UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

JAN 23, 2004

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

SUBJECT: Ethical Screen of Human Studies with MITC

FROM: John M. Carley

TO: Anna Lowit

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 Unpublished study performed by Sensory Testing Laboratory, School of Medicine, Univ.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.

At your request I have screened the referenced document, applying the "Revised Draft Framework for Ethical Review" recently developed by the EPA Science Policy Committee's Human Studies Work Group. The completed "framework" is attached, reflecting separate consideration of each of the two studies reported in this single document. Here is a summary of my observations under the seven headings used in the framework.

1. **Value of the Research to Society**: Societal benefit beyond increase in knowledge is not clear. In both studies new methodology is asserted to yield more reliable results than earlier studies, but the failure to publish the study compromises this potential benefit.

2. **Scientific Validity of the Research** : I defer to others for a full review of the scientific validity of this study. If others conclude it is not valid, I would like an opportunity to reconsider this assessment. From my layman's perspective the research appears generally sound, but the equipment used, which was developed specifically for this research, certainly wasn't standard.

3. **Subject Selection**: No obvious biases; no indication of exploitation of vulnerable populations, but less than complete information.

4. **Risk-Benefit Ratio**: Notwithstanding IRB approval, R/B ratio is not clearly favorable. Would have been improved by publishing results.

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5. **Independent Ethical Review**: Assertion of approvial without any supporting documentation or detail is typical of published studies, but unusual for unpublished studies. Insufficient information is provided to assess the independence or the quality of ethical review.

6. **Informed Consent**: Informed consent is asserted for the olfactory threshold study, without supporting documentation or detail. Informed consent is not mentioned in the report of the eye irritation study. Insufficient information is provided to assess the quality of informed consent.

7. **Respect for Potential and Enrolled Subjects**: Insufficient information is provided to assess this factor.

In summary, this study as reported shows little concern for the safety or welfare of the research subjects. The investigators appear to have been much more concerned about whether the subjects could use the specialized equipment well. All that can be said for the brief, perfunctory references to ethical review and approval and to informed consent is that they are present.

Nonetheless I am aware of no barrier in current law or Agency policy to your giving this study full consideration in your risk assessment. You should, however, check with senior management before determining whether and to what degree to rely on it.

Attachment

Ethical Screen of MITC Human Studies
John M. Carley
January 23, 2004

In vacating EPA's December 14, 2001 press release concerning human studies, the court stated that the consequence of its decision would be to reinstate EPA's "previous practice of considering third-party human subject studies on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide." This "framework" is intended to guide reviewers, and incorporates the Common Rule within the structure of seven factors for assessing the ethical acceptability of clinical studies as defined by Emanuel et al[1]. It assumes a separate assessment of applicable statutory requirements, but includes identification of the specific case context in which each study is considered, and by implication the applicable statutes.

Identification of 3rd Party Human Studies of Toxic Endpoints subject to Ethical Review

1. Identification of Study	Response from Study	Reviewer Comments
a. Bibliographic citation	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.	
b. Author/Investigator name(s) and affiliation(s)	Study Director: Michael J. Russell, UCD School of Medicine, Dept of Anesthesiology, Sensory Testing Lab	
c. Performing institution name(s) and address(es). *Indicate if any hold OHRP Multi-Project Assurance (MPA) or Federal-Wide Assurance (FWA)*	UCD School of Medicine, Dept of Anesthesiology, Sensory Testing Lab	UCD had MPA; now has FWA
d. Sponsor/Funding source name(s) and address(es)	Metam Sodium Task Force	This is a consortium of pesticide registrants of products containing Metam Sodium, formed to share the costs of developing defensive data following the spill of MS into the Sacramento River
e. Dates of research	Olfactory Threshold study: 9/26-11/14/1994 Eye Irritation study: 12/7/1994 – 4/26/95	

2. Review Context			
	a. In what case context is this study being considered?	Risk assessment for Metam Sodium reregistration	MITC is principle degradate (and active form) of metam sodium
	b. Has it been relied on before? Explain	Unk	
	b. What is its anticipated role in the case?	⛁ Critical for determining an RfD, RfC, MOE, or UF	California has used the inhalation study in their risk assessment; our reviewer wants to acknowledge this, explain why we did not use it for this purpose, and show that using it would not have made a significant difference in our assessment.
		⛁ Critical for defining exposure in some way–i.e., duration of effects	
		⛁ Non-critical; substantially supports definition of toxicity	
		⛁ Non-critical; suggestively supports definition of toxicity	
		■ Non-critical; ancillary to the case	

Although they were both reported in a single document, two distinct studies were performed, for different purposes and at different times. Ethical screening of each is separately reported below, beginning with the olfactory threshold study.

