EPA Reviewer: Anna Lowit _____, Date ___
Reregistration Branch II (7509C)
EPA Secondary Reviewer: Judy Facey _____, Date ___
Reregistration Branch II (7509C)

TXR#: 0051475

DATA EVALUATION RECORD

STUDY TYPE: Special Study: Human Eye Irritation and Odor Threshold

DP BARCODE: D303925
P.C. CODE: 068103

TEST MATERIAL: Methyl Isothiocyanate

SYNONYMS: MITC

CITATION: Russell, M.J. and Rush, T.I. (1996) Methyl Isothiocyanate: Determination of human olfactory detection threshold and human no observable effect level for eye irritation. Sensory Testing Laboratory, University of California at Davis. Report No. RR 96-049B. September 10, 1996 MRID 44400401.

SPONSOR: Metam Sodium Task Force

A. SUMMARY: EPA's OPP has evaluated the reviews by California EPA's Department of Pesticide Regulation and has verified the accuracy of information as reported in MRID 44400401.

Extracted directly from the Risk Characterization Document for MITC. Department of Pesticide Regulation, California Environmental Protection Agency July 25, 2003, pp 53-59:

In order to determine the NOEL for human eye irritation produced by MITC vapors, as well as its odor threshold, human volunteers were exposed to air concentrations of MITC in a laboratory setting (Russell and Rush, 1996). The study specifically focused on assessing these parameters at different times of exposure. An olfactometer was used which permitted the operator to dispense the test material through a manifold system. The test material could thus be diluted over a 100-fold concentration range. The material was dispensed by diffusion from a glass vessel which could be maintained at any temperature ±0.1°C over a range of 30 to 70°C. A Total Hydrocarbon Analyzer (THA) was used to monitor the flow of test material during the exposure period. In addition, carbon tube samples were drawn once the system was equilibrated prior to exposure, and at the end of the exposure. The test material was desorbed from the carbon and analyzed by gas chromatography. Every effort was undertaken to minimize the reaction of the test material with the tubing and other equipment used in the delivery system.

In the olfactory threshold study, 33 individuals (16 males, 17 females) with a mean age of 25 years (range, 18 to 34 years) were tested. They were exposed to three positive control

odorants, pyridine, acetic acid, and n-butyl alcohol as well as to MITC. The technician chose the odorant and concentration level. The odorant was dispensed in double blind fashion from one of three presentation ports. The subject was responsible for identifying from which of the presentation ports the odorant was dispersed. A 30-second rest period between exposures was permitted in order to allow the subject to recover prior to the next exposure. The operator tested each subject over the range of concentrations for each odorant until he was assured that the threshold had been adequately ascertained. A standard procedure was employed in order to make this determination. ***The observed odor threshold for MITC ranged from 0.2 to 8 ppm with a geometric mean of 1.7 ppm.***

In the NOEL determination for eye irritation, the olfactometer was modified by attaching goggles to the presentation line. This permitted the test material to be directed only to the eyes. Five parameters were used to ascertain an irritation response: 1. the subjects' subjective estimation of irritation (using the "Likert" scale); 2. photographs of the subjects' eyes prior to and after exposure; 3. blink rate as measured by electromyography; 4. effect upon visual acuity; 5. tear production. Both a positive control (acetic acid) and a negative control (air) were employed. Baseline responses for each of the assessment parameters were determined under pre-exposure conditions ("zero-time controls") and upon exposure to the negative control ("air-only controls") for the prescribed period. A positive irritation response was based on three criteria: 1. the average response must be quantitatively greater than the pre-exposure response; 2. the average response must be greater than pre-exposure and greater than could be expected statistically from individual to individual differences within the group; 3. the average treated response must be greater than the air-only group's response and greater than could be expected from individual differences observed within the group.

Seventy individuals (38 males, 32 females) with a mean age of 32 years (range, 18-67 years; median age, 28 years) were exposed to air, MITC, and/or acetic acid. Between 9 and 16 subjects were examined under each dose/time period combination. Three exposure periods, 14 minutes, 4 hours and 8 hours were used. In the eight hour test, subjective responses, blink rates and tearing were assessed at 0, 1.5, 3, 3.5, 6 and 8 hours (tearing was not measured at 3.5 hours). Two 15-minute rest breaks and a 30-minute lunch break were permitted during the 8-hour period. In the four hour test, these same parameters were assessed at 0, 1, 2, 3 and 4 hours (tearing was not measured at 0, 2 and 3 hours). In the 14-minute exposure protocol, subjective responses and blink rates were measured at 0, 1, 4 and 14 minutes after the start of exposure. Tearing was measured at 14 minutes only. Visual acuity and ocular morphology were assessed at the beginning and end of each exposure period. All analyses were performed in a double-blind manner.

