UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

APR 13, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Initial Ethical Review of MITC Human Odor Threshold and Eye Irritation Studies

FROM: John M. Carley

TO: Anna Lowit, HED

REF: MRID 44400401 Russell, M., Rush, T. (1996) Methyl Isothiocyanate: Determination of Human Olfactory Threshold and Human No Observable Effect Level for Eye Irritation. Unpublished study performed by Sensory Testing Laboratory, School of Medicine, Univ. of California, Davis, and Zeneca Ag Products Western Research Center, Richmond CA. Project numbers MITC-UCD-1A-1993 and MITC-UCD-1B-1994; Report no. RR 96-049B. 136 p.

MRID 46546601 AMVAC (2005) Raw Data for Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation: Supplement to MRID 44400401. Unpublished document. 43 p.

MRID 46558201 Metam Sodium Task Force (2005) Raw Data for Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation: Second Supplement to MRID 44400401. Unpublished document. 13 p.

MRID 46584901 University of California, Davis, Human Subjects Review Committee Records of HS Protocol 89-488, 90-605R, 91-665R, 94-601R, 95-553R, 96-547R, and 97-324R. Unpublished documents. 39 p.

The original report (MRID 44400401) combines two independent studies–one to establish an odor threshold, and one to measure eye irritation–in a single report. Because the two studies were conducted separately and raise different concerns, this review deals with each of them in turn. The first supplemental report (MRID 46546601) provides additional information about the ethical conduct of the eye irritation study. The second and third supplements (MRIDs 46558201 and 46584901) address the ethical conduct of the odor threshold study.

I have performed an initial review of available information concerning the referenced documents. This review characterizes the ethical conduct of the research in terms of both current ethical standards and ethical standards prevailing when the studies were conducted. Each review applies the "Summary Framework for Ethical Assessment Using Seven Criteria of Emanuel et al." developed by the EPA Science Policy Committee's Human Studies Work Group. The completed "framework" is attached. This framework was derived from the work of Emanuel, et al. (2000), which summarizes seven general principles for ethical treatment of human subjects in clinical research. The Emanuel article was primarily directed at those who consider proposals for new medical research and decide which are worthy of funding or approval. These are very different decisions from those we in EPA must make when we determine whether we can ethically consider already-completed human studies.

The Emanuel article reflects current standards for ethical research prevailing in the U.S. This research was conducted in the U.S. in 1992-95 in an institution—the University of California at Davis—holding a "multi-project assurance" from HHS/OPRR promising compliance with the Common Rule. It asserts compliance with both the Common Rule and the Declaration of Helsinki. I have considered both standards to have prevailed when the research was conducted.

I. Ethics Review of the Odor Threshold Study

A. Summary Assessment of Ethical Conduct of the Research

Here is a summary of my observations about the odor threshold study under the seven headings used in the Emanuel framework. Supporting details are in the first attachment.

1. **Value of the Research to Society**: The study has never been published, suggesting that its purpose was not mainly to obtain generalizable knowledge. The study may, however, provide some information that could help inform EPA's assessment of human health risks of MITC. Its stated purpose was "to determine the human olfactory threshold for MITC."

2. **Scientific Validity of the Research**: 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.

3. **Subject Selection**: Methods of recruitment are not described. Subjects were 33 healthy males and females aging from 18 to 34, drawn from the university community surrounding the testing institution. There is no evidence suggesting bias in their selection or that any subjects were from an especially vulnerable population.

4. **Risk-Benefit Ratio**: The research was characterized by the investigator in correspondence with the IRB at different times as of both "no risk" and "minimal risk." The investigator did not change this characterization when MITC was added to the list of odorants he was already testing. There is no documentation of

how risks were characterized to subjects. Benefits to society are not reported. There is no documentation of how risks and benefits were weighed by the investigators or the overseeing IRB. Participants were compensated $25 for participating in the study.