Summary Framework for Ethical Assessment of 3rd Party Human Studies of Toxic Endpoints

The seven sections below correspond to the seven factors defined by Emanuel et al[1] for determining whether clinical research is ethical. The main procedural requirements of the Common Rule are incorporated in summary form within factors 5 and 6.

Responses to each question may take three forms:

- First is a Yes/No/Unknown response, applicable in the great majority of cases. Enter this in the leftmost column, beside the question.
- Second is a quotation from or citation to the study itself, reporting how the study addressed the question, and the basis for the reviewer's Y/N response.
- Finally the reviewer may want to enter comments concerning a specific question.

After answering as many as possible of the specific questions from the study report (and, if available, other documentary sources), the reviewer should enter a summary comment on the 'weight of evidence' addressing each of the seven factors in the shaded header block. These comments taken together would make a starting point for an overall ethical review of the study.

	Quotation or Citation	Reviewer Comments
1. Value of the Research to Society: Societal benefit beyond increase in knowledge not clear. New methodology asserted to yield more reliable results than earlier studies.		
a. What was the stated purpose of the research?	"To determine the human olfactory detection threshold for MITC." (§2.1)	
b. Does it test or anticipate 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 generalizable knowledge? If so, what is the hypothesis?	No	
d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?	NR	Not published.
2. Scientific Validity of the Research: I defer to the science reviewer in this judgment.		
a. Did the research have a clear scientific objective?	Yes	
b. Was the research designed using accepted principles and methods, and reliable practices?	Unk	Defer to Science Reviewer. Equipment was specially designed for this study.
c. Did the research design have sufficient power to definitively test the objective?	Unk	Defer to SR
d. Was data analysis appropriate? Was it complete?	Unk	Defer to SR
3. Subject Selection: No obvious biases; no indication of exploitation of vulnerable populations.		
a. How many subjects were screened as potential subjects? How many were selected? How many actually served as research subjects?	"Thirty-eight human volunteers applied to be test subjects." . . . "[S]creening procedures resulted in a subject population of 33 individuals. . . who ranged in age from 18-34 years." (§2.2)	
b. How were subjects recruited?	"All subjects were recruited from the Sacramento Metropolitan Area." (§2.2)	No further report of how they were recruited

c. Were any potential subjects from groups likely to be vulnerable to coercion or undue influence, such as children, prison-ers, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons?	NR	Children and pregnant women were excluded. No indication that prisoners or mentally disabled or disadvantaged persons were included.
d. Were groups and individuals recruited and enrolled (or excluded) based solely on the scientific goals of the study?	"Applicants were excluded if they scored one standard deviation or more 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." (§2.2)	Screening factors focused on ability to distinguish smells, and freedom from cold or allergy symptoms. Relevance of pregnancy as exclusion factor not clear.
e. Were the subjects who bore the risks and burdens of the research in a position to enjoy its benefits?	NR	No.
f. Were the subjects compensated? How?	NR	
4. Risk-Benefit Ratio: Notwithstanding IRB approval, R/B ratio is not clearly favorable. Would have been improved by publishing results.		
a. What were the risks to individual subjects? Were they minimized?	NR	
b. What (if any) were the direct benefits to individual subjects? What (if any) were the collateral benefits to individual subjects?	NR	No possible direct or collateral benefit to subjects
c. Were the potential benefits to individual subjects proportionate to or greater than the risks?	NR	Zero benefit cannot outweigh any non-zero risk
d. What were the societal benefits of the knowledge gained from the research? How were they distributed?	"Therefore, it is expected that most published odor thresholds are overestimates. Correspondingly, the results of this study are expected to be more reliable because of the advanced design of the olfactometer, and consequently lower than most published thresholds." (§2.12)	Even if control chems thresholds were determined with greater accuracy, failure to publish results compromises their social benefit. Primary benefit was to producers of Metam Sodium.
e. If the research presents no direct benefits to individual subjects, do the societal benefits in terms of knowledge justify the excess risk to individual subjects?	NR	The IRB evidently thought so.
5. Independent Ethical Review : Absence of supporting documentation or detail is similar to many published studies, but unusual for unpublished studies. Insufficient information is provided to assess the independence or the quality of ethical review.		
a. Is compliance with the Common Rule asserted in the research report? Is it documented?	NR	Review by the UCD IRB implies CR com-pliance; UCD had MPA at time of research.
b. Is compliance with another ethical standard asserted? Is it documented? What standard?	"All aspects of this research were performed in accordance with the Helsinki Declaration . . . and the Human Subject's Bill of Rights." (§2.3)	Asserted without detail or documentation.

