



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

OFFICE OF
PREVENTION, PESTICIDES AND TOXIC
SUBSTANCES

May 29, 2009

MEMORANDUM

SUBJECT: Ethics Review of Chlorpyrifos Worker Exposure Study

TO: Anna Lowit, Ph.D.
Health Effects Division

FROM: John M. Carley
Human Research Ethics Review Officer
Office of Pesticide Programs

REF: Honeycutt, R., and M. DeGeare (1993) Worker Reentry Exposure to Chlorpyrifos in Citrus Treated with Lorsban® 4E Insecticide. Unpublished study prepared by H.E.R.A.C., Inc. under study numbers 91-102HE and DECO-HEH2.2-1-182(125)B. 950 p. (MRID 43062701)

Dow AgroSciences (2009) Supplemental Documentation of Ethical Conduct of Honeycutt and DeGeare Study. E-mail submission of May 22, 2009 from Kenneth Racke to Tom Myers. 27 p.

I have reviewed the referenced documents with care, and have concluded that there is no statutory or regulatory barrier to EPA's reliance on this research in its actions under FIFRA or FFDCA.

A. Summary Assessment of Ethical Conduct of the Research

In this study five adult male workers were monitored for dermal and inhalation exposure to chlorpyrifos while picking oranges 43 days after the grove was treated with Lorsban® 4E, and ten more adult male workers were monitored for dermal and inhalation exposure to chlorpyrifos while they pruned lemon trees 2 days after treatment with Lorsban. All fifteen of these subjects also provided blood and urine samples which were analyzed for cholinesterase activity and the presence of chlorpyrifos or its metabolites. In addition, an unreported number of additional workers provided work clothing to the investigators for analysis of chlorpyrifos residues to estimate background levels of contamination in facilities used in the course of field research.

Monitoring of re-entering workers was conducted concurrently with a similar worker exposure study with chlorpyrifos mixers/loaders and applicators in the same area at the same time; in their supplemental submission (pp. 1-2) Dow AgroSciences reports that the workers who provided clothing samples for analysis were consenting participants in the companion study. Field monitoring was conducted at citrus groves in Tulare and Lake Counties in California. Re-entering orange pickers were monitored in December 1991; pruners were monitored in March and April 1992.

Value of the Research to Society: The objective of this study was described in the protocol as “to monitor the exposure of agricultural workers who reenter citrus groves treated with LORSBAN® 4E. The exposure will be measured using dosimetry, biological monitoring, and foliar dislodgeable residue methods. . . . This protocol is intended to apply to citrus and other tree fruit crops.” The purpose of the study was described in the completed study report as “to determine the potential exposure of chlorpyrifos to individuals, who may reenter a citrus grove after treatment with Lorsban 4E in order to maintain the grove (prune trees), or harvest the treated citrus, and who may be exposed to chlorpyrifos in the air or by contact with dislodgeable residue on plant surfaces.” The study was funded by DowElanco, the registrant of Lorsban® 4E, and was undertaken to meet the requirements of re-registration for chlorpyrifos. EPA now proposes to use selected data from this study to support the analysis of animal testing and epidemiological data on developmental effects of chlorpyrifos.

Subject Selection: The fifteen subjects monitored were all experienced citrus workers employed by Mr. Gary Austin of Leffingwell Ag Sales Co. of Terra Bella CA, who also selected the sites at which monitoring was conducted. Monitored subjects were described as males in apparent good health; their ages were not reported. All had Hispanic names. Mr. Austin’s role in recruiting subjects for this research is described as working “through growers and service groups which typically recruit professional citrus pickers and citrus tree pruners.” The report is unclear about exactly what role was played by Mr. Austin in recruiting his own employees as subjects in this study; subjects may have been vulnerable to his influence over their decision to participate in the study. Neither the protocol nor the completed study report mentions any steps taken to protect the subjects from undue influence. The discussion of protocol Deviation 74 (p. 341) mentions that “the availability of test volunteers was severely limited and the discretion of the study director occasionally was used to select a volunteer” [even when background levels of urinary metabolites of chlorpyrifos exceeded the threshold defined in Amendment 16.]

