



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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

December 19, 2016

MEMORANDUM

SUBJECT: Interim Ethics Review of Research Article by D. Gail May et al. on Carbaryl Oral Dosing Study with Human Subjects (1992)

FROM: Michelle Arling, Human Studies Ethics Review Officer (Acting)
Office of the Director
Office of Pesticide Programs

TO: Sarah Gallagher, PhD
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REF: May, D. G., *et al.* Cimetidine-Carbaryl Interaction in Humans: Evidence for an Active Metabolite of Carbaryl. *Journal of Pharmacology and Experimental Therapeutics*. Volume 262, Issue 3, September 1, 1992.

I have reviewed available information concerning the ethical conduct of the study referenced in the research article "Cimetidine-Carbaryl Interaction in Humans: Evidence for an Active Metabolite of Carbaryl" by D. Gail May, *et al.* Because the article was submitted by a registrant in support of EPA's consideration of the physiologically-based pharmacokinetic (PBPK) model for carbaryl, the Agency has requested that the registrant submit information required by 40 CFR 26.1303 by December 21, 2016. Upon submission, EPA will review any such information and revise this ethics review, if appropriate. Based on currently available information concerning the ethical conduct of this study, 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). EPA will ask the Human Studies Review Board (HSRB) to comment on this study.

Summary Characteristics of the Research

The research article summarizes several studies, one of which constituted research with a pesticide involving intentional exposure of human subjects. In this pre-rule study, four male subjects aged 24-43 years old "on two occasions... received an oral dose of 1.0 mg/kg of carbaryl predissolved in 4 ml of PEG [polyethylene glycol] and further diluted in 100 ml of

water. The first occasion served as a control study. One week later, the subjects received 200 mg of cimetidine every 8 hours for 3 days. On the 3rd day, the same dose of carbaryl was given 1 hr [hour] after the last dose of cimetidine.” (p. 1058) Plasma was collected from the subjects at 0, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes after each administration of carbaryl.

According to the study director and an author of the article, Dr. Robert Branch, “the four subjects were recruited from male subjects who worked in the vicinity of the Center for Clinical Pharmacology or the General Clinical Research at Vanderbilt University.” (Attachment 1)

The study was approved prior to implementation by the Institutional Committee for the Protection of Human Subjects (Vanderbilt University), an independent ethics review body. All subjects gave written informed consent before enrollment in the study. The original protocol, informed consent form, and correspondence with the ethics review board are not available to EPA.

The published article contains little information about the ethical conduct of the study. To obtain more information and to confirm that the study underwent an independent ethics review, EPA’s Office of Pesticide Programs contacted Dr. Branch directly by e-mail. EPA’s questions and Dr. Branch’s responses are included as Attachment 1. EPA sought additional information from Dr. Branch, but did not receive any further responses.

1. Value of the Research to Society:

The objective of this study was “to evaluate the effect of cimetidine on carbaryl disposition in a group of normal subjects in order to assess the magnitude of change in overall carbaryl clearance.” (p. 1058) As further described on p. 1058:

If cimetidine inhibits carbaryl metabolism in humans and carbaryl is the active moiety, then higher carbaryl concentrations combined with a possible dynamic effect from cimetidine might be expected to increase inhibition of acetylcholinesterase activity when the drugs are given concomitantly. Conversely, if carbaryl is metabolized to a more active metabolite(s), then inhibition of this conversion would be expected to reduce the dynamic response.

The present studies were designed to evaluate these two alternative possibilities. Initial studies determined the concentrations of carbaryl and cimetidine required to inhibit acetylcholinesterase activity in isolated human red blood cells. These results have been compared to the plasma concentrations of carbaryl required to inhibit RBC acetylcholinesterase activity after administration of carbaryl alone, and after administration of carbaryl following cimetidine pretreatment in normal volunteers.

The results were received for publication on August 15, 1991 and published in *The Journal of Pharmacology and Experimental Therapeutics* in September 1992. EPA is proposing to use the results of this study to validate a PBPK model. If validated and accepted for use, EPA will use this PBPK model in human risk assessments, which will allow for a more

refined risk assessment. EPA anticipates that the PBPK model for carbaryl will be reviewed by the FIFRA Science Advisory Panel in summer 2017.

