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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 Pharmacokinetics Study

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

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

REF: Nolan, R.; Rick, D.; Freshour, N.; and Saunders, J. (1982) Chlorpyrifos: Pharmacokinetics in Human Volunteers Following Single Oral and Dermal Doses. Unpublished study prepared by the Dow Chemical Company under Protocol HEB-DR-0043-4946-4. 28 p. (MRID 124144)

Dow AgroSciences (2009) Supplemental Documentation of Ethical Conduct of Nolan *et al.* Study. E-mail correspondence April 29 through May 8, 2009, between Kenneth Racke and Tom Myers, with attachments. 22 p.

I have reviewed the referenced documents with care. Although there are gaps in the record of the ethical conduct of this research I conclude that there is no statutory or regulatory barrier to EPA's reliance on it in its actions under FIFRA or FFDCA.

A. Summary Assessment of Ethical Conduct of the Research

In this study six healthy adult male volunteers, all salaried employees of Dow Chemical Company, were given a single oral dose and one or two single dermal doses of chlorpyrifos. One subject participating in a pilot phase received a single oral dose of 0.5 mg/kg chlorpyrifos, one month later received a single dermal dose of 0.5 mg/kg chlorpyrifos, and two weeks later received a second dermal dose of 0.5 mg/kg chlorpyrifos. The other five subjects received a single oral dose of 0.5 mg/kg chlorpyrifos and four weeks later received a single dermal dose of 5.0 mg/kg. Doses were administered just after breakfast. Blood samples were drawn before dosing and at pre-selected intervals post-dose; urine was collected from 48 h pre-dose through 120 h post-dose. Blood and urine were monitored for chlorpyrifos and its principle metabolite;

in addition both plasma and erythrocyte cholinesterase activity was monitored. All subjects were monitored until cholinesterase activity returned to baseline levels.

The research was conducted in 1981-1982 at the Dow Chemical Co. facility in Midland Michigan. The study report was completed in August 1982 and submitted to EPA in November 1982.

Value of the Research to Society: The study report describes the objective of this study as “to provide data on the fate of orally and dermally administered chlorpyrifos in man,” and “to define the kinetics of chlorpyrifos absorption, metabolism and elimination. In addition plasma and erythrocyte cholinesterase activities will be determined to compare the biological activity of orally and dermally absorbed chlorpyrifos.” (p. 3) The study was funded by Dow Chemical Company, the registrant of chlorpyrifos, and was submitted to EPA to support that registration. 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 six subjects all responded to an internal advertisement “sent to employees within The Dow Chemical Company Midland, Michigan location inquiring of their interest in volunteering for a chemical metabolism study. . . . The pool of subjects was the ranks of salaried employees of the Midland, Michigan location of The Dow Chemical Company. The population they represented was healthy male Caucasian volunteers.” (DAS Supplement p. 4) Subjects were described as “male Caucasians 27-50 years of age . . . screened by a physician with no other involvement in the study [and] found to be in good general health.” (Study p. 4) Specific criteria for inclusion/exclusion of subjects are not reported; the IRB, however, required as a condition of their approval that women of child-bearing age be excluded. (DAS Supplement p. 20)

Risks and Benefits: Risks and benefits of the research are not discussed in the primary study report. In the “questionnaire” describing the proposed research submitted to the University of Michigan IRB, the investigators described risks and their minimization in these terms:

The proposed doses may depress plasma cholinesterase (CHE) activity but it is highly unlikely that they will produce any clinical signs of CHE inhibition. Plasma CHE depression is currently used to monitor chlorpyrifos exposures. It is completely reversible and is not considered deleterious. The only other anticipated risk is that associated with simple venipuncture.

Doses were selected based on previously reported human studies which indicated these dose levels are safe. A pilot study will be conducted initially in which only one volunteer is given the 0.5 mg/kg oral dose. The purpose of the pilot is to select optimum sampling intervals but will also insure the proposed doses are appropriate before more than one individual is dosed. The doses are to be administered sequentially and the highest dose (5.0 mg/kg dermal) will be administered only if the low dermal dose (0.5 mg/kg) does not depress plasma cholinesterase. This will provide a large margin for safety since in animals plasma cholinesterase depression is observed at 1/100 th dose which produced clinical signs of toxicity.

Trained medical personnel will draw all blood specimens using proper aseptic techniques to minimize the risk due to venipuncture. (DAS Supplement p. 17)

The consent form (DAS Supplement p. 5) does not describe risks to subjects, but simply asserts that they were described to the subject.

