Supplemental Report on the Effects of Acute Exposure To Methyl Isothiocyanate (MITC)

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Prepared for:

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March 11th, 2008

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SYNOPSIS

Toxicology Excellence for Risk Assessment (*TERA*, 2007) estimated a health protective concentration of a 4-hour exposure to MITC as 0.2 ppm. This concentration was based on a benchmark concentration lower limit (BMCL) of 0.20 ppm, which in turn was based on a 4-hour human exposure of Russell and Rush (1996). *TERA* (2007) found that the best estimate of a health protective concentration for a 14-minute exposure to MITC was 0.8 ppm, based on BMCLs of either 0.83 or 0.78 ppm for the 14-minute trial from this same study. An uncertainty factor of 1 was judged to be appropriate with both health protective concentrations.

Based on feedback from EPA staff, a number of issues were subsequently studied in relationship to these judgments; specifically, whether or not eye effects remained as the critical effect after acute exposure, whether or not trigeminal nerve stimulation was the basis for the observed eye effects, and whether or not additional uncertainty factors were needed for deficiencies in the database and for sensitive individuals.

Based on a review of additional literature, we reaffirm the eye is the critical effect after short-term exposures. On the anatomical level, we find that the trigeminal nerve singularly mediates eye feelings and its reflexes, such as tearing and blinking. The positive results of Russell and Rush (1996) are feelings of irritation, tearing and blinking, and are consistent with this singular nerve stimulation, as is the fact that these effects reverse quickly after cessation of exposure. Moreover, more severe effects, such as visual acuity and structural changes, which might be evoked by non-trigeminal nerve mechanisms, were not seen by Russell and Rush (1996). Finally, we find that an uncertainty factor of 1 is appropriate for both database deficiencies and sensitive individuals based on a review of all the available information.

1.0 INTRODUCTION

It is believed that eye irritation, mediated through stimulation of the trigeminal nerve, is the most sensitive endpoint for methyl isothiocyanate (MITC) after acute exposure. This belief is based on a number of human incident reports compiled by the State of California (e.g., Akanda, 2007), and is consistent with the types of irritant effects seen with related chemicals, such as chloropicrin. This belief has also led to the development of short-term guidance levels for California Environmental Protection Agency (Alexeeff et al. 1994) and by U.S. Environmental Protection Agency where "eye irritation can be considered as a biomarker and surrogate for potential respiratory effects" (EPA, 2007, page 21). EPA (2007) goes on to note that eye, nasal, and throat irritation are on the list of adverse effects according to EPA (1994), but at the low end of effect severity. This belief that eye irritation is the most sensitive endpoint has also prompted the development of research directly to humans and specifically, in the Russell and Rush (1996) study, where eye irritation was studied at low concentrations.

Toxicology Excellence for Risk Assessment (*TERA*, 2007) used the results of Russell and Rush (1996) to determine a safe concentration of 0.2 ppm after 4-hour exposure to MITC. This concentration was based on a benchmark concentration lower limit (BMCL) of 0.20 ppm. *TERA* found that the best estimate of a health protective concentration for a 14-minute exposure to MITC was 0.8 ppm, based on BMCLs of either 0.83 or 0.78 ppm for the 14-minute trial. An uncertainty factor of 1 was judged to be appropriate with both health protective concentrations. This is because the principal study contained sensitive individuals and a more conservative BMCL was chosen as the basis for the point of departure.

The U.S. Environmental Protection Agency (EPA) asked for additional evidence to support this belief that eye irritation is the critical effect after short-term inhalation exposure, and in the choice of a 1-fold factor for available uncertainties. In order to address this request, *TERA* reviewed several additional documents and studies to find information on irritation and other effects of MITC. Relevant information was found in a variety of human incident reports and in studies that tested for acute inhalation effects in experimental animals (including inhalation LC_{50} studies). These studies are summarized below.

2.0 METHODS

The chemical structure of MITC is shown below:

$H_3C – N = C = S$

Figure 1. Chemical structure of MITC

Routine literature searches were performed with relevant search terms. In addition, relevant literature was sought from descriptions found in EPA (2007) and California DPR

(2001). Methods used to determine safe concentrations can be found in *TERA* (2007).

