The Effects of Acute Exposure to Methyl Isothiocyanate (MITC)

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Introduction

What is MITC?

- A biocide released by fumigants (i.e. metam-sodium, metam-potassium , and dazomet) in moist soils.
- Airborne vapors cause eye irritation, rashes, headache, nausea, throat irritation, salivation, coughing, and shortness of breath.
- These symptoms suggest that MITC acts directly at the point of contact and portal of entry.
- People at risk include field workers, pesticide handlers, and by-standers near treated areas.

MITC and sensory stimulation

- Isothiocyanates initiate their chemesthetic effects through TRPA1 receptors, which perform as chemesthetic transducers in somesthetic nerves, such as the trigeminal nerve (cranial nerve 5).
- MITC stimulates at low levels, below 1 ppm and the odor threshold, though its threshold lies orders of magnitude above that of other electrophiles, such as the tear gases CS and CR.
- Electrophiles can also damage tissues in a concentration- and time-dependent manner.
- Accordingly, an agent that causes eye irritation before it causes nasal irritation will more likely damage the eye before it damages nasal mucosa.

Acute Air MITC Exposure
↓
Trigeminal Nerve Stimulation
↓
Eye Detection (Feeling)
↓
Eye Irritation

Figure 1. Key events in the MOA of MITC

Methods

BMC and ten Berge Modeling

We applied concentration-time-response methods, including benchmark concentrations (BMCs) and uncertainty factors (UFs) to eye irritation data from the Russell and Rush (1996) study. The analysis accounted for both exposure level and duration to predict the probability of a response.

An algorithm developed by ten Berge (2007) and EPA (2000), available as freely downloadable software, served to estimate the parameters (b_0, b_1, b_2) to describe the relative contributions of concentration and time, and to calculate BMCs.

Russell and Rush (1996)

- 70 human volunteers, whose population included both sexes of different ages with various health conditions.
- Many of these humans were between the ages of 18 and 35, a population considered to be more sensitive to sensory irritants.
- Subjects were exposed, via goggles, to occupationally and environmentally relevant concentrations of MITC
- Five types of ocular responses were measured: perceived irritation (visual analogue scale), rate of blinking, tearing, visual acuity, and structural alterations (hyperemia, edema) evident in photos of the eye.
- Three durations of exposure (eight-hours, four-hours, and 14-minutes) were used, occurring in three non-overlapping phases, such that all testing at eight-hours preceded that at four-hours, and so on. This regimen gave the investigators the opportunity to choose concentrations strategically.
- The levels ranged from 0.22 ppm for eight- and four-hour exposures up to 3.3 ppm for the 14-minute exposures.
- Measurements were taken at intervals throughout the exposure durations.

Results

Table 1. Responders by concentration for each exposure duration in Russell and Rush (1996) based on perceived magnitude of irritation, blink rate, and tearing

Trial	Exposure Level (ppm)	Number of responders	Total Number in Exposure Group
14-MinuteTrial	0	0	10
	0.6	0	9
	1.9	3	9
	3.3	8	9
4-Hour Trial	0	0	12
	0.22	1	12
	0.8	5	9
8-hour Trial	0	0	12
	0.22	0	16

Russell and Rush: Modeling

We used incremental blink rates and ratings from t = 0 minutes to control for each individual's perception. Before the onset of exposure, the subjects indicated little or no discomfort, as shown by a modal rating for perceived irritation of 0% of full scale and a rating below 5% in 90% of measurements.

For irritation and blinking, a response was identified as adverse if **at least one** of following conditions held:

- **a person had a value of z ≥ 2 for the variable on two successive occasions;**
- **a person had a value of z ≥ 2 for the variable at the end of exposure when previous responses displayed an increasing trend**

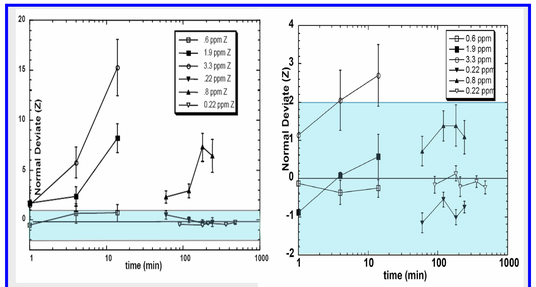

Figure 2. Mean perceived magnitude of irritation (left) and incremental blinks per minute (right) expressed as normal deviates (z), or the number of standard deviations from control, during exposure to MITC. The area shaded in blue highlights the range of normal response (-2 to 2 Normal Deviates from the mean)

Table 2. Individual BMC_{10} and $BMCL_{10}$ estimates by EPA BMDS models at two durations

Duration	Model	p-value for goodness-of-fit[a]	BMC	BMCL
14 minutes	Logistic	0.74	1.4	0.83
	Probit	0.85	1.4	0.78
4 hours	Logistic	0.44	0.37	0.22
	Probit	0.51	0.33	0.20

[a] EPA commonly recommends p > 0.1 as indicative of adequate fit.

