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

OFFICE OF
PREVENTION, PESTICIDES AND TOXIC
SUBSTANCES

May 29, 2009

MEMORANDUM

SUBJECT: Ethics Review of Coulston, *et al.* Chlorpyrifos Human Study

FROM: John M. Carley
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TO: Anna Lowit, Ph.D.
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REF: Coulston, F.; Golberg, L.; Griffin, T. (1972) Safety Evaluation of DOWCO 179 in Human Volunteers. Unpublished study prepared by Institute of Experimental Pathology and Toxicology, Albany Medical College. 68 p. MRID 95175.

Dow AgroSciences: Responses to EPA Questions concerning Coulston, *et al.* Study. E-mail submission from Kenneth Racke to Tom Myers of EPA dated 5/6/09, with attachments. 22 p.

I have reviewed all available information in the referenced documents concerning the ethical conduct of this sub-acute oral toxicity study with adult male human subjects, conducted in 1969-71 and reported in 1972. 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.

A. Scope of Review:

The primary study report (MRID 95975) contains very little information relevant to an ethics review. Therefore I sent a series of general questions to Dow AgroSciences (DAS) in late April. The DAS response submitted on May 6, 2009, provided some additional information as well as two historical documents:

- A note to the record prepared in 1999 by the principal investigator, Dr. Frederick Coulston, reflecting on the conduct of this study.

- A 2000 discussion of scientific and ethical aspects of the Coulston study by two employees of Dow AgroSciences, William Chen and Joel Mattsson.

Drs. Chen and Mattsson cite protocols of 1969 and 1971; these have not been available for review. Efforts to obtain a copy of the 1942 National Academy of Sciences report cited by Dr. Coulston (1999) in the supplemental materials also have not borne fruit.

This review reflects consideration of the primary study report and the supplemental materials provided by DAS in response to my questions. I also reviewed the 1964 World Medical Organization Declaration of Helsinki, as the compilation of ethical standards most relevant to the evaluation of this research.

B. Summary Assessment of Ethical Conduct of the Research

Value of the Research to Society: The study report does not address the justification for the research. Chen and Mattsson (2000) state that the "study was conducted to determine the relative sensitivity of animals and humans to the potential effects of chlorpyrifos." The results of this study have been used in previous EPA assessments, and currently provide the point of departure for the chronic reference dose (RfD) in EPA's Integrated Risk Information System (IRIS).

Scientific Validity of the Research*:* I defer to others for an assessment of the scientific strengths and limitations of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

Subject Selection*:* Subjects were 16 adult males in general good health. Investigators invited about 100 prisoners at the Clinton Correctional Institution in Dannemora NY to an explanation of the program, and then selected 16 volunteers, based on their age and general health. Specific criteria for eligibility and ineligibility are not reported.

Dr. Coulston's 1999 note explains that the investigators followed a protocol for research with prisoners that was originally developed by him and colleagues when testing anti-malarial treatments during World War II. This protocol was reported to have been endorsed by the National Academy of Sciences in 1942, and the experiment is described as having been "done in a proper fashion, comparable to those conducted today."

Risks to Subjects*:* The study report is silent with respect to risks to subjects or to others. Chen and Mattsson (2000) assert that "the administration of chlorpyrifos was terminated when significant plasma cholinesterase inhibition was determined, to ensure that the volunteers were subjected to minimal risk."

Benefits: Both the study report and Chen and Mattsson are silent with respect to foreseeable benefits of the research. It clearly offered no direct benefit to subjects.

Relation of Risks and Benefits: If there was an assessment of the relation between risks to subjects in comparison to foreseeable benefits to the subjects or to others, this assessment is not documented in the available record. Chen and Mattsson cite protocols for this study dated 1969 and 1971 which might provide some insight into these issues, but they are not available for review.

Independent Ethics Oversight: All available documentation is silent concerning any independent ethics oversight of this research.

Informed Consent: What candidates were told and what they agreed to are not reported. The study report is silent concerning consent, but describes participants as "volunteers." Dr. Coulston's 1999 note reports "this experiment was done in a proper fashion equivalent to those conducted today. It was the classical program established in World War II that gave complete credence that the prison inmates were indeed volunteers."

Respect for Potential and Enrolled Subjects: Medical monitoring of all treated subjects was discontinued before their ChE activity returned to pre-test baseline levels. Three treated subjects recorded their lowest levels of ChE activity in the post-test exam, approximately 120 hours after their last dose. The remaining three treated subjects showed some recovery at the post-test exam approximately 200 hours after their last dose, but their ChE activity was still well below their pre-test baseline values.

B. Applicable Ethical Standards

Standards of Ethical Conduct: This study was conducted in 1969-1971, decades before promulgation of EPA's amended Rule for Protection of Human Subjects of Research, the first federal regulation applicable to third-party research such as this. The first guidelines for federally-funded human research were yet to appear. Human research with prisoner subjects was not uncommon at the time; the first U.S. regulations restricting testing with prisoners did not appear until the mid-1970s. The only widely recognized standard for ethical conduct of medical research was the 1964 Declaration of Helsinki, suggested by Drs Chen and Mattsson as the appropriate standard to apply to this research.[1] The full text of the 1964 appears as Attachment 1 to this review, annotated with my comments assessing what is known of the conduct of the Coulston *et al.* study relevant to the provisions of the Declaration.

The Declaration of Helsinki is not cited either in the original study report or in Dr. Coulston's 1999 memoir, and may not have been viewed by the investigators as the prevailing standard when the research was conducted. A protocol developed at the University of Chicago in the early 1940s is cited by Dr. Coulston (1999) as having guided the research; it is not available for review.