In addition to these fifteen subjects, Deviation 31(2)(a) (p. 320) reports that twelve candidates—two more than were eventually monitored—provided urine samples for a pretest of baseline levels of urinary metabolites of chlorpyrifos. These two additional subjects may have been alternates, mentioned in correspondence from the study director to CDFA (DAS Supplement, p. 15 of 27), but the addition of alternate subjects is not addressed in an amendment, as it should have been.

As noted above, an unreported number of employees of the commercial applicator companies whose facilities were used by the investigators as local bases of operations

provided samples of their work clothing for analysis to estimate background contamination levels at these facilities. This sampling activity was added by Amendment 16, but the workers providing the samples were not considered subjects of this research, as they should have been.

Risks and Benefits: Risks and benefits of the research are not discussed in the protocol or completed study report. The consent form approved by the IRB on October 16, 1991 (DAS Supplement p. 10 of 27) and used for the picker-monitoring activity in December 1991 characterized risks of chlorpyrifos in these terms:

Lorsban 4E is of low toxicity but as a pesticide, has the potential to cause health effects if the exposure is great enough. For example, you would have to drink 8 ounces (a small cup) of straight LORSBAN 4E to cause death. You will not get much more than 8/100 of an ounce of LORSBAN 4E on your skin during picking of citrus. Therefore the risk of getting sick from picking LORSBAN-treated fruit is extremely low. This study will result in no increased health risks as I will be doing my job wearing normal protective clothing as called for the by the Lorsban 4E label and will be entering the orchard 21 days after spraying which will give ample time for residues of LORSBAN on fruit to disappear.

No unusual discomforts are expected from wearing the test clothing since this is the type of clothing that is normally worn during the picking of LORSBAN 4E treated citrus.

Participation in research may involve a loss of privacy. . . Your name will not appear in the final report.

The discussion of risks in the revised consent form approved by the IRB on March 18, 1993 and used for the pruner-monitoring activities in March and April 1993 (DAS Supplement pp. 21-22 of 27) was unchanged except for substituting “pruning” for “picking” at two locations and in the last sentence of the first paragraph quoted above, which was altered to read (emphasis added):

This study will result in no increased health risks as I will be doing my job wearing normal protective clothing as called for the by the Lorsban 4E label and will be entering the orchard 2 days after spraying which will give ample time for residues of LORSBAN on fruit to disappear.

It is implausible that workers reentering a treated citrus grove two days after treatment were expected to receive the same exposure as workers reentering 21 or 43 days after treatment, or that all residues of Lorsban were expected to have disappeared after either 2 or 21 days.

Both generations of approved consent forms said further (DAS Supplement pp. 11 and 23 of 27), concerning the benefits of the research:

There are no direct benefits to the participants in this study. However, the information and samples that I provide will help DOWELANCO, the EPA and

CDFA determine any excessive risks that may be involved in [picking/pruning] citrus treated with Lorsban 4E. My participation will also help scientists to understand more about pesticide exposure to workers like myself.

Neither the protocol nor the study report discusses how the investigators or the IRB weighed likely benefits of the research against the risks to individual subjects.

Independent Ethics Review: The original and amended study protocols were reviewed and approved by the Committee on Human Research at the University of California, San Francisco, working under contract to the California Department of Food and Agriculture/ California Department of Pesticide Regulation, who brokered the IRB review of the research. Critical gaps in the record of these reviews in the primary study report are filled by the DAS Supplement, which includes the approved protocol used for monitoring pickers (pp. 7-14), correspondence explaining the revisions made before monitoring of pruners (pp. 15-18), the text of the revised protocol used for monitoring pruners (pp. 19-26), and a copy of the IRB approval letter concerning the revised protocol (p. 27). The record does not show whether the amended protocol was provided to the IRB as well as the revised consent form; protocol amendments 2-20 were all signed long after their indicated effective date, and may not have been documented until the final report was being prepared. The revised consent form was approved after an expedited IRB review, notwithstanding the increased number of subjects, changed procedures and increased number of samples taken, and the increased exposure of subjects.