5. **Independent Ethical Review**: MRID 46584901 documents IRB approval by the University of California, Davis Human Subjects Review Committee, initially in 1989 and in annual renewals for several years thereafter, excluding, however, 1992 and 1993, when the MITC odor threshold study was actually conducted. The description of the study submitted to the IRB is much broader than the MITC study reported here, and it is not clear what the IRB approved. Neither a protocol nor any informed consent material concerning the MITC testing using the olfactometer is available. The IRB did not waive written informed consent, or respond to the investigator's request for a waiver of written informed consent, until three years after the MITC work was completed.

6. **Informed Consent**: Orally informed oral consent is asserted (MRID 46558201) There is no documentation or description of what candidates were told to inform their consent, or of the process by which consent was sought. The investigator requested from the IRB a waiver from the standard requirement of the Common Rule for written consent; the IRB did not respond to this request until after this research was completed.

7. **Respect for Potential and Enrolled Subjects**: The privacy of subjects was not compromised in the report. The freedom of subjects to withdraw from the research was not addressed.

B. Compliance with Ethical Standard Prevailing when the Research Was Conducted

Numerous ethical deficiencies are apparent when this study is reviewed against the principles of the Declaration of Helsinki (1989), with which the author asserts compliance, and the Common Rule, which the IRB was obliged to apply under the terms of the Multi-Project Assurance they held from HSS/OPRR at the time of the research:

- Declaration of Helsinki Basic Principle #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 . . . ."

  The protocol for this research—especially the work with MITC and the olfactometer—was not clearly formulated. Based on the records of the IRB, this "project" began with mailing 11 million "scratch-and-sniff" odor surveys by the National Geographic Society, and later changed into testing some 100-150 people a year in the university community. The MITC work was an aspect of this later phase, and MITC was one of several chemicals used in testing for olfactory threshold.

- Declaration of Helsinki Basic Principle #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. . . ."

  If a careful assessment of risks and benefits was conducted, it was not reported.

- Declaration of Helsinki Basic Principle #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.

  The primary report is entirely silent about consent, and the information provided by the investigator to the IRB about consent was irrelevant to the research with MITC. The IRB failed to notice or respond to the investigator's inappropriate request for waiver of the customary requirement for written informed consent.

- Declaration of Helsinki Basic Principle #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."

  No such statement appears in the protocol.

- Common Rule §111(a)(2): [In order to approve research covered by this policy the IRB shall determine that] "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."

  IRB records do not evidence any discussion of either risks or benefits of the research.

- Common Rule §111(a)(4): [In order to approve research covered by this policy the IRB shall determine that] "Informed consent will be sought from each prospective subject . . ."

  IRB records do not evidence any discussion of informed consent.

- Common Rule §111(a)(5): [In order to approve research covered by this policy the IRB shall determine that] "Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 26.117."

  IRB records do not provide evidence that the board noticed or discussed the investigator's request for waiver of written informed consent.

- Common Rule §115: IRB Records

  IRB records of this research fall well short of the requirements of the Common Rule.

- Common Rule §116: General requirements for informed consent

  The content of the oral informed consent process is not documented. It cannot be determined whether it was consistent with these requirements of the Common Rule.

- Common Rule §117: Documentation of informed consent.

  (a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative.

  (c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

  (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

  (2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

  Informed consent is not documented for this research. The failure either to document consent or to waive the Common Rule requirement to document consent is a serious shortcoming in the conduct of this odor threshold study. Given the investigator's assertion, however, that informed oral consent was obtained, this lapse does not in my judgment amount to clear and convincing evidence that this study was fundamentally unethical.

  Available documentation suggests that the IRB noticed neither the lack of any consent materials nor the investigator's request for waiver of written consent during the first several years they reviewed this research. After the MITC work had been completed they waived written consent based on an argument from the investigator that applied only to the mail-out survey work completed years earlier.

C. Standards for Judging Ethical Acceptability

On February 6, 2006, EPA published a final rule, "Protections for Subjects in Human Research," effective on April 7, 2006. Section 26.1704 of that regulation provides in pertinent part:

> EPA shall not rely on data from any research initiated before [April 7, 2006, the effective date of the final rule] 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.