Subjective (Likert scale) responses. Exposure to 0.8 ppm (800 ppb) MITC resulted in a statistically significant positive response based on averaging the subjective assessments by the subjects using the Likert scale methodology (Table 11a). In that test, as many as 8 out of 9 subjects showed a positive response at 1 and 2 hours, the first two time points examined. (*Note*: judgement of a positive response is itself somewhat subjective in light of the variability observed among control subjects.) Mean responses at those times, expressed as the percentage of the full Likert scale indicated by the subject, were 25%±14% and 26%±14%, respectively, compared to 2%±2% in zero-time untreated controls (a judgement of 50% was stated to be equivalent to the irritation one might expect from the cutting of a single mild onion). One-hour and 2-hour air-only controls exhibited responses of 6%±9%

and 5%±8%, respectively. By 3 and 4 hours, all 9 subjects at 0.8 ppm appeared to respond positively, with mean responses of 39%±19% and 39%±26%, respectively. Air-only controls at the latter 2 times were 5%±6% and 4%±6%, respectively.

Exposure to 0.22 ppm (220 ppb) did not result in a statistically significant mean Likert scale response when compared against air-only controls. Despite the fact that statistical significance *was* achieved at 1 hour when compared against zero-time controls (13%±15% *vs.* 4%±8% among zero-time controls), the lack of statistical significance when compared against air-only controls (which registered 6%±9%) resulted in a judgement of no response.

Shorter exposures to 0.6 ppm did not result in statistically significant Likert scale changes, though 1 of 9 individuals appeared to respond at 4 and 14 minutes. Exposure to 1.9 ppm or 3.3 ppm MITC for 4 or 14 minutes resulted in positive subjective responses at 4 and 14 minutes. At 1 minute of exposure, levels as high as 3.3 ppm did not evoke a statistically significant positive response.

Eyeblink responses. Mean blink rate determinations at 0.8 ppm were statistically significantly increased at the 2- and 3-hour time points compared both to air-only and zero-time controls (Table 11b), with 7 of 9 subjects responding positively. Mean blinks per minute (minus the zero-time rate) were 16±11 and 14±13 at those times. Air-only control rates at 2 and 3 hours were 3±9 and 3±8 blinks per minute, respectively. Statistical significance was not achieved at 1 and 4 hours, though a positive response was indicated in several individuals. The blink response to 0.6 ppm and 1.9 ppm at 1, 4 and 14 minutes did not indicate positivity. At 3.3 ppm, statistical significance was achieved at 4 and 14 minutes. A strong suggestion of a response was also present at 1 minute, though it was not statistically significant.

Tearing, ocular morphology, and visual acuity. No statistically positive tearing responses were observed. However, 2 of 9 individuals exposed to 3.3 ppm MITC showed apparently positive responses at 14 minutes (longer exposures were not evaluated at this concentration).

With respect to the possibility that there were changes in ocular morphology or visual acuity, the following passage is quoted from the study report (page 39):

> Preliminary analysis of the photographs of test subjects' eyes indicated that no notable, exposure related changes were observable in the large majority of tests. In a few tests in which minimal increases in redness and swelling were observed, it appeared that they were more likely to occur in exposures to air than in exposures to MITC. A few individuals evinced a degree of mild edema at the highest level of MITC exposure, but this tended to be canceled out by other subjects who evinced some native edema and redness, pre-exposure in the early morning. Changes in subjects' visual acuity were also few and apparently random. Accordingly the results of the photographic and acuity tests were not considered to provide any meaningful information on chemical exposure. Results from these tests are retained in study records.

Recovery. Rates of recovery from irritating MITC exposures were not evaluated directly. The comments of the test subjects indicated that recovery began immediately upon removal of the

masks, and was complete within 20 minutes at the highest concentration tested, and sooner at lower concentrations.

Tables 11a, 11b, and 12 and Figure 3 summarize the eye irritation results described above.