c. Was the research subject to independent ethical review before it began? How is this documented?	"The University of California, Davis, Human Subjects Review Committee gave approval for testing after review of plans for this study." (§2.3)	Not otherwise documented
d. Was the research subject to ethical oversight while underway? How is this documented?	NR	
6. Informed Consent: Absence of supporting documentation or detail is consistent with usual practice in published studies; unusual for unpublished studies. Insufficient information is provided to assess the quality of informed consent.		
a. Were the individual subjects accurately informed of the purpose, methods, risks, benefits, and alternatives to the research?	"Each subject was informed as to the nature of the study and gave consent to participate." (§2.2)	No further detail reported.
i. How and under what circumstances was informed consent sought?	NR	
ii. Was the research described consistently in recruitment materials and informed consent materials?	NR	
iii. Did the informed consent materials include language limiting the liability of the investigator(s) or sponsor(s) of the research?	NR	
iv. Did the informed consent materials include language limiting the rights of the subject?	NR	
b. How did the investigators verify subjects' understanding of the informed consent materials?	NR	See response for next study
c. Did subjects make a voluntary and uncoerced decision to participate? What steps were taken to minimize the possibility of coercion or undue influence in obtaining consent?	NR	
7. Respect for Potential and Enrolled Subjects: Insufficient information is provided to assess this factor.		
a. Was information about individual subjects managed so as to ensure their privacy?	"The identity of each test subject was coded." (§2.8)	
b. Were subjects free to withdraw from the research without penalty?	NR	
c. Was any additional information about risks and benefits to the subjects gained in the course of the research? Was it provided to the subjects already enrolled?	NR	

	d. Was the welfare of the subjects monitored throughout their research participation? Were subjects who experienced adverse reactions, untoward events, or changes in clinical status provided with appropriate treatment? Were any subjects removed from the study for their own welfare?	NR	No adverse events reported
	e. Was any provision made for monitoring subject welfare after completion of the research?	NR	
	f. Were subjects informed of what was learned from the research?	NR	

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

Abstract: Many believe that informed consent makes clinical research ethical. However, informed consent is neither necessary nor sufficient for ethical clinical research. Drawing on the basic philosophies underlying major codes, declarations, and other documents relevant to research with human subjects, we propose 7 requirements that systematically elucidate a coherent frame-work for evaluating the ethics of clinical research studies: (1) value- enhancements of health or knowledge must be derived from the research; (2) scientific validity-the research must be methodologically rigorous; (3) fair subject selection-scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio-within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review- unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent-individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects-subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical. These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted.

Summary Framework for Ethical Assessment of 3rd Party Human Studies of Toxic Endpoints

The seven sections below correspond to the seven factors defined by Emanuel et al[1] for determining whether clinical research is ethical. The main procedural requirements of the Common Rule are incorporated in summary form within factors 5 and 6.

Responses to each question may take three forms:

ii. First is a Yes/No/Unknown response, applicable in the great majority of cases. Enter this in the leftmost column, beside the question.
iii. Second is a quotation from or citation to the study itself, reporting how the study addressed the question, and the basis for the reviewer's Y/N response.
iv. Finally the reviewer may want to enter comments concerning a specific question.

After answering as many as possible of the specific questions from the study report (and, if available, other documentary sources), the reviewer should enter a summary comment on the 'weight of evidence' addressing each of the seven factors in the shaded header block. These comments taken together would make a starting point for an overall ethical review of the study.

	Quotation or Citation	Reviewer Comments

1. Value of the Research to Society: Societal benefit beyond increase in knowledge not clear. New methodology asserted to yield more reliable results than earlier studies.		
a. What was the stated purpose of the research?	"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." (§3.1)	
b. Does it test or anticipate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being?	NR	No
c. Does it test a hypothesis that can generate important generalizable knowledge? If so, what is the hypothesis?	NR	No hypothesis stated
d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?	NR	Social benefit unclear. Not published.
2. Scientific Validity of the Research: I defer to the science reviewer for this judgment		
a. Did the research have a clear scientific objective?	**Yes**	
b. Was the research designed using accepted principles and methods, and reliable practices?	**Unk**	Defer to Science Reviewer
c. Did the research design have sufficient power to definitively test the objective?	**Unk**	Defer to SR.
d. Was data analysis appropriate? Was it complete?	**Unk**	Defer to SR
3. Subject Selection: No obvious defects, but important gaps in the information.		
a. How many subjects were screened as potential subjects? How many were selected? How many actually served as research subjects?	"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." (§3.2)	Number screened was not reported.
b. How were subjects recruited?	"Volunteers from the Sacramento Metropolitan area applied to be test subjects." (§3.2)	
c. Were any potential subjects from groups likely to be vulnerable to coercion or undue influence, such as children, prison-ers, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons?	NR	Children and pregnant women were excluded. No indication that prisoners or mentally disabled or disadvantaged persons were included.