In addition, section 26.1703 of the final rule provides in pertinent part:

> 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) or child.

I have applied the standards in sections 26.1704 and 26.1703 in arriving at the conclusions below.

D. Conclusions

All subjects were at least 18 years old. Female subjects said they were not pregnant; this was a requirement to participate in the research. Section 26.1703 does not prohibit reliance on this study.

Although there are serious 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. Deficient documentation does not itself constitute evidence that the ethical conduct of this study was deficient relative to standards prevailing when it was conducted.

From the documentation available I have identified many deficiencies relative to the standards of the 1989 Declaration of Helsinki and the Common Rule, with both of which the study asserts compliance. These ethical deficiencies do not, in my judgment, amount to "clear and convincing evidence" that this study was "fundamentally unethical." This review, however, does not take a position on either the persuasiveness of the evidence or the overall significance of the identified deficiencies relative to the prevailing ethical standards. This decision is deferred pending review of the research by the Human Studies Review Board as required by EPA regulation before EPA takes an action relying on this study.

II. Ethics Review of the Eye Irritation Study

A. Summary Assessment of Ethical Conduct of the Research

Here is a summary of my observations about the eye irritation study under the seven headings used in the Emanuel framework. Supporting details are in the second attachment.

1. **Value of the Research to Society**: The study has never been published, suggesting that its purpose was not mainly to obtain generalizable knowledge. The study may, however, provide some information that could help inform EPA's assessment of human health risks of MITC.

Its purpose was stated in the study report as "to determine the concentrations of MITC vapor that, after various periods of exposure, would produce no observable irritation responses in the eyes of normal, human volunteer test subjects." In the informed consent materials the purpose was stated as "[t]he State of California wants to establish eye irritation levels for . . . MITC as a potential warning signal to exposed workers. . . . [T]his study is designed to provide these data."

2. **Scientific Validity of the Research**: 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.

3. **Subject Selection**: Subjects were healthy males and females aged 18 to 67, drawn from the community of the testing institution. It is impossible to be sure how many subjects actually participated, since it is reported that many of them took part in more than one phase of this four-phase study under different identifiers. It appears likely that subjects included at least some students of the investigators, and perhaps also colleagues or employees of the investigators. This could lead to either or both undue influence in recruiting or bias in reporting subjective effects. I found no other indication that subjects were members of particularly vulnerable populations.

4. **Risk-Benefit Ratio**: Risks to subjects were characterized as transient eye irritation and tearing. The study report does not address steps taken to minimize risks to subjects, or possible alternative methods to obtain similar information. Expected societal benefits are not discussed in the report, or in the documentation of the ethics committee's review. There is no discussion of how societal benefits were balanced against the risks to individual subjects. Participants were compensated for participating in each phase of the study, $60-250 depending on its duration.

5. **Independent Ethical Review**: Initial approval and annual renewals with protocol revisions were provided by a registered IRB and are documented. There is no documentation of IRB discussion. Documentation of risk minimization and of risk/benefit balancing is weak, and recruiting of students or employees as subjects could have involved undue influence.

6. **Informed Consent**: Consent materials are brief but clear, and include all elements required by the Common Rule.

7. **Respect for Potential and Enrolled Subjects**: The privacy of subjects was not compromised. They were free to withdraw at any time, although compensation would have been reduced for early withdrawal.

B. Compliance with Ethical Standard Prevailing when the Research Was Conducted

Some minor deficiencies are apparent when this study is reviewed against the principles of the Declaration of Helsinki (1989), with which it asserts compliance, and the Common Rule,

which the IRB was obliged to apply under the terms of the Multi-Project Assurance from HHS/OPRR held by UC-Davis at the time of this research.

Although documentation of risk reduction and societal benefits is weak, and there is some possibility of undue influence in the recruitment as subjects of students of the investigators, there is no clear evidence that the conduct of this research fell short of Common Rule standards.