Table 11a. Mean perception-of-eye-irritation (Likert scale) data, human subjects (Russell and Rush, 1996)

Units: % of total line distance (standard deviation)

4-hr trial

	Time points, hours					
	0	1	2	3	4	# subjects
Air-only control	1% (2%)	6% (9%)	5% (8%)	5% (6%)	4% (6%)	12
p-value #1[a]	n/a	n/a	n/a	n/a	n/a	
p-value #2[b]	n/a	0.08	0.07	0.02	0.07	
0.22 ppm	4% (8%)	13% (15%)	8% (10%)	6% (8%)	6% (7%)	12
p-value #1[a]	0.21	0.16	0.43	0.55	0.49	
p-value #2[b]	n/a	0.02	0.05	0.16	0.42	
0.8 ppm	2% (2%)	25% (14%)*	26% (14%)*	39% (19%)*	39% (26%)*	9
p-value #1[a]	0.57	0.00	0.00	0.00	0.00	
p-value #2[b]	n/a	0.00	0.00	0.00	0.00	

[a]p-value #1, t-test against air-only control subjects
[b]p-value #2, t-test against zero-time values
*Judged a positive irritation response. An irritation effect is considered to have been detected only if both statistical tests indicate significant differences and if mean is higher than the zero-time mean.

8-hr trial

	Time points (hours)						
	0	1.5	3	3.5	6	8	subjects
Air-only control	1% (1%)	9% (10%)	12%(15%)	6% (10%)	15%(19%)	8% (13%)	12
p-value #1[a]	n/a	n/a	n/a	n/a	n/a	n/a	
p-value #2[b]	n/a	0.04	0.03	0.16	0.03	0.09	
0.22 ppm	2% (2%)	5% (4%)	5% (4%)	4% (4%)	8% (8%)	6% (5%)	16
p-value #1[a]	0.23	0.18	0.10	0.44	0.18	0.46	
p-value #2[b]	n/a	0.01	0.00	0.24	0.01	0.00	
0.8 ppm	Not done						n/a
p-value #1[a]							
p-value #2[b]							

[a]p-value #1, t-test against air-only control subjects
[b]p-value #2, t-test against zero-time values

Table 11b. Mean eyeblink data, human subjects (Russell and Rush, 1996)

Units: Blinks per minute minus zero-time rate (standard deviation)

4-hr trial

	Time points, hours					
	0	**1**	**2**	**3**	**4**	**# subjects**
Air-only control	n/a	3 (6)	3 (9)	3 (8)	3 (8)	12
p-value #1[a]		n/a	n/a	n/a	n/a	
p-value #2[b]		0.13	0.24	0.23	0.18	
0.22 ppm	n/a	-5 (6)	-2 (6)	-5 (5)	-3 (4)	12
p-value #1[a]		0.00	0.13	0.01	0.03	
p-value #2[b]		0.02	0.35	0.01	0.04	
0.8 ppm	n/a	7 (7)	16 (11)*	14 (13)*	12 (11)	9
p-value #1[a]		0.15	0.01	0.03	0.052	
p-value #2[b]		0.00	0.00	0.01	0.01	

[a]p-value #1, t-test against air-only control subjects
[b]p-value #2, t-test against zero-time values
*Judged a positive irritation response. An irritation effect is considered to have been detected only if both statistical tests indicate significant differences and if mean is higher than the zero-time mean.

8-hr trial

	Time points (hours)						
	0	**1.5**	**3**	**3.5**	**6**	**8**	**# subjects**
Air-only control	n/a	-2 (7)	-3 (7)	-1 (5)	-1 (7)	0 (7)	12
p-value #1[a]		n/a	n/a	n/a	n/a	n/a	
p-value #2[b]		0.42	0.15	0.48	0.54	0.97	
0.22 ppm	n/a	-3 (6)	-2 (5)	-2 (5)	-2 (4)	-2 (5)	16
p-value #1[a]		0.62	0.67	0.55	0.81	0.48	
p-value #2[b]		0.07	0.15	0.10	0.12	0.19	
0.8 ppm	Not done						n/a
p-value #1[a]							
p-value #2[b]							

