



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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

December 16, 2015

MEMORANDUM

SUBJECT: Materials for Review by Human Studies Review Board for its
January 12 - 13, 2016 Meeting

TO: Jim Downing
Designated Federal Official
Human Studies Review Board
Office of Science Advisor (8105R)

FROM: Maureen Lydon
Human Research Ethics Review Officer
Office of the Director
Office of Pesticide Programs (7501P)

This memorandum describes the materials that the Environmental Protection Agency's (EPA's) Office of Pesticide Programs is providing for review by the Human Studies Review Board (HSRB or Board) at the teleconference and virtual meeting scheduled for January 12 - 13, 2016. During the January discussion, EPA will ask the Board to respond to specific science and ethics questions focused on the research identified below.

1. Research discussed in the article 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, from the *Journal of Exposure Science and Environmental Epidemiology* (2008) 18, 564-570; and
2. Five completed studies focused on "Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support their Use of the EPA Repellency Awareness Graphic"

TCVP Research Article

The article 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, discusses 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).

As discussed in EPA's science review memo, for purpose of risk assessment, EPA is proposing that the transferable residue data from the Davis study be used to assess the potential from residential post-application exposures to adults (non-cancer and cancer) and children (non-cancer only) from actively registered TCVP pet collars. The transferable residue data have been determined to be acceptable for regulatory purposes. As discussed in EPA's ethics review memo, the conduct of studies 1 and 2 was not deficient relative to the ethical standards prevailing at the time the research was conducted. As explained above and in EPA's ethics review memo, consistent with 40 CFR §26.1706, EPA must obtain the views of the Human Studies Review Board (HSRB).

Charge Questions:

Science:

1. Is this research scientifically sound, providing reliable pet fur transferable residue data for use in evaluating potential exposures of adults and children from contact with pets treated with tetrachlorvinphos containing pet collars?

Ethics:

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?

Five Completed S.C. Johnson Mosquito Repellent Studies to Support Use of EPA Repellency Awareness Graphic

EPA would like to discuss with the board five completed studies focused on "Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support their Use of the EPA Repellency Awareness Graphic." The five studies are all based on the same protocol and are listed in the "documents" section of this memo.

The protocol for this study was approved by the overseeing institutional review board, the Schulman Associates Institutional Review Board (SAIRB), and submitted to EPA in draft form for review. The protocol and EPA's review, dated March 31, 2015, were discussed in a public meeting by the Human Studies Review Board (HSRB) on April 22-23, 2015. Per the final HSRB meeting report, dated June 23, 2014, the HSRB concluded that "the amended protocol, when approved by the SAIRB, should meet all applicable ethical standards for the protection of human subjects of research, and all requirements for documentation of ethical conduct of the research. If this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA's reliance on it in actions under FIFRA or Section 408 of FFDAC."

Copies of the five completed studies based on the protocol have been mailed to each HSRB member. The science and ethics review memos for each study are being provided via email to the HSRB.

The purpose of these studies was to establish the complete protection time (CPT) of specific insect repellent products, previously registered and assessed by EPA, in the field against populations of wild mosquitoes, using human subjects. These data are required to establish the median complete protection time (CPT) against mosquitoes for use in the EPA Repellency Awareness Graphic on pesticide product labels. The studies were conducted in substantial compliance with the applicable requirements of 40 CFR 26, subparts K and L. EPA also has concluded that the studies provide scientific data that are acceptable.

Charge Questions Applicable to Each Study:

Science:

1. Is the study sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?

Ethics:

2. Does the available information support a determination that the research was conducted in substantial compliance with 40 CFR part 26, subparts K and L?

Documents for Review:

TCVP Research Article

1. Article 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, from the *Journal of Exposure Science and Environmental Epidemiology* (2008) 18, 564-570. This article is accessible at: <http://www.readcube.com/articles/10.1038%2Fsj.jes.7500647>

OPP is hoping to receive a copyright release from the publisher. If that occurs, EPA can email a copy of the published article to the HSRB members.

2. Ethics Review of Davis et al Research on Flea Collars with TCVP. (Attachment 1 to the ethics review is being transmitted to the HSRB as a separate file.)
3. Science Review of “Davis et al., 2008. Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos” for HSRB Consideration

Mosquito Repellent Studies

1. Mark 5 Study

Laznicka, E. (2015) Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic –Project Number 867E1.

Unpublished document prepared by S. C. Johnson & Son, Inc., 1525 Howe Street Racine, WI 53403, October 21, 2015, 150 p. (MRID 49765901) (D430181)

2. Mark 2 Study

Palm, J. M. (2015) Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic – Project 864E1. Unpublished document prepared by S. C. Johnson & Son, Inc., 1525 Howe Street Racine, WI 53403, September 24, 2015. 154 p. (MRID 49750201) (D430001)

3. Mark 4 Study

Laznicka, E. (2015) Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic – Project Number 866E1. Unpublished document prepared by S. C. Johnson & Son, Inc., 1525 Howe Street Racine, WI 53403, October 21, 2015. 149 p. (MRID 49766001) (D430168)

4. Mark 3 Study

Palm, J. (2015) Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic – Unpublished document prepared by S. C. Johnson & Son, Inc., 1525 Howe Street Racine, WI 53403. September 24, 2015. 149 p. (MRID 49750101) (D430002).

5. Mark 8 Study

Talbert, C. (2015) Field Testing of S.C. Johnson Personal Mosquito Repellent Products to Support Their Use of the EPA Repellency Awareness Graphic – Unpublished document prepared by S. C. Johnson & Son, Inc., 1525 Howe Street Racine, WI 53403. October 21, 2015. 154 p. (MRID 49761601)(D430082)

6. Five EPA ethics review memos, one for each of the aforementioned completed studies.
7. Five EPA science review memos, one for each of the aforementioned completed studies.
8. SAS program and excel file. The excel file contains the repellency duration data for the 5 completed studies. The SAS program uses that excel file and calculates the median CPT (using Kaplan Meier) and 95% confidence interval for each of the five studies.