Toxicity in Experimental Animals

Both humans and rats exhibited joint effects of concentration and duration. The rat studies by their design could address relative potency of exposure by site and could reveal differences in the pattern of potency by site.

The animal studies with exposures beyond the acute scenario also indicate sensitivity of the eye to MITC. A comparison of the 20-day NOAEL of 6.7 and 33 ppm of BASF (1987) for lung and nasal effects with the eight-hour human NOAEL of 0.22 ppm for the eye yields a difference of 30- and 150-fold, respectively. A comparison of the 90-day Rosskamp et al. (1978) lung and nasal NOAEL of 10 ppm with the human NOAEL of 0.22 equals ~45-fold.

See handout for detailed information

Jackson et al. (1981)

- An acute four-hour inhalation study with MITC
- Seven groups of 10 (five per sex) Sprague-Dawley rats.
- Rats were exposed to 0, 94, 166, 190, 210, 263 or 548 ppm (corresponding to 0, 282, 496, 570, 628, 786, or 1640 mg/m^3, respectively).
- Clinical signs of eye irritation (lacrimation and closed or partially closed eyes) were observed in 100% of the rats within 15 minutes of exposure at 94 ppm.
- Lung effects (dyspnea and gasping) were seen at 263 and 548 ppm at 15-minutes of exposure. Clinical signs of lung effects were not observed at 94 ppm until after two-hours.
- Other effects included sneezing, hunched or prone posture, rubbing of chin or paws, peripheral vasodilatation, excessive salivation and, at the higher concentrations, convulsions and death.
- Clearly illustrates that eye symptoms are the first to develop in time; signs of nasal and lung irritation develop later.
- As Figure 2 shows, only at combinations of exceedingly high concentrations and long durations, does the potency of MITC to irritate the lung catch up with its ability to irritate the eye.

Table 3. Benchmark doses for eye and lung irritation, based on the data from Jackson et al. (1981) and NOAELs from BASF (1987), show a clear magnitude of difference between eye and lung responses.

At 1.5 hours of exposure

Effect	Best-fitting model	BMD	BMDL
Eyes	Gamma	48	6.1
Lungs	Quantal-Linear or Weibull	650	520
Difference (Lungs/Eye)		**14x**	**85x**

At 2.5 hours of exposure

Effect	Best-fitting model	BMD	BMDL
Eyes	Gamma	48	6.1
Lungs	Multistage	140	96
Difference (Lungs/Eye)		**3.0x**	**16x**

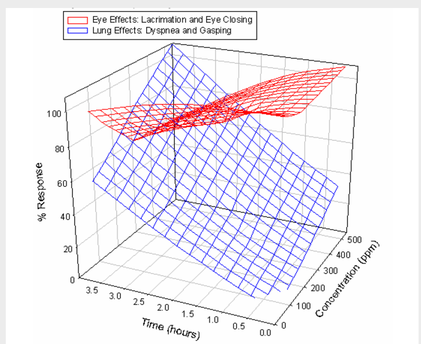

Figure 3. Eye and lung responses, manifested as lacrimation or lid closing and dyspnea or gasping vs. concentration and duration of exposure. The combined percentage of responses of the two measures assumed independence of each and was corrected for joint-responses. Based upon data from Jackson et al. (1981).

Discussion

Intra-Species Factor: Using Chemical-Specific Information to Refine the Factor

1. Direct contact with the eye stimulates the trigeminal nerves as discussed above. This MOA supports the minimal toxicokinetic variation among humans and a reduced factor from the default value of 3 for this subfactor.
2. The fact that the eye effects are very likely to be the first response in human exposures, and are the first response in experimental animal inhalation exposures adds to the weight of evidence that the effect is direct acting.
3. Since the pathway of exposure is direct MITC-containing air where surface reaction with the trigeminal nerve evokes sensations in the eyes and, furthermore, since internal dose or target tissues are not a concern for MITC because eyes are stimulated by surface concentrations, of the parent (rather than a reactive metabolite), no relevant variability in human toxicokinetics is expected.
4. There is only minor variation in ocular sensitivity among subjects aged 18 to 35 (Cain et al. 2005,2007). Young adults appear to be more sensitive than older adults, and women more so than men. Both of these sensitive groups were included in the Russell and Rush study. This MOA supports the minimal toxicodynamic variation among humans and a reduced factor from the default value of 3 for this subfactor.
5. Data from asthmatics involved in the California exposure incidents is not inconsistent with the hypothesis that eye stimulation precedes lung effects—this also indicates little toxicodynamic variability.