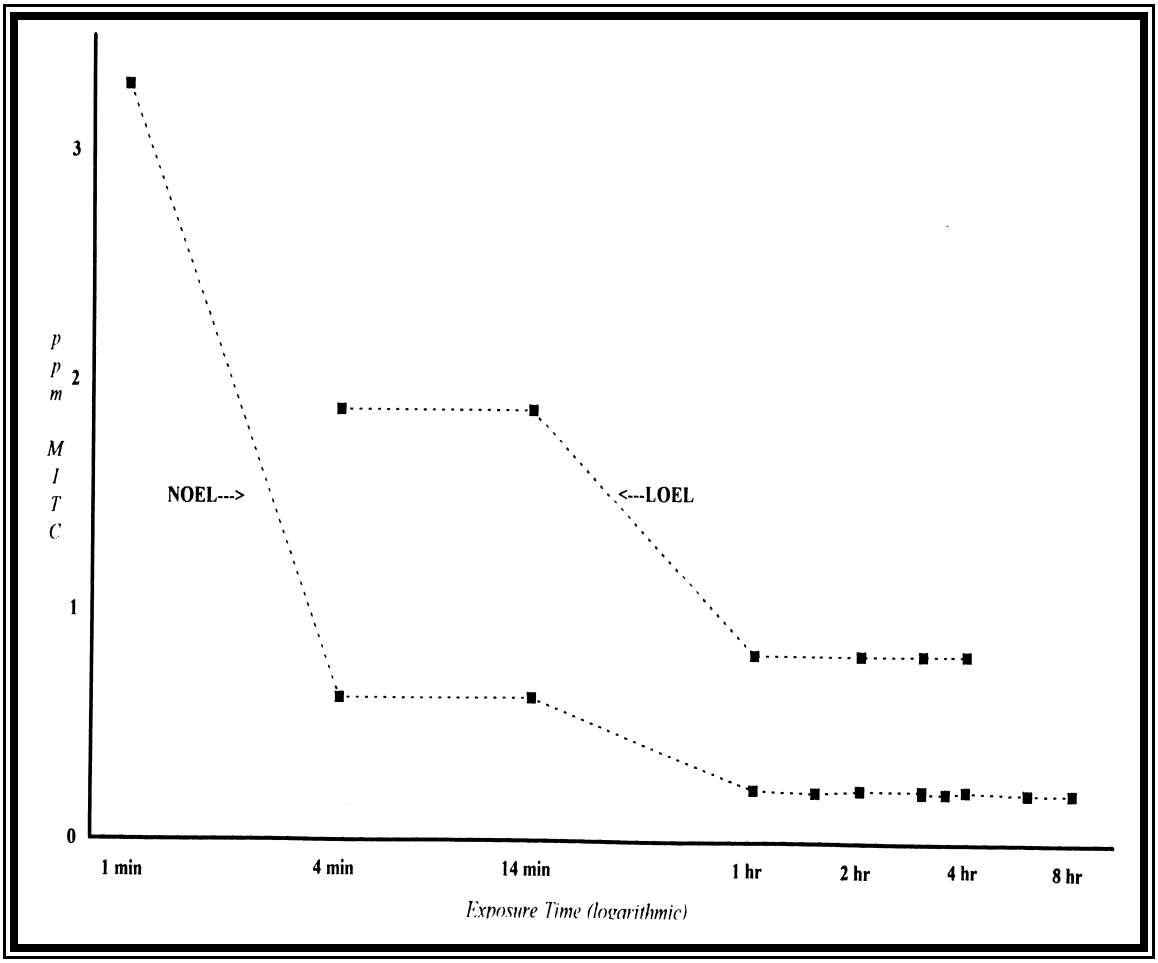
[a]p-value #1, t-test against air-only control subjects
[b]p-value #2, t-test against zero-time values

Table 12. Summary of MITC eye irritation effects, human subjects (Russell and Rush, 1996)

Exposure time	NOEL (ppm)	LOEL (ppm)	Source of observed Effect
1 minute	3.3	-	-
4 minutes	0.6	1.9	Subjective eye irritation
14 minutes	0.6	1.9	Subjective eye irritation
1 hour	0.23[a]	0.8	Subjective eye irritation
1.5 hours	0.22[a]	-	-
2 hours	0.23[a]	0.8	Subjective eye irritation and blink rate
3 hours	0.23[a]	0.8	Subjective eye irritation and blink rate
3.5 hours	0.22[a]	-	-
4 hours	0.23[a]	0.8	Subjective eye irritation
6 hours	0.22[a]	-	-
8 hours	0.22[a]	-	-

[a]The slightly different values obtained at the low dose NOEL level (0.22 and 0.23 ppm) reflected the fact that they were derived from tests performed on different days.