Informed Consent: According to the study report, “prior to the initiation of the study, the volunteers were briefed in Spanish/English on the design of the study, potential exposure to chlorpyrifos, toxicity of chlorpyrifos (acute and chronic), as well as potential risks involved in participating in the research. . . . The acknowledgement and consent forms for all volunteers are found in the raw data.” (p. 59)

The consent forms included in the DAS Supplement were approved by the IRB and used in the research. They are above average for the period when this work was conducted, and meet basic standards for content. They are, however, misleading with respect to the margin of exposure. As noted above, the discussion of risk in the revised, pruner consent form states that all Lorsban residues were expected to have disappeared within 2 days of treatment; the picker consent form states that residues were expected to have disappeared after 21 days. Both these statements may have misled participating workers; they were certainly shown to be untrue by the eventual residue data collected from dosimeters. Both versions of the consent form erroneously describe the timing of some sampling procedures relative to the day of spraying—an apparent carryover from the companion handler study consent form—when the appropriate frame of reference for this study would have been the day of reentry.

Respect for Potential and Enrolled Subjects: The consent form informed subjects that they were free to decline to participate or to withdraw from the research without affecting their employment. As noted above, it is not reported what steps, if any, were taken to ensure that their recruiter/employer did not exercise any undue influence over their choices.

Although subjects were assured in the consent form that their names would not appear in the final report, their privacy was severely compromised by including the full names and Social Security Numbers of all monitored subjects in Appendix F to the study report (pp. 443-447).

B. Applicable Standards

This research was initiated in the fall of 1991, a few months after promulgation of the Common Rule and many years before EPA's amended Rule for the Protection of Human Subjects of Research became effective on April 7, 2006. It was conducted in California, where state regulations in effect at the time (CCR Title 3, Section 6710, as amended 26 Sept 1988, copy attached) required pre-study approval by the Director of the California Department of Pesticide Registration and by an IRB registered with the U.S. Department of Health and Human Services.

The report of this research was submitted to EPA in December 1993, 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 supplemental material provided by Dow AgroSciences was submitted voluntarily.

This research meets the definition of "research involving intentional exposure of a human subject" in the rule at 40 CFR §26.1102(i) because it involved monitoring of scripted exposure to residues of product provided by the sponsors under conditions specified by the investigators. The Agency's rule defines standards for EPA to apply in deciding whether to rely on research involving intentional exposure of human subjects. (See 40 CFR §26 subpart Q.) The acceptance standards applicable to this research 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.

§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.

C. Compliance with Applicable Standards

This research was reviewed and approved in advance by the Committee on Human Research, UCSF, as were amendments made before pruner monitoring in 1992. Although there is no direct evidence of prior approval by the Director, CDPR, the record clearly shows that the investigators were working through CDPR in their correspondence with the UCSF IRB. The consent forms state that “CDFA is overseeing this study and coordinating this application of the contractor to the Committee on Human Research.” The research appears to have complied with the substance of the California state requirements.

The fifteen subjects monitored in the study were all males, and as experienced agricultural workers can be presumed to have been adults. In the absence of any information suggesting that any of the subjects were under 18, 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 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.”

As noted above, the available evidence indicates substantial compliance with the California state requirement for prior approval by a registered IRB and by the Director of CDPR. The letter of approval from the UCSF Committee on Human Research (CHR), however, states clearly that “all protocol changes involving subjects must have prior CHR approval.” (p. 417) Many of the reported 20 amendments (pp. 290-310) and 81 deviations (pp. 311-343) did “involve subjects” and thus should have been reported to the IRB; many of the amendments to study procedures and schedules should have been reflected in an appropriately revised consent form. Of particular concern are the following amendments and deviations:

- A-10 (p. 300), D-31 (p. 318-325), D-74 (p. 341)

Addition of pre-screening for 3,5,6-TCP in urine of candidates significantly changed procedures and eligibility criteria. Although it is reported in A-10 that “potential study participants will be allowed to read and sign the consent form prior to collecting this sample” and further (D-31, p. 320) that 12 volunteers were screened for 10 slots in the two pruner field studies, it is not stated whether candidates were actually all consented before providing the first pre-test urine samples. Deviation report #74 (p. 341) further indicates that even after this amendment, because “the availability of test volunteers was severely limited”, the study director accepted some volunteers with background levels of 3,5,6-TCP above the threshold level defined in A-10.