- **Based on these considerations, a CSAF of 1, rather than the default value of 3-fold, is reasonable for the lack of toxicokinetic variability among humans to this critical effect of eye irritation (see table 4).**
- Because the CSAF for the critical endpoint, eye effects, is less than the default, we then consider other potential critical effects and what the appropriate uncertainty factor(s) would be, in order to determine the final critical effect.

Table 4. Chemical-specific adjustments to default uncertainty factors result in an overall uncertainty factor of 1 for MITC

Uncertainty Factor	Default Uncertainty Factor	Justification for Using a Non-Default Factor	Data-supported Uncertainty Factor
Database	10	Both human & experimental animal data unequivocally indicate that eye irritation is the critical effect	1
Interspecies	10	The health protective value is based on human data	1
Toxicokinetics	3	Kinetic variability not expected, since eye effects are caused by trigeminal nerve stimulation	1
Toxicodynamics	3	Russell and Rush (1996) tested younger adults who appeared somewhat more sensitive Children appear to have no greater sensitivity to irritating stimuli than do young adults Boys & girls do not differ, but women (which have been tested) have better sensitivity than men Data from MITC incidents in asthmatics is not inconsistent with eye stimulation preceding lung effects	1 to 2
LOAEL to NOAEL Adjustment	10	An adequate benchmark dose assessment negates the need for this factor	1
Subchronic to Chronic Adjustment	10	The acute endpoint is appropriate for this assessment	1
Overall Factor (with a conservative BMCL)			1

UFs for Nasal and Lung Irritation

The IPCS (2005) guidelines recommend that once an evaluation of UFs is done for the critical effect, in this case eye irritation, and the CSAF is less than the default value of 10-fold, then additional evaluation is needed for other closely related effects. For MITC, nasal and lung irritation are closely related effects. Thus, it is appropriate to consider whether UFs for these endpoints would suggest a safe concentration after short-term exposure that is lower than that based on eye irritation.

A clear >16-fold separation exists in rats among LOAELs for eye and lung irritation after 2.5 hours from Jackson et al. (1981); this difference is much larger at shorter exposures (i.e. 1.5 hours) and further reduces concern that eye effects are not the most sensitive endpoint. Because the difference is >10-fold, a UF applied to the experimental animal NOAEL for lung irritation will not result in a lower safe concentration than that determined by eye irritation in humans. Thus, a UF applied to the effects in experimental animals for lung irritation does not result in a lower concentration than the choice of eye effects in humans as the basis for the health protective concentration after short-term exposure.

Health Protective Values

The best estimate of a health protective concentration for a four-hour exposure is 0.2. This is determined by dividing the average of the $BMCL_{s10}$ of either 0.20 or 0.22 ppm of the Russell and Rush (1996) four-hour trial found by a UF of 1 for eye irritation, as discussed above. The best estimate of a health protective concentration for a 14-minute exposure is 0.8 ppm. This value is determined by dividing the average of the $BMCL_{s10}$ of either 0.83 or 0.78 ppm for the Russell and Rush (1996) 14-minute trial found by an UF of 1.

The current assessment has considered the human data in sufficient depth that an UF can be derived based on the entirety of the data, and additional conservatism is unwarranted. The fact that Russell and Rush (1996) used sensitive individuals further supports a safe concentration of up to 0.2 ppm for four hours and up to 0.8 ppm for 14 minutes as health protective values.

TERA's judgment of a four-hour health protective value of 0.2 ppm is four-fold lower than that determined by the National Advisory Committee (NAC, 2008) for its Acute Exposure Guideline Levels (AEGL) of 0.8 ppm. However, our judgment of a 14-minute health protective value of 0.8 ppm is identical to NAC (2008) 10-minute value. In both cases, the Russell and Rush (1996) study formed the basis of the NAC evaluation and an UF of 1 was the collective best judgment.

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from Melissa Kohrman (Kohrman@tera.org)

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