In the IRB “questionnaire” the investigators described the benefit of the research in these terms:

The volunteers who participate in this study will accrue no direct benefit. The study will result in new data on the rate and extent to which chemicals like chlorpyrifos are absorbed through the skin. In addition, these data may lead to a more precise means to quantitate chlorpyrifos exposures. This would help define and control occupational exposures, and aid physicians treating cases of acute overexposure. (DAS Supplement p. 19)

The study report does not discuss how the investigators weighed likely benefits of the research against the risks to individual subjects. The University of Michigan IRB stated in their approval letter (DAS Supplement p. 20): “The risks of the individuals involved are felt to be minor, and the potential medical benefits of this investigation are of importance.”

Independent Ethics Oversight: The study report is silent concerning ethics oversight. In responding to EPA’s questions concerning ethics oversight, Dow AgroSciences reported:

Two ethical reviews of the protocol prior to study initiation were completed. The first was a review by the Dow Human Health Research Review Committee, which reviewed the protocol and approved on December 3, 1981. The second was a review of the protocol by the University of Michigan Ethical Review Committee (The Committee to Review Grants for Clinical Research and Investigation Involving Human Beings) which approved on December 10, 1981. (DAS Supplement p. 7)

Documentation of these ethics reviews is incomplete—neither the protocol reviewed nor the consent documents used were included. Correspondence provided in the DAS Supplement documents approval by both panels, and includes as well the close-out report from the investigators to the University of Michigan IRB.

Informed Consent: The study report states simply that volunteers “were briefed and admitted to the study after giving their written informed consent.” (p. 4) The supplement describes the process in greater detail:

[Volunteers] were each given a copy of the protocol one week prior to meeting for the briefing. Essential features of the study were gone over and time allotted for questions. Topics covered during the briefing included:

- Study objective – Define the pharmacokinetics of chlorpyrifos in male volunteers following a single oral and two dermal doses.

- What chlorpyrifos is and background metabolism data.
- A summary of the pilot and what participation in the study would involve – physician exams, what they will be asked to take and how they will be administered, collection of urine and blood specimens, abstaining from all drugs, collection of a 48 hour post dosing fecal sample, cholinesterase determination, analysis of samples.
- Benefits of participation (i.e. benefit to science and will provide meals while at medical for sample collection but no money, gifts, or promotions) and the risks (i.e., venipuncture, expected to produce some depression of plasma cholinesterase but should not depress RBC cholinesterase or produce clinical signs of cholinesterase depression).
- Certification of Volunteers (identity of volunteers is unknown when reported) and disposition of data resulting in a company report and could be submitted in for publication in a scientific journal.

The volunteers were also informed that participation was entirely voluntary and they may refuse to participate or withdraw at any time and for any reason. If they had questions during the course of study they were advised to contact either Dr. Rich Nolan (study director) or James Saunders. Any adverse effects should be reported to either of the above or Dr. Fred Brenner. (DAS Supplement pp. 4-5)

The form signed by subjects does not characterize the nature and purpose of the research, or its risks and benefits, but does include the assertion that the volunteer read the protocol. The protocol has not been submitted to EPA, so the completeness of the information provided to the volunteers cannot be assessed.

Respect for Potential and Enrolled Subjects: The consent form included standard language in two places informing subjects that they were free to withdraw from the research at any time, and that “no prejudice will result if I choose to withdraw.” (DAS Supplement p. 5) Privacy of the subjects was not compromised in the study report or supplemental materials.

B. Applicable Standards

This research was conducted by a third party in late 1981 and 1982, many years before EPA’s amended Rule for the Protection of Human Subjects of Research became effective on April 7, 2006.

The report of this research was submitted to EPA in November 1982, 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 materials submitted by Dow AgroSciences in May 2009 were submitted voluntarily.

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.

§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

The proposed research was approved in advance by both the Dow Human Health Research Review Committee and the University of Michigan Committee to Review Grants for Clinical Research and Investigation Involving Human Beings.

The six subjects monitored in the study were all adult males; the Agency’s reliance on the study would not be 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.”

Although there remain significant gaps in the documentation of the ethical conduct of this research, such gaps do not in themselves constitute “clear and convincing evidence.” I found no evidence that this research was fundamentally unethical.

The greatest cause of ethical concern is that subjects were all employees of the sponsor, which could have made them vulnerable to undue influence in their decision to participate in the

research. The evidence shows, however, that they were repeatedly assured that they were free to refuse to participate or to withdraw. In some cases employee-subjects may also influence the outcome of a study, but in this case all endpoints were analytical, uninfluenced by any subjective judgments by the subjects. Based on this reasoning, on my finding no clear and convincing evidence to the contrary, and on the evidence that it was overseen by the independent University of Michigan IRB, I conclude that this study met the standards of ethical conduct for this type of third-party research prevailing when it was conducted.

Available evidence indicates that this research satisfied the substantive requirement of FIFRA §12(a)(2)(P) for fully informed and fully voluntary participation of the subjects.

Conclusion

I find no barriers in FIFRA 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.