2. Subject Selection:

- a. Demographics.* A total of four males, aged 24-43 years old, were enrolled in the study. According to the article, the subjects were nonsmoking and drug-free.

Dr. Branch's responses imply that he may have been a subject in the study, as well as the primary investigator. In response to questions about recruitment, Dr. Branch noted "...subjects were researchers themselves, *like myself...*" and for the "initial study at that time [Dr. Branch was] *noted to have an age of 43 years.*" (emphasis added) [At least one study participant was 43 years old, according to the article.] Dr. Branch responded to a question on compensation of subjects by stating "*with the exception of myself*, our standard practice in remuneration for participation was \$100 for each study day, \$50 for taking a drug suspected of inducing a drug interaction. I have no direct recollection for this study, but anticipate that *each of the other subjects* received \$250." (emphasis added) EPA attempted to clarify Dr. Branch's role in the study through phone calls and emails to Dr. Branch, as well as by contacting Dr. Branch's institution by phone and email. EPA has not received any response to these requests for more information.

- b. Inclusion/Exclusion Criteria.* According to information provided by Dr. Branch, the inclusion criteria were: male, over 18 years old, no history of chronic disease, non-smokers, drug and alcohol free, not receiving any therapeutic drugs, and normal physical evaluation. The exclusion criteria for subjects, according to Dr. Branch, included: female, "a history of chronic disease or recent acute medical problem, smoking, daily alcohol intake, therapeutic and non-therapeutic drug intake for the week prior to starting the study and for the duration of the study, abnormal physical examination. Patients with "abnormal hematology, renal and liver function tests as defined by outside the laboratory reference limits at Vanderbilt at that time."

- c. Pregnancy and Nursing Status.* All study participants were male.

- d. Recruitment.* Participants were recruited from a group of persons that "had previously been involved in short term drug disposition studies conducted from the Center of Clinical Pharmacology." Dr. Branch noted "subjects were either researchers themselves, like myself, or had previously been involved in volunteer drug disposition studies from a pool of highly motivated, high [sic] intelligent individuals."

3. Risks and Benefits:

- a. Risks.* The article does not describe the risks to study participants specifically. It notes that "carbaryl has been shown to inhibit acetylcholinesterase activity at low concentrations (Hayes, 1982)." (p. 1058) Further, the article notes that "previously published data and pilot tolerance studies in normal human subjects have shown that carbaryl in doses of 0.1, 0.5, and 1.0 mg/kg are well tolerated without symptoms." (p. 1058) Dr. Branch noted that "in single, higher doses, anticholinesterase inhibition causes a well described spectrum of symptoms including dry eyes and mouth, GI

disturbance and CNS [central nervous system] effects. This short term exposure was not expected to cause any additional short term adverse effects.” According to a fact sheet from the National Pesticide Information Center, “early symptoms of acute carbaryl exposure may include headache, malaise, muscle weakness, nausea, gastrointestinal cramps, sweating, and restlessness. Signs of acute carbaryl intoxication may include pin-point pupils, tearing, excessive salivation, nasal discharge, vomiting, diarrhea, muscle twitching, slurred speech, and ataxia. Severe poisonings can result in convulsions, CNS depression, coma, and death.”

(<http://npic.orst.edu/factsheets/archive/carbtech.pdf>) Dr. Branch noted that the risks in the study were minimized by selecting a dose “based on providing measurable levels of drug and measurable changes in anticholinesterase without inducing symptoms.”

- b. Benefits.* There were no direct benefits to the subjects participating in the study. The study evaluated the effects of cimetidine on carbaryl metabolism. According to the article, the findings “suggest that acute administration of cimetidine might reduce carbaryl toxicity in an overdose situation, provided it is administered soon after exposure.” (p.1061) This finding, if confirmed, could benefit persons exposed to carbaryl by refining how the toxicity of carbaryl is evaluated. Further, EPA is proposing to use the results of this study to validate a PBPK model. If validated and accepted for use, EPA will use this PBPK model in human risk assessments, which will allow for a more refined risk assessment. EPA anticipates that the PBPK model for carbaryl will be reviewed by the FIFRA Science Advisory Panel in summer 2017.
- c. Risk-Benefit Balance.* The potential societal benefits of understanding the interaction between carbaryl and cimetidine outweigh the risks associated with the study.