3.0 RESULTS AND DISCUSSION

3.1 Is Eye Irritation the Critical Effect After Acute Exposure?

3.1.1 Review of Relevant Studies

A listing of human studies is shown in Table 1. The most definitive study on ocular effects of MITC is that of Russell and Rush (1996). These investigators measured five types of ocular responses in humans: perceived irritation (by way of a visual analogue scale), an increase in the rate of blinking, tearing, visual acuity, and structural alterations (hyperemia, edema) evident in photos of the eye. They reported changes in perceived irritation, rate of blinking, and tearing in some individuals at some exposure times and concentrations. An 8-hour No Observed Adverse Effect Concentration (NOAEC) was 0.22 ppm. Recovery from symptoms began immediately after removal of MITC and was complete within 20 minutes of exposure to the highest concentration, and substantially sooner at lower concentrations. Visual acuity and structural alterations (such as redness and swelling) were not affected.

As indicated in *TERA* (2007), the 5 assays of Russell and Rush (1996) would inevitably differ in sensitivity, as appropriate to gauge severity of effects. Furthermore, chemesthetic sensation, a term that can include feeling irritation, also allows a distinction between a feeling of irritation, normally an aversive event, and non-aversive feelings from chemicals, such as those from the bubbles of champagne. Like other compounds, MITC can cause chemesthetic sensations without signs of classically defined irritation. This was seen in the Russell and Rush (1996) study where perceived irritation was the first observed and strongest response as concentration and time increase, and where visual acuity and structural alterations, definitive signs of irritation, were absent.

Akanda (2007) reported on a series of illnesses associated with exposures to agricultural uses of metam sodium, metam potassium and dazomet from 1992 to 2003. All of these chemicals release MITC as the active ingredient. Symptoms of eye, skin and respiratory irritation were reported to occur as well as systemic symptoms such as headaches, nausea and vomiting (see Table 11 of Akanda on page 24). The frequency of symptoms including the eye were ~85% of the total. Non-eye related symptoms were ~15% of the total. Table 2 summarizes these results. Several exposures were to residences where emergency personnel were summoned. In several of these cases, emergency personnel were also reported to develop symptoms, which in all cases included burning or watering eyes or eye irritation; one case also included trouble breathing. In one case, only children were exposed while waiting for a school bus; symptoms in these children were reported as burning and watery eyes. Collectively, Akanda (2007) shows that eye irritation is the most commonly reported symptom in humans following exposure to MITC, and that it frequently, and often exclusively, appears before other symptoms.

O'Malley et al. (2005, page 34) reported on the effects of metam-sodium on human bystanders following shank-application in Arvin, California and found that, of 178 subjects with symptoms, 173 (~97%) had either burning or tearing eyes and sore throat (Table 1). Other reported symptoms with lesser frequency included headaches, vomiting, nausea, and asthma and lower respiratory irritation; several of these subjects were also noted to have eye irritation. Concentrations from this incident were estimated at 0.4-0.8 ppm for a 1-hour TWA and 1.6 to 2.4 ppm for a short-term TWA (ibid, page 37). Collectively, O'Malley et al. (2005) also shows that eye irritation is the most commonly reported symptom in humans following exposure to MITC, and that it frequently, and often exclusively, appears before other symptoms.

DPR (2001) described a human exposure in Earlimart, CA where MITC was improperly applied to agricultural fields, where it then spread to nearby neighborhoods. Symptoms of eye irritation were present in most reported cases in all of the zones studied: 81% of the 136 cases in zone A, 61% of the 18 cases in zone B, 50% of the 10 cases in zone C and 60% of the 5 cases in zone D (DPR 2001). Other non-specific symptoms and respiratory complaints were reported in each of these zones, but in a lower number of people in zones A & B, which were closest to the incident. Concentrations of MITC in this incident approximated 0.5 to 1 ppm (as time-weighted averages) as reported by O'Malley et al. (2004). Collectively, this report indicates that eye irritation was the most frequent endpoint exhibited by the Earlimart residents at each of the exposure concentrations, and it occurred in the greatest number of people over the entire exposure area.

DPR (2004, page 9) reported that 123 of 138 workers were possibly exposed following a sprinkler application of metam-sodium to a field adjacent to the grape arbor in which they were working in Kern County. Symptoms reported were: "primarily eye irritation, with some workers additionally reporting respiratory irritation and/or systemic symptoms." The exposure concentrations and times were unknown. This report suggests that eye irritation is the most commonly reported symptom in humans following exposure to MITC, and that it does or can occur without other symptoms.