C. Standards for Judging Ethical Acceptability

On February 6, 2006, EPA published a final rule, "Protections for Subjects in Human Research," effective on April 7, 2006. Section 26.1704 of that regulation provides in pertinent part:

> EPA shall not rely on data from any research initiated before [April 7, 2006, the effective date of the final rule] 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.

In addition, section 26.1703 of the final rule provides in pertinent part:

> 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) or child.

I have applied the standards in sections 26.1704 and 26.1703 in arriving at the conclusions below.

D. Conclusions

All subjects were at least 18 years old. Female subjects said they were not pregnant; this was a requirement to participate in the research. Section 26.1703 does not prohibit reliance on this study.

Although there are some minor 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. Deficient documentation does not itself constitute evidence that the ethical conduct of this study was deficient relative to standards prevailing when it was conducted.

From the documentation available I have identified only minor deficiencies relative to the standards of the 1989 Declaration of Helsinki, with which the study asserts compliance, and the Common Rule. These deficiencies do not, in my judgment, amount to "clear and convincing evidence" that this study was "fundamentally unethical." This review, however, does not take a

position on either the persuasiveness of the evidence or the overall significance of the identified deficiencies relative to the prevailing ethical standards. This decision is deferred pending review of the research by the Human Studies Review Board as required by EPA regulation before EPA takes an action relying on this study.

Attachments

Cited reference:

Emanuel, E.; Wender, D.; Grady, C. (2000) What Makes Clinical Research Ethical? JAMA 283:2701-2711.

Framework for Ethical Assessment
Using Seven Criteria of Emanuel et al.[1]

April 13, 2006

MRID 44400401 Russell, M., Rush, T. (1996) Methyl Isothiocyanate: Determination of Human Olfactory Threshold and Human No Observable Effect Level for Eye Irritation. Unpublished study performed by Sensory Testing Laboratory, School of Medicine, Univ. of California, Davis, and Zeneca Ag Products Western Research Center, Richmond CA. Project numbers MITC-UCD-1A-1993 and MITC-UCD-1B-1994; Report no. RR 96-049B. 136 p.

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MRID 46584901 University of California, Davis. Human Subjects Review Committee records of HS Protocols 89-488, 90-605R, 91-665R, 94-601R, 95-553R, 96,547R, and 97-324R. Unpublished documents. 39 p.

1. Value: The study has never been published, suggesting that its purpose was not mainly to obtain generalizable knowledge. The study may, however, provide some information that could help inform EPA's assessment of human health risks of MITC. Its stated purpose was "to determine the human olfactory threshold for MITC."
a. What was the stated purpose of the research? "to determine the human olfactory detection threshold for MITC" (44400401 p. 12)
b. Does it evaluate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being? No.
c. Does it test a hypothesis that can generate important knowledge about structure or function of human biological systems, with or without immediate practical application? No.
d. Will society benefit from the knowledge gained from this research? Will its results be disseminated? It has not been published.
e. What government, organization, company and/or institution(s) funded the research? Metam Sodium Task Force
2. Scientific Validity: 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.
a. Did the research have a clear scientific objective? See 1(a) above.
b. Was the research designed using accepted principles, methods, and reliable practices? I defer to the science reviewer. The equipment is reported to have been "specifically designed and constructed for this project." (44400401, p. 13)
c. In what way were human subjects intentionally dosed in this research, and what were the endpoints identified or quantified? Subjects were exposed to an airstream capable of delivering any of five odorants at any of nine concentrations. Upon each exposure they reported whether they could detect the odorant. No other endpoints were identified or quantified.

d. Did the research design have sufficient power to definitively test the objective?
I defer to the science reviewer

e. To what purpose is the study used, or proposed for use, in the Agency?
To inform the weight-of-evidence assessment of MITC for reregistration/tolerance reassessment

3. Fair Subject Selection: Methods of recruitment are not described. Subjects were 33 healthy males and females aging from 18 to 34, drawn from the university community surrounding the testing institution. There is no evidence suggesting bias in their selection or that any subjects were from an especially vulnerable population.

a. Were the groups and individuals recruited and enrolled determined solely on the basis of the scientific goals of the study?
"Thirty-eight human volunteers applied to be test subjects. . . . Applicants were excluded if they scored [significantly] below the mean on the Smell Identification Test, indicated a significant history of smell dysfunction, evinced current symptoms of cold or allergy, indicated pregnancy, or failed to complete an initial training exercise as an olfactometer subject." (44400401 p. 12)

b. Were any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group? All subjects were adults; females said they were not pregnant. There is no indication that members of vulnerable groups were recruited, but recruitment methods are not reported.