[1] Chen and Mattsson may have relied on a later revision for some of their quotations attributed to the 1964 Declaration, which are not to be found in the original.

FIFRA §12(a)(2)(P), requiring fully informed and fully voluntary consent from subjects of research with pesticides, did not enter the Federal Insecticide, Fungicide and Rodenticide Act until late 1972, after this research was conducted.

Regulatory Standards for Relying on Human Research: This research was submitted to EPA in 1972, long before EPA's amended Rule for the Protection of Human Subjects of Research became effective on April 7, 2006, and thus was not subject to the requirement of 40 CFR §26.1303 to document its ethical conduct when it was submitted. The supplemental information provided by Dow AgroSciences has been 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). Because this research was conducted before April 7, 2006, the following provisions of 40 CFR 26 Subpart Q, as amended effective August 22, 2006, define the applicable regulatory standards of acceptability:

> **§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.

C. Compliance with Applicable Standards

Attachment 1 presents my assessment in detail of how the conduct of this research compared to the applicable guidance in the 1964 Declaration of Helsinki. In general, there is insufficient information available to reach a confident conclusion that it did or did not meet the standard of the 1964 Declaration.

This study involved research with adult males, and thus EPA is not prohibited to rely on it by 40 CFR §26.1703.

This study reports research conducted many years ago, before any of our current standards of ethical research conduct were in place. The standards of ethical research conduct prevailing when it was conducted are uncertain, but certainly permitted similar studies using prisoner volunteers. The record is sketchy and characterized by critical gaps, but gaps do not

themselves constitute “clear and convincing evidence” as required by the regulatory standard. I therefore find that EPA is not prohibited to rely on it by 40 CFR §26.1704.

D. Conclusion

If this study is determined to be scientifically valid and relevant, I find no statutory or regulatory barrier to EPA’s reliance on it in actions under FIFRA or §408 of FFDCA.

Attachment 1: Provisions of the 1964 WMA Declaration of Helsinki Applied to Coulston *et al.*

Provisions of the 1964 WMA Declaration of Helsinki
Applied to Coulston *et al.* (1972) Chlorpyrifos Study

Declaration of Helsinki

RECOMMENDATIONS GUIDING DOCTORS IN CLINICAL RESEARCH
Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964

INTRODUCTION

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

The Declaration of Geneva of The World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics which declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

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 each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

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

I. BASIC PRINCIPLES

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

   The study report does not address the justification for the research. Chen and Mattsson (2000) state that the "study was conducted to determine the relative sensitivity of animals and humans to the potential effects of chlorpyrifos." Hazard and mode of action of chlorpyrifos had been well established through animal studies conducted by these and other investigators before this study in humans was conducted. The

rationale for the selection of dose levels is not reported; Chen and Mattsson state that doses "were carefully chosen to ensure no harm would occur."

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

   Dr. Coulston and his colleagues were scientifically qualified to conduct toxicology studies and associated chemical analyses. In his 1999 supplemental comments Dr. Coulston adds that the study "was supervised by the chief medical officer" of the prison; Chen and Mattsson report that the Scientific Director of the research, Dr. Golberg, was a physician.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

   The study report does not identify the objective of the research, does not acknowledge or characterize any risk to the subjects, and does not discuss the relation of the importance of the objective to the risk to subjects. Chen and Mattsson characterize the primary objective of the study as "to determine the dose response of . . . plasma cholinesterase activity."

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.

   If this project was preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subjects or to others, this assessment is not documented in the available record. The study report is silent with respect to risks to subjects or to others. Chen and Mattsson (2000) assert that "the administration of chlorpyrifos was terminated when significant plasma cholinesterase inhibition was determined, to ensure that the volunteers were subjected to minimal risk." Both the study report and Chen and Mattsson are silent with respect to foreseeable benefits of the research. Protocols for this study dated 1969 and 1971 are referred to by Chen and Mattson, but are not available for review.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

   There was no reason for the investigators to believe the personalities of the subjects were liable to be altered by their exposure to chlorpyrifos.

II. CLINICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(This section is inapplicable to the Coulston et al. study)

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

2. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.

3. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

III. NON-THERAPEUTIC CLINICAL RESEARCH
(This section applies to the Coulston et al. study)

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

   Chen and Mattsson (2000) assert that "the administration of chlorpyrifos was terminated when significant plasma cholinesterase inhibition was determined, to ensure that the volunteers were subjected to minimal risk." There is no further discussion of stopping rules or other steps designed to protect the life and health of subjects.

2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.

   The study report is silent concerning what was explained to the subjects by the investigators or by the medical staff of the prison. Dr. Coulston's 1999 note reports that "we actually invited about 100 [candidates], explained the program to them and selected 16 based on their age and their physical and clinical health."

3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

   The study report is silent concerning consent, but describes participants as "volunteers." Dr. Coulston's 1999 note reports "this experiment was done in a proper fashion equivalent to those conducted today. It was the classical program established

in World War II that gave complete credence that the prison inmates were indeed volunteers." Surrogate consent by a guardian was not an issue in this study.

3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.

Care was taken to ensure all subjects were in good general physical health before selecting them to participate. Their mental state is not reported. As prisoners their legal status clearly made them unable to fully exercise their powers of choice, but the constraints may not have extended to their choice whether to participate in this research.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.

It is not reported whether consent was obtained in writing.

4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.

No information is available concerning these matters.

4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued.

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

The study report is silent concerning the subjects' freedom to withdraw from the research. The shorter duration of treatment at each successively higher dose level, not otherwise explained, may reflect a judgment by the investigators that to continue treatment may have been harmful to the individuals receiving the higher doses.