity of TCVP is included in research article. Toxicity of TCVP discussed in research proposal in ORD file

Requirement	Y/N	Comments/Page References
		The consent form in ORD file discusses researchers' perspective on risk to participants.
(2) The measures proposed to minimize risks to the human subjects;	N	The consent form in ORD file discusses researchers' perspective on risk to participants.
(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	Benefits are discussed in Davis et al research article and in ORD file in research proposal (e.g. approach section and section on improvements in risk assessment/management).
(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	N	The research proposal in ORD file explains why study as proposed is needed (in section on improvements in risk assessment / Management.)
(5) The balance of risks and benefits of the proposed research.	N	The benefits of the proposed research is discussed. Researchers did not see risk to participants in study given that the families involved already used flea collars on their dogs.
§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	There is evidence of IRB approval and draft consent forms in ORD file provided to HSRB.
§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	There is information in the Davis et al research article and in the research proposal in the ORD file.
§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.	Y	The draft consent forms are included in the ORD file provided to the HSRB.
§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y But see note.	Note: The ORD file includes certification of IRB approval and institutional endorsement.
§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.	Y	The ORD file includes certification of IRB approval and institutional endorsement.
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research	Y	The ORD file includes draft consent forms.
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.	Y	EPA reached out to the MSU IRB to attempt to obtain documentation. MSU IRB confirmed that they did not maintain records beyond required retention time.