- 4. Independent Ethics Review:** According to the article and Dr. Branch, the study was reviewed and approved by the Vanderbilt Institutional Committee for the Protection of Human Subjects. Dr. Branch noted that the research “was also reviewed for scientific merit and ethical conduct by the Vanderbilt General Clinical Research Center.” Dr. Branch indicated he no longer has access to the records associated with the study. EPA contacted the Vanderbilt Institutional Committee for the Protection of Human Subjects and Vanderbilt Clinical Trials Center by email and by phone to request records relating to the ethical conduct of the study discussed in the article. The email inquiries are included as Attachment 2; EPA did not receive a written response from either entity. In a phone conversation on 12/9/2016, a representative of the Vanderbilt Institutional Committee for the Protection of Human Subjects indicated they could only provide records associated with the review of research to the primary investigator. In a phone conversation on 12/15/2016, a representative of the Vanderbilt Clinical Trials Center indicated that the General Clinical Research Center no longer exists and suggested contacting the Institutional Committee for the Protection of Human Subjects to request the records associated with Dr. Branch’s research.
- 5. Informed Consent:** Dr. Branch noted that he does not have access to the files for this study and could not provide a copy of the informed consent form. As explained above, neither independent ethics body that Dr. Branch indicated had reviewed the study was able to provide EPA with a copy of the informed consent form approved as part of this study. Dr. Branch affirmed that all subjects received “a full oral explanation for the motivation and

design for the study” and signed a written consent form prior to enrolling in the study. Dr. Branch said that “each was judged to understand the study design as well as the science behind the study.” Further, Dr. Branch noted that subjects were fully informed both orally and in writing of the identity, nature and function of the test substances to which they would be exposed.

- 6. Respect for Subjects.** To the best of Dr. Branch’s recollection, the standard practice for compensation in studies like the one referenced in the article “was \$100 for each study day, \$50 for taking a drug suspected of inducing a drug interaction.” Dr. Branch’s estimate of the total compensation for a subject’s participation in the study was \$250.

Dr. Branch said that during the consent process, it was made clear to subjects that participation in the study was completely voluntary and that they were free to withdraw from the study at any time. Dr. Branch said that “the one stopping rule was that if a subject experienced unpleasant symptoms on the first dose, the study would not continue in that individual, but their samples would be analyzed to see if that individual handled the compound differently from others.” According to Dr. Branch, no subjects developed any adverse symptoms during the study and no subjects withdrew.

The subjects’ identities are not revealed in the article. According to Dr. Branch, the subjects’ identities were protected by the standard practice in place when the study occurred “not to record names on biological samples or symptom scores over time, but to use the number in order of study access.”

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 by a person with the intention to submit the results to EPA.

The study was likely conducted in 1990 or 1991, received for publication August 15, 1991 and published in September 1992. This study was funded in part by a U.S. Public Health Service grant. The U.S. Public Health Service falls under the Department of Health and Human Services (HHS). HHS adopted its Policy for the Protection of Human Subjects (45 CFR 46) in 1974, and substantially revised it in 1981. This rule is the basis for the Common Rule for the Protection of Human Subjects, which since 1991 adopted by many federal agencies. Because the study was funded in part by a grant supported by an agency under HHS, it is reasonable to apply the ethical standards of the 1981 amendments to this study. The rule requires review of proposed research and establishes criteria for approval of such research: risks to subjects must be minimized and reasonable in relation to anticipated benefits (to subjects and/or to resulting knowledge), equitable subject selection, documented informed consent from participants, protection of subjects’ privacy and confidential data, and additional safeguards to protect vulnerable subjects.

Standards Applicable to the Documentation of the Research

This article was submitted by a registrant in support of EPA's consideration of the PBPK model for carbaryl. 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 apply. Under 40 CFR §26.1303, the entity submitting data to EPA is required to provide, at the time of data submission, information concerning the ethical conduct of human subject research. If the data submitter cannot access such information, they are required to describe, at a minimum, their efforts to obtain the information.