CalEPA DPR (2002c) conducted a human health assessment on a metam sodium spill in the Sacramento River in 1991, which released MITC. The 1-hr TWA concentrations at the river's edge were estimated to be between 3 and 650 ppm (ibid, page 21). Of the 848 exposure-related hospital patients, 64% reported headache, 49% eye irritation, 42% throat irritation, 46% nausea, 30% dizziness, and less than 30% shortness of breath, diarrhea, nasal irritation, and chest tightness (ibid, page 22). Alexeeff et al. (1994) also used the exposures resulting from this spill, in part, to develop 1-hour reference exposure levels (RELs) for MITC. Although the Alexeeff et al. (1994) used experimental animal data to develop their No Observed Adverse Effect Concentration (NOAEC) and REL,[1] they

[1] Alexeeff et al. (1994) based their Level 1 REL (associated with discomfort) on a NOAEC for eye irritation in cats at 35 ppb for 4 hours; and their Level 2 REL (associated with disability) on respiratory tract irritation in rats at 2.9 ppm for 4 hours. The choices behind these REL developments also indicate that eye symptoms are of the most concern for discomfort and occur first as concentrations increase.

indicated that nausea, headache, and eye irritation were the most commonly reported symptoms at the start of the spill, and that eye irritation occurred during the duration of the episode (even up to 21 days after the spill). The observations made by Alexeeff et al. (1994) indicate that eye irritation occurs first as concentrations increase, and is also a prevalent finding as concentrations decrease after the spill. Collectively, these two reports show that eye irritation is a commonly reported symptom in humans following exposure to MITC, and that it can occur at relatively lower concentrations than other effects.

The California EPA (2001) reported that occupational illness was experienced near Cuyama Elementary School after a sprinkler application of metam-sodium. Of 10 workers, 6 reported symptoms. The most common symptoms reported were teary eyes, eye irritation, headache, nausea, cough, and upper respiratory pain or irritation (see Table 3 of CalEPA, 2001, on page 6). Tearing of the eyes, the most common symptom, was present in four workers. The concentrations of MITC are unknown.

Acute exposure inhalation information has also been gathered in experimental animals by a number of investigators as shown in Table 3.

Jackson et al. (1981) exposed six groups of 10 rats to MITC in doses ranging from 0.282 to 1.64 grams/m^3 (~94 to 550 ppm) in air. For every group, lacrimation and the closing of eyes were the first responses and the ones with highest frequency throughout all exposures (Jackson et al. 1981, table 2). Other effects included sneezing, hunched or prone posture, rubbing of chin or paws, peripheral vasodilatation, excessive salivation, dyspnea, and gasping, and at higher concentrations convulsions and death. This study shows that eye symptoms are the first to develop.

Other experimental animal studies of acute duration as shown in Table 3, but these studies were not reviewed in detail due to the unavailability of the original literature. Several studies show low concentrations without effect, and several studies report effects of irritation, followed by more severe symptoms. The first effect to occur as exposure concentration increase is ocular mucosa discomfort in cats at 0.035 ppm for 4 hours (Nesterova, 1969, as cited by Alexeeff et al. 1994). This is followed by lacrimation in cats at 0.070 ppm for 4 hours (Nesterova, 1969, as cited by Alexeeff et al. 1994), upper respiratory tract irritation in rats at 2.9 ppm for 4 hours (Nesterova, 1969, as cited by Alexeeff et al. 1994), and upper respiratory tract irritation in mice at 4 ppm for 4 hours (Nesterova, 1969, as cited by Alexeeff et al. 1994). However, the effects reported in cats are thought by some to be grossly inaccurate and not reproducible for humans (Russell and Rush, 1996).

Collectively, these experimental animal studies show that eye irritation occurs before other symptoms in both time and concentration, and support the observations in humans of the sensitivity of ocular tissues.

3.1.2. Trigeminal Nerve Stimulation

The trigeminal nerve, the fifth and largest cranial nerve, mediates all somatic sensation of the face, including that from the surface of the eye and the mucosa of the nasal and anterior oral cavities. The nerve has three divisions, hence its name (origin: three of one birth). Two of those divisions, the ophthalmic and maxillary divisions, innervate the nasal mucosa (see Fig. 2) and one, the ophthalmic division, innervates the cornea-conjunctiva of the eye. Even though the cornea has no blood supply, deriving its oxygen from the atmosphere, it has rich innervation by the ciliary nerves, part of the trigeminus. The innervation gives the cornea the capacity to mediate just two kinds of sensation, thermal and irritating/painful. Other sites, such as the nose and probably even the conjunctiva, allow for more nuances in sensation. Both in the cornea and other sites, the trigeminal nerve responds to chemicals via free, unmyelinated nerve endings. When stimulated, these can trigger reflexes, as well as sensations. Stimulation of any branch of the trigeminal nerve can apparently cause blinking, for example, though not with equal efficiency (Dauverne & Evinger, 2007). The vigor of reflexes often associates well with magnitude of stimulation (e.g., Jalowayski, Johnson, Wise, et al., 2001), which invites use of objective measures to assay efficacy of a stimulus.

