MEMORANDUM

SUBJECT: Ethics Review of Exposure Study Involving Applicators in Vineyards Using Handheld Foggers

FROM: Michelle Arling, Human Studies Ethics Review Officer
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Office of Pesticide Programs

TO: Dana Vogel, Director
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REF: Thouvenin, I, Bouneb, F, Mercier, T. Operator dermal exposure and individual protection provided by personal protective equipment during application using a backpack sprayer in vineyards. Journal of Consumer Protection and Food Safety. (2016) 11:325-336. DOI: 10.1007/s00003-016-1049-z

I have reviewed available information concerning the ethical conduct of the study with human subjects referenced above. In addition to published article referenced above, available information includes the study's design document and consent form, obtained through correspondence with one of the study's authors, Thierry Mercier. If the research is determined to be scientifically acceptable, I find no barrier in regulation to the U.S. Environmental Protection Agency's reliance on this research article in actions under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) or §408 of the Federal Food, Drug and Cosmetic Act (FFDCA). The EPA will consult with the Human Studies Review Board (HSRB) on this study.

Summary Characteristics of the Research

The study was conducted "to monitor the dermal exposure of operators using … mist-blower power sprayers for application of fungicides in vineyards" (p. 325) and to evaluate the effectiveness of the personal protective equipment (PPE) worn by the applicators. The study was "based on the whole-body dosimetry method documented in the Organisation for Economic

Cooperation and Development" (p. 326)[1]. A fungicide (Selva®) that contained cymoxanil was used for the study. The study was conducted in France and funded by ANSES, the French agency for food, environmental, and occupational health and safety.

A total of 10 male applicators were enrolled in the study: 4 individuals who worked for a vine growing farm and 6 individuals from a contract application company (p. 326). The applicators were monitored while performing using their own equipment and engaging in their normal application practices. Applicators wore two dosimeters – an inner dosimeter, which was a 2-piece cotton garment, and an outer dosimeter, which was a coverall. Hand exposure was measured through a standard hand wash procedure, conducted at times the applicator would normally wash their hands and at the end of the day. Applicators also wore gloves, which were collected and analyzed. Head exposure was measured through analysis of the coverall hood and a bandana worn on the head (at the applicator's discretion).

To obtain more information, I contacted the corresponding author, Thierry Mercier. Mr. Mercier provided the consent form and study design document. The consent form was provided in French; a translated version is included as an attachment to this memo. Mr. Mercier requested that the study design document be considered confidential. Where necessary, it has been referenced, but the full document will not be made public with this memo.

1. **Value of the Research to Society**: The objective of this study was to assess the protective factor of personal protective equipment worn by applicators using handheld foggers in vineyards. Monitoring applicators under their normal conditions and analyzing the dosimeters for residues provides the best estimate of exposure. The data generated from this study can be used to refine risk assessments and to establish the level of protection provided by various types of PPE.

2. **Subject Selection**:

   a. ***Demographics.*** The study included 10 male subjects, ranging in age from 24 years old to 55 years old. Subjects had from 0.2 years to 38 years of experience performing the tasks monitored (p. 327).

   b. ***Eligibility Criteria.*** The study design document notes that applicators were required to have experience performing the tasks being monitored, consider themselves in good health, be willing to participate in the study, and be willing to provide written consent to participate.

   c. ***Recruitment.*** No information on subject recruitment is included in the article or study design document. Mr. Mercier noted that growers were contacted for potential participation in the study, and that employers were told that it was necessary for the applicators to have freedom to choose whether to participate.

3. **Risks and Benefits**:

[1] OECD/GD (97)148 (1997) Guidance document for the conduct of studies of occupational exposure to pesticides during agricultural application. OECD Environmental Health and Safety Publications, Paris. https://one.oecd.org/document/ocde/gd(97)148/en/pdf

a. ***Risks.*** Workers enrolled in the study were performing their normal work tasks and wearing their normal PPE, subjecting them to risks from exposure to the pesticide and risk of heat-related illness. Subjects faced a small risk of skin irritation from the hand washing and risk of embarrassment from having a study staff person assist them with donning and doffing the dosimeters. The additional risks associated with participation in the study were minimal beyond the risks associated with the workers' normal tasks.

b. ***Benefits.*** There were no directs benefits to the subjects participating in the study. ANSES benefited from the generation of data of this study to better understand the level of protection provided by PPE and the predicted levels of occupational exposure experienced by vineyard applicators using handheld foggers. Accurate data on exposure and PPE performance can be used to inform risk assessments.

c. ***Risk-Benefit Balance.*** Risks to subjects were effectively minimized within the study design. The potential societal benefits of understanding the protection offered by the use of PPE during handheld fogger spraying in vineyards and the exposure patters of workers outweigh the risks associated with the study.