4. Favorable Risk-Benefit Ratio: The research was characterized by the investigator in correspondence with the IRB at different times as of both "no risk" and "minimal risk" (MRID 46584901) The investigator did not change this characterization when MITC was added to the list of odorants he was already testing. There is no documentation of how risks were characterized to subjects. Benefits to society are not reported. There is no documentation of how risks and benefits were weighed by the investigators or the overseeing IRB. Participants were compensated $25 for participating in the study.

a. Were the risks to individual subjects minimized?
Risks to subjects are not identified. The original protocol sent to the IRB characterized the research as of "no risk"; in subsequent renewal applications it was characterized as "minimal risk." Under the Common Rule definition, "minimal risk" is equivalent to the risks of everyday life.

b. If the research presents no health-related benefits to individual subjects, what are the societal benefits in terms of knowledge from the study, and do these justify the excess risk to individual subjects?
There is no discussion of benefits to society or others, and no record of how the IRB weighed expected societal benefits against the incremental risks to subjects.

c. What compensation was paid to the participants in the study?
$25.

5. Independent Review: MRID 46584901 documents IRB approval by the University of California, Davis Human Subjects Review Committee, initially in 1989 and in annual renewals for several years thereafter, excluding, however, 1992 and 1993, when the MITC odor threshold study was actually conducted. The description of the study submitted to the IRB is much broader than the MITC study reported here, and it is not clear what the IRB approved. Neither a protocol nor any informed consent material concerning the MITC testing using the olfactometer is available. The IRB did not waive written informed consent, or respond to the investigator's request for a waiver of written informed consent, until three years after the MITC work was completed.

a. Was the research asserted to have been overseen by an ethics review body (ERB)? What ERB? The research was overseen by the University of California, Davis Human Subjects Review Committee.

b. Was the research subject to independent review by individuals unaffiliated with the clinical research?
Yes

c. Was the research conducted in compliance with the Common Rule?
The research was initially asserted to be "no-risk", and in subsequent renewal requests as "minimal risk". The investigator requested a waiver of signed consent, but this was not acknowledged or approved by the IRB. A note to the file dated Dec 23, 1996, and included in MRID 46558201, asserts that the consent process was entirely oral. In the absence of a waiver by the IRB of the requirement for written consent, this is non-compliant with the Common Rule.

d. Does/did the research institution (or any institution participating in the research) hold a Federal Wide Assurance or, previously, Multi-Project Assurance during the period of the study?
UC-Davis held a Multi-Project Assurance from the DHHS/OHRP at the time of this research, under which they had committed to comply with the Common Rule in all research with human subjects conducted at their institution, without regard to whether it was supported by the federal government.

e. Was the research conducted in compliance with another standard? What standard?
"All aspects of this research were performed in accordance with the Helsinki Declaration for Testing and Protection of Human Subjects and the Human Subject's Bill of Rights." (44400401 p. 13) This assertion is not supported by documentary evidence.

6. Informed Consent: Subjects did not provide written consent. Orally informed oral consent is asserted. There is no documentation of the information provided to candidates to inform their consent or of the process by which consent was sought.

a. Does the research assert that informed consent was obtained from participants?
"[T]est subjects gave consent verbally, rather than by signing a document. . . . all of the test subjects were informed verbally of the risks they were taking, and gave consent after being informed of the risks. They were not exposed to any odorants until they had given informed consent" (Supplement p. 5)

b. How and under what circumstances was informed consent obtained?
Methods and circumstances are not reported, nor is there any documentation of the information provided to candidates to inform their consent.