Figure 3. Human MITC eye irritation results (Russell and Rush, 1996)



B. CONCLUSIONS: EPA's conclusions on this study are stated below. EPA's RfC methodolgy document (1994) includes eye, nasal, and throat irritation in the list of adverse effects. Therefore, where DPR lists a NOEL (no-observed-effect-level), EPA will note a NOAEL (no-observed-*adverse*-effect-level):

- For a one-minute exposure, the NOAEL for eye irritation is 3.3 ppm due to a lack of response in any parameter tested.
- For exposures 4-14 minutes, the NOAEL for eye irritation is 0.6 ppm based on responses on the Likert subjective scale at 1.9 ppm.
- For exposures of 1-8 hours, based on the statistically significant subjective (Likert scale) responses at 0.8 ppm MITC at 1-4 hours and the statistically significant eyeblink responses at 2 and 3 hours, 0.22 ppm was designated as the NOAEL for this study
- The NOAEL for eye irritation was consistent for the 1-8 hour measurements. It is reasonable to assume that exposures up to 24 hours would likely yield a similar response.

C. ETHICAL CONSIDERATIONS:

Ethical aspects associated with human subject testing are provided in a separate memo from J. Carley (1/23/04). Overall, this study appears to have been conducted in an ethical manner.

D. COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

DATA FOR ENTRY INTO ISIS

Special Study

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
068103	44400401	Special study: Human eye irritation and odor threshold	Human	1 min to 8 hours	Air	Olfactometer and Goggles	0 - 3.3 ppm	0, 0.22,0.6, 0.8, 1.9, 3.3 ppm	0.22 ppm	0.6 ppm	Eye, nose	

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

TOXICOLOGY SUMMARY REPORT WORKSHEET

I. STUDY IDENTIFICATION

Active Ingredient: Methyl Isothiocyanate (MITC)
Formulated Product Name: Metam Sodium
Chemical Code #: 616 **ID #:** SBRA-162876E
Document #: 50150-142 **Record #:** 149369
EPA Reg. #: NA **SB 950 #:** 742
Study Type: Determination of Olfactory Threshold and No Observable Effect Level for Eye Irritation in Humans
Full Study Title: Methyl Isothiocyanate: Determination of Human Olfactory Threshold and Human No Observable Effect Level for Eye Irritation
Company Sponsor: Metam Sodium Task Force
Conducting Laboratory: Sensory Testing Laboratory, School of Medicine, University of California, Davis, Davis, CA and Zeneca Ag Products, Western Research Center, Richmond, CA
Final Report Date: September 10, 1996
Study Dates: Olfactory Threshold Study: September 26, 1994 to November, 14, 1994; Eye Irritation Study: December 7, 1994 to April 26, 1995

II. CONCLUSIONS

Does this study as reported demonstrate a possible adverse health effect? If so, in what area?

The authors of this report concluded that the olfactory threshold for MITC is 1.7 ppm (5 mg/m3) with a range from 0.2 to 8 ppm. The NOEL for eye irritancy is 3.3 ppm (10 mg/m3) for a 1 minute exposure. The NOEL is reduced to 0.22 ppm (0.6 mg/m3) for 1 to 8 hour exposures to the test material. Long term low level exposure to MITC may result in eye irritation at levels below the olfactory threshold.

Very briefly describe the nature of the study, including the study type, species, strain, and dose levels:

50150-142; 149369; "Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation"; (M.J. Russell and T.I. Rush; Sensory Testing Laboratory, School of Medicine, University of California, Davis, Davis, CA and Zeneca Ag Products, Western Research Center, Richmond, CA; Study Nos. MITC-UCD-1A-1993 and MITC-UCD-1B-1994; 9/10/96).

Metam Sodium degrades rapidly to methyl isothiocyanate (MITC) upon application to moist soil. The question has been posed as to whether MITC is detectable as an odor prior to the manifestation of any toxic effects. Eye

irritancy is considered to be the most sensitive toxic parameter.