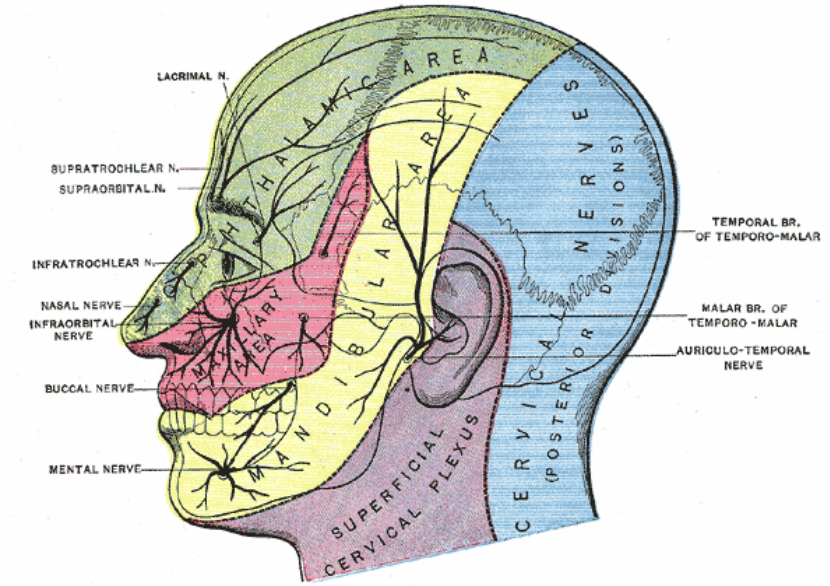

Figure 2. Dermatomes (distinct areas of neural innervation) on the face and head. Dermatomes of the face represent the pattern of innervation from the divisions of the trigeminal nerve (ophthalmic area, maxillary area, and mandibular area). The many branches of the nerve have their own names, some shown. As the figure indicates, inervation from no other somesthetic nerve overlaps with that of the trigeminal. From Gray's Anatomy, in the public domain.

Most volatile organic compounds (VOCs), e.g., solvents, have some ability to stimulate the trigeminal nerve, some with moderate potency though many with low potency that might require concentrations in the hundreds, thousands, or even tens of thousands of

ppm. Linear solvation energy relationships (LSERs), which describe the transport of molecules from the vapor phase to a biophase, can account for more than 90% of the variance in such thresholds in humans (see Abraham, Kumarsingh, Cometto-Muñiz, & Cain, 1998). Although the eye and the nose usually have comparable thresholds, they require their own coefficients in the LSER equations (Abraham, Gola, Cometto-Muñiz, & Cain, 2001). [The LSER for the eye can also account Draize scores in rabbits for bulk chemicals (Abraham, Hassanisadim, Jalai-Heravi, et al., 2003).]

Some noncorrosive chemicals from plants have potency beyond that explained by passive transfer. These have become objects of intense scrutiny as it has become evident that they stimulate through mechanisms essentially unknown until quite recently, mechanisms that have likely evolved to detect them. Methyl isothiocyanate (MITC) falls into this category. One of a variety of isothiocyanates found in edible plants or extracts, MITC appears notably in capers, a piquant spice found along the Mediterranean Sea. The compound comprises 4.5% of the volatile compounds of caper bud oil and 20% from caper leaf oil (El-Ghorab, Shibamoto, T., & Ozcan, 2007). Capers play a role in Mediterranean cuisine as an ingredient of anchovy paste, pasta, and sauces.

Other isothiocyanates appear in caper oils, just as MITC appears in other pungent natural products, such as mustard oil. These produce pungency through modulation of ion flux across neural membranes, in some instances receptor-gated and in other cases not (Jordt, Bautista, Chuang, et al., 2004). A group of cation channels, known as the transient receptor potential (TRP) family, mediates the flux (see also Bandell, Story, Hwang, et al., 2004).

A member of the TRP family, the TRPA1 occurs frequently in unmyelinated peptidergic endings of the trigeminal nerve, namely, in polymodal nociceptive fibers that respond to noxious stimulation of more than one sort, such as noxious heat or cold, mechanical forces, and pungent compounds. Mutant mice without the gene for expression of the TRPA1 channels showed no sensitivity to isothiocyanate or thiosulfinate compounds, the latter important in the pungency of onion and garlic, yet normal sensitivity to some other forms of noxious stimulation (Bautista, Jordt, Nikai, et al., 2006).