7. Respect for Potential and Enrolled Subjects: The privacy of subjects was not compromised. The freedom of subjects to withdraw from the research was not addressed.

a. Was information about individual subjects managed so as to ensure their privacy?
Yes.

b. Were subjects free to withdraw from the research without penalty?
Not reported.

[1] Emanuel, E; Wender, D; Grady, C (2000) What Makes Clinical Research Ethical? JAMA 283:2701-2711.

Framework for Ethical Assessment
Using Seven Criteria of Emanuel et al.[1]

April 13, 2006

MRID 44400401 Russell, M., Rush, T. (1996) Methyl Isothiocyanate: Determination of Human Olfactory Threshold and Human No Observable Effect Level for Eye Irritation. Unpublished study performed by Sensory Testing Laboratory, School of Medicine, Univ. of California, Davis, and Zeneca Ag Products Western Research Center, Richmond CA. Project numbers MITC-UCD-1A-1993 and MITC-UCD-1B-1994; Report no. RR 96-049B. 136 p.

MRID 46546601 AMVAC (2005) Raw Data for Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold And Human No Observable Effect Level for Eye Irritation: Supplement to MRID 44400401. Unpublished document. 43 p.

1. Value: The study has not been published, suggesting that its purpose was not mainly to obtain generalizable knowledge. The study may, however, provide some information that could help inform EPA's assessment of human health risks of MITC.
a. What was the stated purpose of the research? "[T]o determine the concentrations of MITC vapor that, after various periods of exposure, would produce no observable irritation responses in the eyes of normal, human volunteer test subjects." (MRID 44400401, p. 26). In the informed consent materials the purpose was stated as "[t]he State of California wants to establish eye irritation levels for . . . MITC as a potential warning signal to exposed workers. . . this study is designed to provide these data." (MRID 46546601, p. 11)
b. Does it evaluate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being? No.
c. Does it test a hypothesis that can generate important knowledge about structure or function of human biological systems, with or without immediate practical application? No.
d. Will society benefit from the knowledge gained from this research? Will its results be disseminated? It has not been published.
e. What government, organization, company and/or institution(s) funded the research? Metam Sodium Task Force
2. Scientific Validity: 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.
a. Did the research have a clear scientific objective? See 1(a) above.
b. Was the research designed using accepted principles, methods, and reliable practices? I defer to the science reviewer.
c. In what way were human subjects intentionally dosed in this research, and what were the endpoints identified or quantified? Subjects wore goggles into which air with measured concentrations of MITC was routed, and exposure continued for durations from a few minutes to 8 hours. Endpoints measured were subjective judgments of irritation, blink rate, tearing, and visual acuity.

d. Did the research design have sufficient power to definitively test the objective?
I defer to the science reviewer

e. To what purpose is the study used, or proposed for use, in the Agency?
To inform the weight-of-evidence assessment of MITC for reregistration/tolerance reassessment

3. Fair Subject Selection: It is impossible to tell how many subjects actually participated, since it is acknowledged that many of them took part in more than one phase of this four-phase study under different identifiers. It appears likely that subjects included at least some students of the investigators, and perhaps also colleagues or employees of the investigators. This could lead to either or both undue influence in recruiting or bias in reporting subjective effects. There is no other indication that subjects came from particularly vulnerable populations. All were over 18 and said they were not pregnant.

a. Were the groups and individuals recruited and enrolled determined solely on the basis of the scientific goals of the study?
The supplement indicates that subjects were to include students and "normal adult volunteers", who would be contacted "in person: home or work"; "in person: public place"; and through "in-class announcement." (MRID 46546601, p. 25) "Applicants were excluded if they reported any abnormal eye irritability, wearing contact lenses, frequent headaches, recent asthma attacks, or pregnancy." (44400401p. 27)

b. Were any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group?
"Volunteers from the Sacramento Metropolitan area applied to be test subjects. . . . Applicants were excluded if they reported any abnormal eye irritability, wearing contact lenses, frequent headaches, recent asthma attacks, or pregnancy. These screening procedures resulted in a subject population of 70 individuals . . . who ranged in age from 18 to 67 years. . . Participants in the previous odor threshold study were invited to participate in this study as well, and they were used when possible. . . . Many of the subjects participated in the study on several occasions in the successive trial series and when different exposure levels were offered, taking new subject identification numbers on every occasion." Recruiting in person at subjects' homes or workplaces, and through in-class announcements, could involve undue influence, especially if subjects were students or employees of the investigators, and could introduce possible bias in subjective reporting of effects.