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 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.

In addition, FIFRA §12(a)(2)(P) applies. This passage 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 has submitted this study for review by the HSRB in conformance with 40 CFR §26.1604.

Compliance with Applicable Standards

As noted in the article, all of the subjects in this study were over 18 years old and were male. The research did not involve intentional exposure of any pregnant or nursing female subjects or any children. Therefore, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

Based on the information obtained from Dr. Branch, subjects provided written informed consent after receiving information about the study, the risks and benefits of their participation, and their ability to withdraw at any time. The protocol underwent independent ethics review and approval by Vanderbilt Institutional Committee for Protection of Human Subjects. The study

was designed with a dose that should allow measurable results without causing adverse effects. Based on these facts, and the absence of any information suggesting that the research was fundamentally unethical or intended to harm participants, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(b)(1).

Neither Dr. Branch nor the Vanderbilt Institutional Committee for Protection of Human Subjects were able to provide EPA with documentation related to the ethical conduct of the study, including the protocol, correspondence with the Vanderbilt Institutional Committee for Protection of Human Subjects, information provided to participants, and written informed consent form; however, absence of information does not indicate ethical deficiencies. Based on my evaluation of the research article and the information provided by Dr. Branch, I concluded that the conduct of the research was not 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 (based on knowledge available at the time the study was conducted) or impaired their informed consent. The study was reviewed and approved by the Vanderbilt Institutional Committee for Protection of Human Subjects. The study purpose and potential risks were explained to subjects, only subjects with the capacity to understand the potential risks were allowed to participate, and all subjects provided written informed consent. The study sponsor took adequate precautions to ensure participants' safety by choosing a dose level expected to provide measurable results without causing adverse effects, excluding subjects with medical conditions that could increase the likelihood of an adverse effect (e.g., subjects with abnormal liver function test results), and conducting the research in a clinic with trained medical professionals. Dr. Branch's description of the informed consent process does not seem inconsistent with the standards in place at the time this study was conducted. Subjects' confidentiality was maintained by using numbers rather than names to identify them. Therefore, reliance on this study is not prohibited by 40 CFR §26.1704(b)(2).

There is no clear and convincing evidence to suggest that subject selection was inequitable, that any party exerted undue influence around subjects' decision to participate, or that there was a lack of fully informed, fully voluntary consent. According to Dr. Branch, the test subjects were recruited from among previous participants in drug disposition studies. There is no clear and convincing evidence to suggest that these subjects were vulnerable to undue influence regarding their decision about whether to participate in the research.

Although I was unable to confirm whether Dr. Branch was a participant in the study, there is no indication that participation in a study by the study investigator was, at the time of the study, fundamentally unethical or inconsistent with the prevailing ethical standards at the time. The article and Dr. Branch both indicate that all subjects gave written informed consent; there is nothing to indicate that Dr. Branch did not participate based on fully informed, fully voluntarily consent.

Based on these facts, I conclude that the study was not deficient relative to the prevailing ethical standards in a way that placed participants at increased risk of harm or impaired their informed consent.

The consent process described by Dr. Branch seems to satisfy the requirements of FIFRA §12(a)(2)(P). Subjects received information about the study, potential risks and benefits, and the

pesticide involved prior to enrolling in the study. The study director made clear that participation was voluntary and subjects could withdraw at any time.

The ethics-related documentation required under 40 CFR 26, subpart M was not submitted to EPA with the article; EPA has requested that the data submitter provide the information required by the regulation or documentation of efforts to obtain the information no later than December 21, 2016. Because a final determination on the ethical conduct of the study may be affected upon submission of additional information under 40 CFR 26.1303, this document is an interim ethics determination. A final ethics determination will be made upon receipt of the information from the data submitter.

Conclusion

Pending review of any additional information submitted under 40 CFR 26.1303, 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.

cc: Jeff Dawson
Anna Lowit
Christine Olinger

Attachment 1: Questions to and responses from Dr. Branch
Attachment 2: Email requests for IRB records