Cells transfected with human TRPA1 channels responded not only to the isothiocyanate and thiosulfinate compounds, but also to the unsaturated aldehydes acrolein and 2-pentenal. Other work showed involvement of TRPA1 in stimulation from cinnamaldehyde and the vasoactive peptide bradykinin, known for its role in sensations of pain (Bandell et al., 2004). Other chemesthetic stimuli, such as eugenol (active ingredient in cloves), gingerol (active ingredient in ginger), and methyl salicylate (active ingredient in wintergreen), failed to stimulate via TRPA1 channels.

The variety of agonists for TRPA1 posed a question about what these had in common and whether all of them stimulated TRPA1 directly or whether some stimulated indirectly, as through a receptor possibly coupled to TRPA1. The answer regarding commonality of exogenous stimuli seems to lie in the particular chemical reactivity of the stimuli. They all possess an electrophilic carbon or sulfur atom that can react with the nucleophilic

sulfur atom in cysteine sidechains of TRPA1 (Hinman, Chuang, Bautista, and Julius, 2006; Peterlin, Chesler, & Firestein, 2007). The reaction, which leads to covalent bonding, has the novel property of reversibility. In such cases, TRPA1 behaves as a ligand-gated excitatory channel. In other cases, presumably when it mediates endogenous chemicals, such as bradykinin, TRPA1 behaves as a receptor-operated excitatory channel. Receptors for that action remain unspecified.

In summary, MITC displays its high potency to stimulate chemesthesis as an agonist for a recently well-characterized ion channel that exists in polymodal nociceptive fibers of the trigeminal nerve. The polymodal properties of the fibers come in part from polymodal responsiveness of the channel itself, TRPA1. The mechanism through which isothiocyanates activate the channel entails reversible covalent modulation. The reversibility of the reaction most likely accounts for why stimulation with various pungent culinary ingredients of the appropriate class leaves chemesthetic sensitivity unaltered.

Thus, the mechanism of ocular irritation of MITC appears to be direct stimulation of the trigeminal nerve, a point that was also discussed in the chloropicrin report of *TERA* (2005). The available information from MITC exposure incidents generally support the inference that ocular irritation is a more sensitive indicator than respiratory irritation for MITC (as discussed above), as also appears to be the case for chloropicrin. This analysis mollifies a concern that certain individuals, such as asthmatics, might be uniquely sensitive to the ocular effects of MITC exposure, because asthma would not be expected from trigeminal nerve stimulation.

3.2. Choice of Uncertainty Factors

As further discussed by *TERA* (2007), because these BMCs developed from the Russell and Rush (1996) study are based on human data, no uncertainty factor (UF) for extrapolation from experimental animals is needed in developing short-term exposure limits. Similarly, the lower limits to the BMCs, or BMCLs, are NOAEL surrogates, and so no UF is needed for extrapolation from LOAEL to NOAEL. Nor is an uncertainty factor for duration needed, since the estimated safe concentrations are for the tested durations.

An uncertainty factor for insufficient database could be contemplated if some question existed as to whether effects in the eye were not the critical effect after short-term exposures. However, a review of the available literature, summarized in the preceding sections, indicates that eye effects are seen first, or at least concurrently, in nearly all human exposures where concentrations and exposure times are often not known, and perhaps more importantly, eye effects are seen first in controlled exposures to experimental animals in both time and concentration. No study reviewed indicates that an effect other than this eye irritation is likely to be seen at lower concentrations after short-term exposure. Thus, an uncertainty factor for database deficiency does not appear to be warranted for short-term safe concentrations, if effects in the eye, such as that described by Russell and Rush (1996), are the basis of the assessment.

An uncertainty factor for protecting sensitive populations should also be considered in this risk assessment. As described previously by *TERA* (2007), the choice of UF for protection of sensitive populations involves several considerations. First, a reduced factor for intraspecies variability is often used for irritants, based on the premise that minimal variability for direct contact effects exists, and that only dynamic, not kinetic variability, is relevant for such effects. The fact that the eye effects are likely due to a direct-action on trigeminal nerves, and that a steep dose-response curve may exist, also indicates little population variability in kinetics. Thus, metabolic or physiologic differences among individuals are unlikely to play a major role in the response of eye irritation. Based solely on these considerations, a default UF of ≤3 would then represent the potential for any toxicodynamic variability.