- A-11 (p. 301), D-2 (p. 311), D-5 (p. 312), D-12 (p. 314), D-15 (p. 315)

This change from testing only pickers re-entering after 21 (or more) days to testing pruners re-entering after 2 days resulted in enrolling five more subjects than previously planned and in exposing ten subjects to different and probably higher levels of residues of chlorpyrifos than were associated with the original design.

- A-16 (p. 306)

This amendment adds to the protocol's list of materials to be analyzed "certain typical work clothes including but not limited to pants, shirts, shoes, boots, etc., (these are not to be test dosimeters but work clothes from employees of the commercial applicator). . . ." It is characterized as adding matrices for analysis, but in fact, by collecting clothing for analysis from workers not otherwise involved in this research, it added those workers to the ranks of the subjects of the research. It is reported in the DAS Supplement that the workers providing the sample clothing were consenting participants in a concurrently conducted study of handler exposure; nonetheless their participation in this study should have been acknowledged.

- D-8 (p. 313) and D-16 (p. 315)

Both these deviations report that wearing protective sleeves was standard practice among both pickers and pruners to protect themselves from citrus thorns, but that this was unknown when the protocol was developed. Once the investigators learned of the practice, workers were permitted to wear the sleeves and the sleeves were collected and analyzed. This should have been addressed in an amendment to the protocol and accompanying changes to the consent form. That the investigators were unaware of this practice suggests less than adequate preparation for the research, which was intended to monitor exposure of workers wearing their normal protective clothing. It is troubling that appropriate changes were not made in the amended consent form for pruners after the investigators learned of the practice of wearing protective sleeves in the earlier monitoring of pickers.

- D-11 (pp. 313-314)

This deviation reports that the investigators were unaware that citrus pickers and pruners do not work by the hour, or typically take rest or meal breaks during their work day. This suggests less than adequate preparation for the research, which was intended to monitor exposures of workers engaged in their normal work practices. Again appropriate changes were not made in the amended consent form once the investigators became aware of this practice.

- D-25 (p.317)

This deviation reports the discovery by the investigators that re-entrant citrus pickers and pruners were not, as they had thought, required by the state of California to be monitored for cholinesterase inhibition. This suggests less than adequate preparation for the research, and again no changes were made in the amended consent form when the investigators learned of the change.

Although there are significant gaps in the documentation of the ethical conduct of this research, such gaps do not in themselves constitute “clear and convincing evidence.” In fact, the conduct of this study is much better documented than most field exposure research from this period. I found no evidence that this research was fundamentally unethical. Based on the evidence that its conduct was supervised by the California state authorities, I conclude that it met the standards of ethical conduct for this type of research prevailing when it was conducted. I found no clear and convincing evidence to the contrary.

In this study, researchers informed the 15 monitored 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 FIFRA §12(a)(2)(P) or in 40 CFR §26.1703 or §26.1704 to EPA’s reliance on this study 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.

Attachment: CCR Title 3, Section 6710 (26 Sept 1988)

California Code of Regulations, Title 3

Action taken 26 Sept 1988

Amend Section 6710 to read:

6710. Studies on Pesticide Safety.

- (a) No person shall conduct any study in which human subjects are to be experimentally exposed to pesticides, unless the director has approved the study. Each applicant shall give assurance (1) that the health of the participants is not likely to be endangered, (2) that participants shall be informed of the potential risks, and (3) that all persons that might be exposed will be under medical supervision. Any university or medical institution in California which has a Human Subjects Review Committee approved by the U. S. Department of Health and Human Services to review studies on human beings shall be considered to have complied with the above for studies as approved by the committee.
- (b) The director shall deny approval for studies which do not meet the criteria specified in subsection (a). The director may consult the State Department of Health Services for advice regarding approval when he or she determines this to be necessary.
- (c) Any recommendations by the Human Subjects Study Committee of the California Health and Welfare Agency for protecting the health of persons who may be exposed to pesticides shall be conditions on the approval of these studies.
- (d) The commissioner or director may order any employee exposure in these studies to cease immediately and the director may summarily cancel approval whenever it is deemed advisable in the interest of employee or public safety.

NOTE: Authority: Sections 407 and 12981, Food and Agriculture Code.

Reference: Sections 12980 and 12981, Food and Agriculture Code.