d. Were groups and individuals recruited and enrolled (or excluded) based solely on the scientific goals of the study?	"Applicants were excluded if they reported any abnormal eye irritability; wearing of contact lenses; frequent headaches; recent asthma attacks, or pregnancy; or if their eyes were observably irritated (swelling or redness) when they arrived for testing."	Relevance of pregnancy as exclusion factor not clear.
e. Were the subjects who bore the risks and burdens of the research in a position to enjoy its benefits?	NR	No.
f. Were the subjects compensated? How?	NR	
4. Risk-Benefit Ratio: Notwithstanding reported IRB approval, R/B ratio is not clearly favorable. Would have been improved by publication.		
a. What were the risks to individual subjects? Were they minimized?	"It is important to recognize that the effects that were detected by the tests of irritation used in this study are observable, reproducible responses. There is no evidence to suggest that they represent any degree of injury, either permanent or temporary, impaired functional capacity, or deleterious effects." (§3.12.2)	Risk minimization not discussed
b. What (if any) were the direct benefits to individual subjects? What (if any) were the collateral benefits to individual subjects?	NR	No possibility of direct or collateral benefit to subjects
c. Were the potential benefits to individual subjects proportionate to or greater than the risks?	NR	Zero benefit cannot outweigh any non-zero risk
d. What were the societal benefits of the knowledge gained from the research? How were they distributed?	"Previously published values for cat eye-irritation responses after 4 hours' exposure to MITC (Nesterova, 1969-2) are approximately an order of magnitude less than those reported in this study. . . .Nesterova's values are considered grossly inaccurate and not reproducible for humans." (§3.13)	Any potential societal benefit from more accurate estimates of NOEL for eye irritation are compromised by failure to publish these data.
e. If the research presents no direct benefits to individual subjects, do the societal benefits in terms of knowledge justify the excess risk to individual subjects?	NR	The IRB apparently thought so.
5. Independent Ethical Review: Insufficient information available to assess quality of ethical review		
a. Is compliance with the Common Rule asserted in the research report? Is it documented?	No	Review by the UCD IRB implies CR compliance; UCD had MPA at time of research.
b. Is compliance with another ethical standard asserted? Is it documented? What standard?	"As in the previous odor threshold study, this study was conducted in accordance with the Helsinki Declaration . . . and the Human Subject's Bill of Rights." (§3.3)	Asserted without detail or documentation.
c. Was the research subject to independent ethical review before it began? How is this documented?	"Approval for testing was obtained after review of plans for this study by the University of California, Davis, Human Subjects Review Committee." (§3.3)	Not otherwise documented

d. Was the research subject to ethical oversight while underway? How is this documented?	NR	
6. Informed Consent: Insufficient information available to assess quality of informed consent		
a. Were the individual subjects accurately informed of the purpose, methods, risks, benefits, and alternatives to the research?	**NR**	Material reported in 6(a) for odor threshold study may also apply to this one.
i. How and under what circumstances was informed consent sought?	**NR**	
ii. Was the research described consistently in recruitment materials and informed consent materials?	**NR**	
iii. Did the informed consent materials include language limiting the liability of the investigator(s) or sponsor(s) of the research?	**NR**	
iv. Did the informed consent materials include language limiting the rights of the subject?	NR	
b. How did the investigators verify subjects' understanding of the informed consent materials?	"They were first given a written and verbal explanation of the procedures to be followed and they were questioned to verify their understanding" (§3.8)	The focus here was on how to use the equipment only.
c. Did subjects make a voluntary and uncoerced decision to participate? What steps were taken to minimize the possibility of coercion or undue influence in obtaining consent?	NR	
7. Respect for Potential and Enrolled Subjects: Insufficient information available to assess this factor.		
a. Was information about individual subjects managed so as to ensure their privacy?	"The close-up photographs of subjects; eyes . . . were identified only by a test subject number written on the filter paper taped under the subject's right eye, and by another number that indicated whether it was the pre- or post-exposure photo." (§3.9.2)	
b. Were subjects free to withdraw from the research without penalty?	NR	
c. Was any additional information about risks and benefits to the subjects gained in the course of the research? Was it provided to the subjects already enrolled?	NR	
d. Was the welfare of the subjects monitored throughout their research participation? Were subjects who experienced adverse reactions, untoward events, or changes in clinical status provided with appropriate treatment? Were any subjects removed from the study for their own welfare?	NR	

	e. Was any provision made for monitoring subject welfare after completion of the research?	NR	
	f. Were subjects informed of what was learned from the research?	NR	