The study specifically focused on determining both the olfactory threshold of MITC and the no observed effect levels (NOEL) for eye irritation at different times of exposure. The equipment employed was an olfactometer which permitted the operator to dispense the test material through a manifold system in which it could be diluted over a 100 fold range. The material was dispensed by diffusion from a glass vessel which could be maintained at any temperature ± 0.1 degree C over a range of 30 to 70 degrees C. The initial concentration of the test material was further diluted with nitrogen. The concentration of the test material in the system was determined by weighing the glass vessel prior to and at the end of the exposure period. The flow of dilution nitrogen was calibrated from a primary standard frequently throughout the study. A Total Hydrocarbon Analyzer (THA) was used to monitor the flow of the test material during the exposure period. In addition, carbon tube samples were drawn once the system had equilibrated prior to exposure and at the end of the exposure. The test material was desorbed from the carbon and analyzed by gas chromatography. Every effort was undertaken to minimize the reaction of the test material with the tubing and other equipment used in the delivery system.

In the olfactory threshold study, 33 individuals whose mean age was 25 years old (range 18 to 34 years old) were tested. They were exposed to three other positive control odorants, pyridine, acetic acid and n-butyl alcohol as well as MITC. The technician chose an odorant and a particular concentration level. The odorant was dispensed from one of three presentation ports in a double blind manner. The subject was responsible for identifying which of the presentation ports the odorant was being dispensed. A 30 second rest period between exposures was permitted in order to allow the subject to recover prior to the next exposure. The operator tested each subject over the range of concentrations for each odorant until he was assured that the threshold had been adequately ascertained. A standard procedure was employed in order to make this determination. A geometric mean was calculated based on the results of the 33 subjects.

The geometric mean for the odor threshold for MITC was calculated to be 1.7 ppm with a range from 0.2 to 8 ppm.

In the NOEL determination for eye irritancy, the olfactometer was modified by attaching goggles to the presentation lines which permitted the test material to be directed to the eyes. Five parameters were used to ascertain an irritancy response: 1) the Likert scale for subjective estimation of irritation, 2) photographs of the subjects' eyes prior to and after the exposure, 3) blink rate increase as measured by electromyography, 4) effect upon visual acuity, and 5) tear production. In this study, both a postive control, acetic acid, and a negative control, air, were employed. Baseline responses for each of the assessment parameters were determined under both pre-exposure conditions and upon exposure to the negative control for the prescribed exposure period. A postive irritancy response was based upon fulfilling 3 criteria: 1) the group's average response must be quantitatively greater than the pre-exposure response, 2) the group's average response must be greater than the pre-exposure response than would be expected statistically from individual to individual differences within the group, 3) the group's average response must be greater than the air-only group's

response than would be expected from the individual differences observed within the groups.

A total of seventy subjects ranging in age from 18 to 67 years old (mean age: 32 years old, median age: 28 years old) were exposed to the different test materials using three testing paradigms. They were exposed for 8 hours, 4 hours and 14 minutes. In the eight hour exposure protocol, response parameters were assessed prior to the initiation of the exposure, at 1.5 and 3 hours, prior to 15 and 30 minute break periods, and at 3.5 and 6 hours, followed by a 15 minute break and a final assessment at 8 hours. In the four hour exposure scenario, all of the response parameters were assessed prior to exposure initiation. At 1, 2, 3 and 4 hours, the Likert test and the blink rate measurement were undertaken. Tear production was measured at 1 and 3 hours intervals. Visual acuity was assessed at the beginning and end of the exposure. In the 14 minute exposure protocol, the pre-exposure values for the irritancy parameters were determined. Blink rate and Likert test assessments were undertaken at 2, 5, and 15 minutes after activation of flow for the test material (note: one minute elapsed before the material reached the goggles). Other assessments were performed prior to and at the end of the exposure period. In this shortest exposure scenario, the subjects were exposed to only MITC or air. All of the exposures were performed in a double blind manner.

In the 8 hour exposure, subjects were exposed to 0.22 ppm of MITC. A significant irritancy response to the test material was not noted at this level. Likewise, the subjects exposed to 0.22 ppm of MITC for 4 hours did not evoke a postive response for any of the parameters. A four hour exposure to 0.8 ppm of MITC resulted in a positive response at 1 hour and thereafter based on the Likert scale assessment. At this exposure level, the blink rate was significantly increased at the 2 and 3 hour time points. Exposure to 1.9 ppm of MITC for 14 minutes resulted in a positive Likert scale response at 4 and 14 minutes of exposure. Even at 3.3 ppm of MITC, a positive response was not evoked after 1 minute of exposure. The other parameters did not indicate a postive irritancy response at any of the exposure levels. Recovery from any indicated effects was noted to occur within 20 minutes after the cessation of the exposure.

_____ _____
Staff Toxicologist Date