However, this default factor can also be investigated. For example, ocular irritation shows only minor variation in sensitivity among subjects aged 18 to 35 years and screened for ocular health (e.g., Cain et al., 2005, 2007). The chemesthetic studies also show quite steep stimulus-response (psychometric) functions at threshold. Furthermore, chemesthetic sensitivity diminishes little, if at all, from early to late adulthood, with some acceleration of loss in the seventh decade (Wysocki, Cowart, and Radil, 2003). Even subjects in old age may have thresholds only double those of younger adults. Since the age of the majority (58%) of subjects in Russell and Rush (1996) lay below 35 years, the majority of subjects were from the sensitive age range, and, further, since the effect of age on chemesthetic sensitivity is small, age should have had little or no influence on the results. Rather, the sensitive portion of the distribution was well-represented in the Russell and Rush (1996) population, since young adults constituted the majority of the sample. Moreover, persons less than 18 years appear to have no greater sensitive to irritating stimuli than do young adults. Children between five and 14 years evinced essentially the same sensitivity as subjects aged 15 to 20, and 21 to 54 (Hummel et al., 2007), which is not inconsistent with irritation to the eyes as the apparent first effect in children and adults Akanda (2007). Boys and girls did not differ significantly. Thus, toxicodynamic variability is likely to be smaller that the default value of 3-fold would indicate.

TERA (2007) also discussed other considerations within this default dynamic uncertainty factor of 3-fold. Specifically, persons with respiratory allergies were allowed to participate in the Russell and Rush (1996) study. In addition, Russell and Rush (1996) included both males and females, younger and older subjects, smokers and nonsmokers, allergic and non-allergic subjects, and those exposed and not exposed to chemicals in the workplace. This inclusiveness suggests enough diversity in the Russell and Rush (1996) study to represent a range in the population, with the more sensitive portion of the population generally being well-represented. Because of this, BMCLs developed from the Russell and Rush (1996) study by *TERA* (2007) would appear to address most of the uncertainty in dynamic variables, which would also argue for a smaller default value of 3-fold.

One additional concern noted in an analysis on chloropicrin (*TERA*, 2005) was the

potential for effects on asthmatics. This concern potentially also relevant for MITC since the Russell and Rush (1996) study excluded persons with symptoms of cold or allergy during the exposures, or who had recent asthma attacks. Unfortunately, there are relatively few and inconsistent data on this issue and the relative sensitivity of asthmatics versus healthy individuals to the respiratory irritant effects of sensory irritants is not generally known. No respiratory effects were monitored in the Russell and Rush (1996) study. However, data from an extensive review of the NO_2 literature (Dourson, unpublished observations) indicate that asthmatics are only about 2-fold more sensitive than healthy individuals to respiratory effects at lowest effect concentrations. In addition, the chloropicrin analysis of *TERA* (2005) indicated that respiratory effects only occurred at concentrations above the BMCL for ocular irritation, thus ocular irritation is considered the more sensitive endpoint. Based in part on an evaluation of the *TERA* (2005) report, EPA concluded that a factor of 1 was appropriate for the intraspecies uncertainty factor for chloropicrin. In reaching that conclusion, EPA evaluated the incident reports for chloropicrin, and determined that the data do not suggest that individuals with asthma are more sensitive to chloropicrin.

As for chloropicrin, the mechanism of ocular irritation of MITC is direct stimulation of the trigeminal nerve endings, as discussed earlier in this report. In addition, a review of human exposures and experimental animal toxicity studies in this report also shows that ocular effects occur either first in time and concentration, or concurrently with other effects. These facts mollify a concern that asthmatics might be more sensitive to the ocular effects of MITC exposure.

A final consideration in the choice of uncertainty factor reflects the interplay between identification of the $BMCL_{10}$ and the uncertainty factor for human variability. The $BMCL_{10}$ represents the lower bound on the response of a small percentage (10%) of a test population selected to represent the sensitive end of the general population. Indeed, based on a visual estimate of the BMC modeling results from *TERA* (2007), the best estimate of the response at the $BMCL_{10}$ for overall effects can be estimated at 1-3%. Thus, the response at the $BMCL_{10}$ is very near a true threshold in the test population. Moreover, the chosen BMCLs are from the individual time trials found in Table 4 of *TERA* (2007), and are expected to be lower than BMCLs that might be projected from the BMCs calculated using the preferred approach, and found in *TERA* (2007) Table 3. This added conservatism in choice of BMCL argues for a reduced uncertainty factor to adequately protect the sensitive end of the general population.[2]

Further support for an uncertainty factor smaller than the default value of 3 for toxicodynamics is provided by the data of Kjaergaard et al. (1992) and other data discussed above demonstrating that the threshold for sensitive individuals is within a

[2] *TERA* discussed with EPA staff whether the ongoing revisions of the EPA's BMD/C software would allow the estimation of lower limits integrated over time, like for the ten Berge model described by *TERA* (2007). Dr. Jay Zhao of EPA (NCEA, Cincinnati, Ohio, 513-569-7373) indicated that current revisions would not have this feature, but that categorical regression, another EPA model, could be used for this determination.

factor of 2 of the (average) response of young adults. Note that the Kjaergaard ratio is between the mean response of the young adults and a highly sensitive group, while the extrapolation in the *TERA* (2007) assessment is from the lower bound on the 10% response in young adults. In light of the 1 to 3% expected response at the BMCL, and the choice of BMCLs from individual time trials, rather than composite values, a UF as low as 1 applied to the $BMCL_{10}$ seems reasonable.

