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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 16, 2009

MEMORANDUM

SUBJECT: Ethics Review of Pre-Rule Intentional Exposure Human Toxicity Study

TO: Mary Manibusan, MPH, Chief
Toxicology and Epidemiology Branch
Health Effects Division Division

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

REF: Lisi, P. (1992) Sensitization Risk of Pyrethroid Insecticides. *Contact Dermatitis*, 26:349-350. (MRID 47852801)

I have reviewed the referenced document and determined that all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied. If this study is determined to be scientifically valid and relevant, I find no regulatory barrier to EPA's reliance on it in actions under FIFRA or §408 of FFDCA.

Summary Characteristics of the Research

In this research, 230 subjects were patch tested with seven different pyrethroids (allethrin, cypermethrin, deltamethrin, fenothrin, fenvalerate, permethrin, and resmethrin) at three different concentrations (5%, 2%, and 1%). The research was conducted at the *Istituto di Clinica Dermatologica e Venereologia* at the University of Perugia, Italy. The research was reported in a "short communication" in *Contact Dermatitis* in May 1992.

The author reported two cases of irritant reactions to resmethrin, two cases of allergic reactions to fenvalerate, and one case of allergic reaction to cypermethrin, but the author stated without explanation that the reaction to cypermethrin "was not clinically relevant." (p. 349) The two irritant reactions to resmethrin were reported in non-atopic subjects with venous leg ulcers, and the two allergic reactions to fenvalerate were reported in subjects with chronic contact dermatitis of the hands. No other irritant or allergic reactions were reported. The author concluded that pyrethroids are "only very slight cutaneous irritants or sensitizers." (p. 350)

1. **Value of the Research to Society:** The author stated that "[t]he aim of the present study was to establish the irritation and sensitization risks of the most widely used pyrethroids." (p. 349) If deemed scientifically valid and relevant and ethically acceptable, this study will be considered in EPA's review of animal and human data concerning a potential relationship between exposure to pesticides containing pyrethroids and allergic responses.
2. **Subject Selection**: The 230 subjects included 162 men and 68 women, aged from 19 to 78, who were patients at the dermatological clinic where the research occurred. Eighty-two of the subjects were current agricultural workers, and 28 were former agricultural workers. Fifty-four of the subjects (18 of whom were current or former agricultural workers) had been admitted or treated for irritant or allergic contact dermatitis of the hands, and the remaining 176 had been admitted to the clinic for non-allergic skin disorders. No information is provided about how the subjects were approached or recruited into the study. There is no evidence suggesting that any subjects came from an especially vulnerable group.

3. **Risk-Benefit Ratio**: Risks and benefits of the research are not discussed in the article. The article does not identify societal benefits of the research or how they would be distributed, or the risks to individual subjects, or how the investigators weighed likely benefits of the research against the risks to individual subjects.

4. **Independent Ethics Review**: The article is silent concerning any independent oversight of the ethical conduct of the research.

5. **Informed Consent**: The article is silent about informed consent, but the subjects are referred to as "volunteers." (p. 349)

6. **Respect for Potential and Enrolled Subjects**: There is no identifying information about any of the subjects in the article. It is not reported whether subjects were free to withdraw from the research.

Applicable Standards

This research was conducted in Italy before May 1992, many years before EPA's amended Rule for the Protection of Human Subjects of Research became effective on April 7, 2006.

The summary description of the research was obtained from the published literature by EPA through its own efforts; because it was not submitted by an outside entity it is not subject to the requirements of 40 CFR §26.1303. EPA attempted without success to reach the author, hoping to obtain more information about the conduct of the research.

Standards Applicable to the Conduct of the Research

Although the research was conducted after §12(a)(2)(P) entered the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) in 1972, §12(a)(2)(P) does not apply to this research because it was conducted outside the territory of the United States, with no intention of submission to EPA.

The only widely recognized standard for ethical conduct for research performed in Italy in 1990 or 1991 (when this research was probably conducted) was the 1989 Declaration of Helsinki. The full text of the 1989 Declaration is attached.

Standards Applicable to EPA's Reliance on the Research

This work meets the definition of "research involving intentional exposure of a human subject" in the rule at 40 CFR §26.1102(i). 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.
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> **§26.1704. Prohibition of reliance on unethical human research with nonpregnant adults conducted before April 7, 2006.** Except as provided in §26.1706, in actions within the scope of §26.1701, EPA shall not rely on data from any research initiated before April 7, 2006, if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. This prohibition is in addition to the prohibition in §26.1703.

Compliance with Applicable Standards

The article is silent with respect to three of the basic principles of the 1989 Declaration of Helsinki – written informed consent, ethics oversight, and prior assessment of risks and benefits. Deficient documentation, however, does not itself constitute evidence that the research was inconsistent with these standards.

The 230 subjects in the study were all adults, and there is no evidence to suggest that any of the 68 female subjects were pregnant or nursing. Therefore, EPA's reliance on the study is not prohibited by 40 CFR §26.1703.

40 CFR §26.1704 forbids EPA to rely on data from pre-rule research—such as this study—if there is "clear and convincing evidence that the conduct of the research was fundamentally unethical…, or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted." The significant gaps in the documentation of the ethical conduct of this research do not meet the standard of "clear and convincing evidence." I found no evidence that this research was fundamentally unethical, or that its conduct was significantly deficient relative to standards prevailing when it was conducted. Therefore, 40 CFR §26.1704 does not prohibit EPA reliance on this research.

Conclusion

Although there are many significant gaps in the documentation of the ethical conduct of this study, there is no clear evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways. Gaps in documentation of ethical conduct of the research were common in published articles of this period, and do not constitute evidence that the ethical conduct of this study was deficient relative to standards prevailing when it was conducted.

I find no barrier in law or regulation to reliance on MRID 47852801 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

World Medical Association Declaration of Helsinki

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by The World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The Purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to

participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient–including those of a control group, if any–should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers–either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

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