4. **Independent Ethics Review**: There is no information about independent ethics review of the research in the study report. According to the publication, "[t]he study is based on the whole-body dosimetry method documented in the Organisation for Economic Cooperation and Development (OECD 1997)" (p. 326).[2] The OECD document does not include a recommendation or requirement for independent ethics reviews for whole-body dosimetry studies. Dr. Mercier confirmed that the study did not undergo independent ethics review.

5. **Informed Consent**: The publication does not include information about subjects' consent to participate. The study protocol noted that a signed informed consent form would be obtained from each worker prior to his participation in the study. The consent process included providing the potential subjects with a full explanation of the study and its requirements, and any potential risks. It also included a discussion of the individuals' right to withdraw from the study at any time and for any reason without jeopardizing their employment.

Dr. Mercier confirmed that the subjects provided written informed consent and shared a copy of the consent form in French. The consent form covers the voluntary nature of participation, describes the purpose of the study and study procedures, explains measures to be taken to protect the subjects' identities, and discusses the risks and benefits of participation. Lastly, the consent form includes the subjects' right to not enroll or to withdraw from the study at any point without giving a reason and without incurring penalty.

6. **Respect for Subjects**: The consent form notes that subjects were free to withdraw at any time, for any reason, and without forfeiting benefits to which they were entitled. The consent form notes that every effort to protect subjects' confidentiality would be made.

[2] Organisation for Economic Co-operation and Development. Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application. OCDE/GD(97)148. 1997.

Subjects' identities were protected; subjects were identified by number and no subject's identity was revealed in the study report.

No subjects withdrew or were withdrawn from the study.

Applicable Standards

Standards Applicable to the Conduct of the Research

The portions of EPA's regulations regarding the conduct of research with human subjects, 40 CFR part 26 subpart A - L, do not apply since the research was neither conducted nor supported by EPA, nor was it conducted or supported by a person who did so with the intention to either to submit results of the research to EPA for consideration in connection with any action that may be performed by EPA or to hold the results of the research for later inspection by EPA under any regulatory statute administered by EPA.

The article notes that the study was conducted in accordance with the Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application.[3] This document notes that informed consent should be obtained from subjects, that subjects should be "told to use the pesticide and carry out work activities according to their normal practice" (OECD, p. 25), and that subjects should understand that they are free to withdraw at any time for any reason (OECD, p. 25).

Standards Applicable to the Documentation of the Research

EPA identified this study through a review of the public literature. No person has independently submitted the published article or any results of this research to EPA. Consequently, the requirements for the submission of information concerning the ethical conduct of completed human research contained in EPA regulations at 40 CFR part 26, subpart M do not apply.

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 this study—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(b).** EPA must not rely on data from any research subject to this section 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

[3] *Id.*

> 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.

The study was conducted in 2014. The prevailing ethical standards include the Declaration of Helsinki (2013), the Nuremberg Code (1947), and the Belmont Report (1979). The Declaration of Helsinki underwent a number of revisions through 2013; some of the key principles are:

1. Research must be scientifically sound and conducted by qualified personnel.
2. There must be a clear purpose and protocol, reviewed and approved by an independent ethics committee.
3. The importance of the study's objective must outweigh the inherent risks to subjects, and measures to minimize risks must be implemented. The interests of science and society should never take precedence over considerations related to the well-being of the subject.
4. Respect the privacy of subjects and confidentiality of their personal information.
5. Participants should give prior, informed, voluntary consent and have the freedom to withdraw from the study.

Some key principles of the Nuremberg code are that participation must be voluntary and the subjects must be informed of the nature, duration, and purpose of the test and hazards reasonably expected; the research must avoid unnecessary physical and mental suffering; the benefits must outweigh risks; and subjects must have freedom to withdraw. Three key principles from the Belmont Report are: respect for persons (e.g., informed consent); beneficence (as in "do no harm" and maximize benefits/minimize risks); and justice (including equitable selection of participants and avoiding the exploitation of vulnerable populations).

The Office of Pesticide Programs has a long-standing position that, although there may be gaps in the documentation of the ethical conduct of human research, deficient documentation does not itself constitute evidence that the ethical conduct of the study was deficient relative to the standards prevailing when the research was conducted.

Finally, I defer to scientists for a review of the scientific validity of this human research; if any of the research is determined not to have scientific validity, it would not be ethical to rely on it in regulatory actions under FIFRA.

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.

EPA will submit this study for review by the Human Studies Review Board (HSRB) in conformance with 40 CFR §26.1604.