Thus, an uncertainty factor on the order of 1, as used by EPA for chloropicrin and by *TERA* (2007) for MITC, is still our best judgment of the appropriate human variability uncertainty factor. A value of 1-fold would be consistent with the low estimated response at the conservative point of departure. The resulting 4-hour safe concentration of MITC at 0.2 ppm and 14-minute concentration of MITC at 0.8 ppm would be health-protective values.

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Table 1. Effects Of Inhalation Exposure To MITC In Humans.

Concentration	Exposure	Symptoms	Reference/Notes
0.22 ppm	4hr, 8hr	None	Russel and Rush 1996 Effects in the eye were only monitored. Visual acuity and structural alterations were not affected
0.6 ppm	14 min	None	
0.8 ppm	4hr	Tearing, Eye irritation	
1.9 ppm	14min	Tearing, Eye irritation	
3.3 ppm	14min	Tearing, Eye irritation	
Unknown	Unknown	Eye, skin and respiratory irritation; systemic effects included headache, nausea and vomiting; all-eye effects were ~85%; all non-eye effects were ~15%	Akanda, 2007
0.4-0.8 ppm (1-hr TWA) or 1.6-2.4 ppm (short-term TWA)	Unknown	Burning or tearing eyes and sore throat in 97% (173/178 subjects); headaches, vomiting, nausea in ~41% (73/179 subjects); asthma/lower respiratory irritation in ~19% (33/178 subjects).	O'Malley et al. 2005
Zone A (<0.6 miles) 0.5-1 ppm based on a 1-hr TWA	Unknown	Eye or upper respiratory irritation in 81% of 136 cases Headache, nausea, abdominal pain, diarrhea, malaise in 57% of 136 cases Asthma or lower respiratory irritation in 12% of 136 cases	DPR 2001 and O'Malley et al. 2004 In all cases reported in all zones (A-D): all eye effects were ~76%; all non-eye effects were ~24% of which, only 1 person showed a respiratory symptom and this person did not report a specific residence in relation to the incident. (Estimates of concentration were found
Zone B (0.61-0.82 miles) 0.5-1 ppm based on a 1-hr TWA	Unknown	Eye or upper respiratory irritation in 61% of 18 cases Headache, nausea, abdominal pain, diarrhea, malaise in 78% of 18 cases Asthma or lower respiratory irritation in 6% of 18 cases	

Concentration	Exposure	Symptoms	Reference/Notes
Zone C (0.83-1.08 miles)	Unknown	Eye or upper respiratory irritation in 50% of 10 cases Headache, nausea, abdominal pain, diarrhea, malaise in 100% of 10 cases Asthma or lower respiratory irritation in 30% of 10 cases	in O'Malley et al. 2004)
Zone D (>1.08 miles	Unknown	Eye or upper respiratory irritation in 60% of 5 cases Headache, nausea, abdominal pain, diarrhea, malaise in 60% of 5 cases Asthma or lower respiratory irritation in 100% of 5 cases	
Unknown	Unknown	123 of 138 workers possibly exposed from sprinkler application of metam-sodium; symptoms were "…primarily eye irritation, with some workers additionally reporting respiratory irritation and/or systemic symptoms."	DPR 2004
3-650 ppm	Unknown	848 exposure-related hospital patients, 64% reported headache, 49% eye irritation, 42% throat irritation, 46% nausea, 30% dizziness, and less than 30% shortness of breath, diarrhea, nasal irritation, and chest tightness	Alexeeff et al. 1994 and DPR 2002c
Unknown	Unknown	10 workers possibly exposed to metam-sodium from an agricultural field application near a school; the most common symptoms experienced were "teary eyes, eye irritation, headache, nausea, cough, and upper respiratory pain or irritation."	CalEPA 2001

Table 2. Frequency of Illnessess Associated with Exposure to Agricultural uses of MITC Releasing Chemicals. Adapted from Akanda (2007).

Type of illness	Number of cases	Percent of total
eye	294	37.8%
eye, skin,	3	0.4%
eye, systemic	112	14.4%
eye, respiratory	102	13.1%
eye, skin, systemic	5	0.6%
eye, skin, respiratory	4	0.5%
eye, respiratory, systemic	116	14.9%
eye, skin, respiratory, systemic	21	2.7%
All eye effects	**657**	**84.4%**
skin	21	2.7%
systemic	34	4.4%
respiratory	14	1.8%
skin, systemic	11	1.4%
skin, respiratory	4	0.5%
respiratory, systemic	32	4.1%
skin, respiratory, systemic	4	0.5%
All non-eye effects	120	15.4%

Table 3. Effects From Inhalation Exposure To MITC In Multiple Species

Species	Concentration	Exposure	Symptoms	Reference/Notes
Rat	0.282 g/m3 (94.3ppm)	4hr	Less Severe: Licking inside of mouth, sneezing, lacrimation, eyes closed, hunched or prone posture, rubbing of chin or paws on mesh, excessive salivation, peripheral vasodilation More Severe: dyspnoea, gasping	Jackson et al. 1981 Within 15 minutes of exposure, lacrimation and/or eye closing were observed first in all animals at all dose groups (see Table 2 on page 24 of this study)
	0.496 g/m3 (166ppm)	4hr	Less Severe: Sneezing, lacrimation, eyes closed, hunched or prone posture, rubbing of chin or paws, peripheral vasodilation, excessive salivation, More Severe: dyspnoea, gasping	
	0.570 g/m3 (191ppm)	4hr	Less Severe: Sneezing, lacrimation, eyes closed, hunched or prone posture, rubbing of chin or paws, peripheral vasodilation, excessive salivation More Severe: dyspnoea, gasping	
	0.628 g/m3 (210ppm)	4hr	Less Severe: Sneezing, lacrimation, eyes closed, hunched or prone posture, rubbing of chin or paws, peripheral vasodilation, excessive salivation More Severe: dyspnoea, gasping, convulsion	
	0.786 g/m3 (263ppm)	4hr	Less Severe: Sneezing, lacrimation, eyes closed, hunched or prone posture, rubbing of chin or paws, peripheral vasodilation, excessive salivation More Severe: dyspnoea, gasping	

Species	Concentration	Exposure	Symptoms	Reference/Notes
	1.65 g/m3 (552ppm)	4hr	Less Severe: Sneezing, lacrimation, eyes closed, hunched or prone posture, rubbing of chin or paws, peripheral vasodilation, excessive salivation More Severe: dyspnoea, gasping, convulsion, death	
Original literature not available for studies shown below				
Rat	29.6 mg/m3 (9.90ppm)	0.5 hours	Death (LC 100)	Ullmann 1985b (nose only) (as cited by DPR 2002c)
Rat	207ppm	1hr	Death (LC50)	Clark and Jackson (as cited by Alexeeff et al. 1994)
Rat	1900 mg/m3 (640ppm)	1hr	Death (LC50)	Clark and Jackson 1977 (as cited by DPR 2002c) (whole body)
Cat	35 ppb	4hr	Ocular mucosa discomfort	Nesterova 1969 (as cited by Alexeeff et al. 1994)
Cat	70ppb	4hr	Lacrimation	Nesterova 1969 (as cited by Alexeeff et al. 1994)
Rat	2.9ppm	4hr	Upper respiratory tract irritation	Nesterova 1969 (as cited by Alexeeff et al. 1994)
Mouse	4ppm	4hr	Upper respiratory tract irritation	Nesterova 1969 (as cited by Alexeeff et al. 1994)
Mouse	10ppm	4hr	Death (LC50)	Nesterova 1969 (as cited by Alexeeff et al. 1994)
Mouse	75-79 mg/m3 (25 -26ppm)	4hr	Death (LC80-100)	Nesterova 1969 (as cited by DPR 2002c)
Rat	540 mg/m3	4hr	Death (LC50)	Jackson et al. (as cited

Species	Concentration	Exposure	Symptoms	Reference/Notes
	(181ppm)			by DPR 2002c)
Rat	84 ppm	24 days	Decreased body weight gain	Schering AG 1980 (as cited by DPR 2002c)
Rat	5.1 mg/m3 (1.7ppm)	4 weeks	Nasal epithelial atrophy	Klimisch et al. 1987(as cited by DPR 2002c)
Guniea Pig	0.21 ppm	1 month	No sensitization	Nesterova 1969 (as cited by DPR 2002c)
Rat	100ppm	12-13 weeks, 4days (1 hour /day & 4 hour/day)	Apathy, wet/bloody noses and mouths, 80% mortality	Rosskamp 1978 (as cited by DPR 2002c)
Cat	0.033 ppm	4 month	No effects	Nesterova 1969 (as cited by DPR 2002c)
Rat	0.153 ppm	4 month	LOEL - vascular disturbances of the lung	Nesterova 1969 (as cited by DPR 2002c)