4. Favorable Risk-Benefit Ratio: The study report does not address steps taken to minimize risks to subjects, or possible alternative methods to obtain similar information. Expected societal benefits are not discussed in the report, or in the documentation of the ethics committee's review. Participants were compensated $60-250, depending on the duration of each phase of the study.

a. Were the risks to individual subjects minimized?
Risk minimization is not directly discussed. Materials submitted to the IRB emphasized that doses were low compared to animal NOAELs. (MRID 46546601) The informed consent materials told potential subjects "[t]here is no known long-term risk though you may experience irritation and tearing of the eyes that quickly goes away at the end of exposure. The maximum exposure level is well below any known health risk." (MRID 46546601 p. 11)

b. If the research presents no health-related benefits to individual subjects, what are the societal benefits in terms of knowledge from the study, and do these justify the excess risk to subjects?
Indirect reference is made to the potential for this study to establish threshold levels for eye irritation that would help regulatory authorities to determine safe exposures for workers. It is acknowledged there is no direct benefit to the subjects. There is no direct discussion of benefits to society or others, and there is no record of how the IRB weighed expected societal benefits against the incremental risks to subjects.

c. What compensation was paid to the participants in the study?
$60 for a single, acute exposure; $75 for one-hour exposure; $150 for four-hour exposure; $250 for eight-hour exposure; all prorated in case of early withdrawal.

5. Independent Review: Initial approval and annual renewals with protocol revisions were provided by a registered IRB and are documented. There is no documentation of IRB discussion.
a. Was the research asserted to have been overseen by an ethics review body (ERB)? What ERB? The research was reviewed and approved by the University of California, Davis Human Subjects Review Committee. The IRB required annual renewal of approval, and received progress reports and protocol revisions.
b. Was the research subject to independent review by individuals unaffiliated with the clinical research? Yes
c. Was the research conducted in compliance with the Common Rule? UC Davis held a Multi-Project Assurance from HHS/OPRR at this time of this research, under which they committed to comply with the Common Rule in all research they conducted with human subjects. The study report does not assert compliance with the Common Rule.
d. Does/did the research institution (or any institution participating in the research) hold a Federal Wide Assurance or, previously, Multi-Project Assurance during the period of the study? UC-Davis held a Multi-Project Assurance from the DHHS/OHRP at the time of this research
e. Was the research conducted in compliance with another standard? What standard? "[T]his study was conducted in accordance with the Helsinki Declaration . . . and the Human Subject's Bill of Rights." (p. 27)
6. Informed Consent: Consent materials are brief, but clear, and include all elements required by the Common Rule.
a. Does the research assert that informed consent was obtained from participants? "Each subject was informed as to the nature of the study and gave written consent to participate." (MRID 44400401, p. 27). Informed consent materials were included in the supplemental report (MRID 46546601.)
b. How and under what circumstances was informed consent obtained? Methods and circumstances are not reported. The IC materials are clear that the subject can expect no benefit from participation, and is free to withdraw at any time.
7. Respect for Potential and Enrolled Subjects: The privacy of subjects was not compromised. They were free to withdraw at any time, although compensation would have been reduced for early withdrawal.
a. Was information about individual subjects managed so as to ensure their privacy? Yes.
b. Were subjects free to withdraw from the research without penalty? Yes, although compensation would have been reduced for early withdrawal. No early withdrawals were reported.

[1] Emanuel, E; Wender, D; Grady, C (2000) What Makes Clinical Research Ethical? JAMA 283:2701-2711.