Compliance with Applicable Standards

All of the subjects in this study were adult males. Therefore, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

There is no clear and convincing evidence that the conduct of the research was fundamentally unethical. All subjects provided informed consent to participate in the study. The application rate for the test substance was based on the labeled rate of use and applicators wore protective equipment for the duration of their participation, indicating no intent to seriously harm the participants existed. Based on these findings, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(b)(1).

The research was designed with a clear purpose and scientific objectives, and it was overseen by qualified personnel. The study team followed a written study protocol based guidance from OECD for conducing occupational exposure studies. Only self-reported healthy adults were eligible to enroll. Subjects used a pesticide product at the labeled application rate while wearing the label-specified PPE and performing their normal tasks. Subjects were required to provide written informed consent as a condition of enrolling in the study. Subjects received information about the study, potential risks and benefits, and the pesticide involved prior to enrolling in the study. The consent form made clear that participation was voluntary and that subjects could withdraw at any time. The risks to subjects were similar to the risks they would encounter while performing their normal work tasks and reasonable relative to the expected benefits of the research. The confidentiality of subjects was maintained during the study and in the publication of the article.

Given this information and the absence of any information suggesting that 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 or impaired their informed consent, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(b)(2).

The consent form included in the study report seems to satisfy the requirements of FIFRA §12(a)(2)(P).

Conclusion

I find no barrier in law or regulation to reliance on this research 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.

Attachments

Attachment 1: Consent form (translated)

Attachment 1
Consent form (translated)

Study Number: ChR-15-19603

Operator Identification No.: ___

CONSENT TO PARTICIPATE IN AN EXPOSURE STUDY
THE APPLICATOR

Titre de l'étude:

« Determination of operator dermal exposure and protective factors provided by personal protective equipment during foliar application using a backpack sprayer in vineyards »
French translation: Determination of skin exposure and protection factors provided by personal protective equipment (PPE) during foliar application using a vine backpack sprayer.

Study manager and telephone contact: For any questions
during or after the study, I can contact the study manager, representing ANSES (National Agency for Food, Environmental and Health Safety). work), [redacted] or the Study Director, [redacted].

Objective of the study:

I volunteer to participate in an experimental study conducted by STAPHYT on behalf of ANSES. The objective of this study is to better understand the level of protection provided by PPE and the levels of exposure to which I may be subjected during a working day in the context of foliar treatments on vines that I commonly practice in my profession.

For this study, I will use SELVA (containing cymoxanil and copper oxychloride) which will be provided to me by study staff.
The exposure levels will be estimated from the quantities of cymoxanil which will be measured on the one hand on the dedicated clothing that I will wear and on the other hand in the hand washing that will be carried out.

Procedure: If

I choose to volunteer for this study, I will have to carry out the treatment of the vines under normal practice conditions.
To carry out the various tasks in the study, I will wear equipment over my underwear to measure the quantities of product to which I will potentially be exposed: a long-sleeved t-shirt and long cotton underpants. . Over these clothes, I will wear a category III type 4 protective suit. I will also wear waterproof gloves (nitrile). This equipment will be my usual work equipment or the equivalent. All of these clothes will be provided to me by the study staff on the same day of the study.

The study staff will be responsible for explaining to me how to equip myself at the start of work. At the end of the work day (and during breaks if necessary), study staff will help me remove clothing used during work.

Under the guidance of study staff, I will also have to carry out hand washing operations (in order to recover any product that may be there).
Photographs or video recordings may be taken during my work.
These videos and photos will be kept by the study manager with the study archives.

Benefits: I have no direct benefit from participating in this study.

Risks incurred: As part of this study, the operator is not exposed to any risks other than during normal use of SELVA.

SELVA is dangerous for the environment (classified N, risk R50/53) but is not classified with respect to humans.

A copy of the safety data sheet and a copy of the label of the product that will be used during the study are available to me from the study team if I request them. I had the opportunity to ask any questions that seemed important to me and I am satisfied with the answers received.

I am experienced for the work that I will carry out as part of this study and I will comply with Good Agricultural Practices. I confirm that I have no health problems that could interfere with the study.

Confidentiality: All elements concerning me will be coded according to usual scientific practices.
No information about me will be given to anyone orally. The study report is a scientific document. The results concerning me will be transmitted to me personally if I request them but I must treat them confidentially. If a study report were published, it would not contain any identifying information.

My consent: My signature below indicates that I have chosen to volunteer for this experimental study and respect the requests above. I have the right not to accept or withdraw from the study whenever I wish, without reason, obligation, penalty or inconvenience to my employment. I understand the information above and have received a copy of this consent form.

_____

Name of participant and signature Date :

_____

Name of the Study Director’s representative and signature Date: