Benchmark Concentration Modeling on the Effects of Acute Exposure to Methyl Isothiocyanate (MITC)

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1.0 INTRODUCTION[1]

When injected below the surface of soil, certain fumigants form a gas that permeates the medium and kills pests, such as insects, nematodes, microorganisms, and weeds. This mode of action belongs to the fumigants metam sodium, metam potassium, and dazomet, where the degradate methyl isothiocyanate (MITC) provides the pesticidal properties. As a vapor, MITC can move off-site. Bystanders near treated areas, as well as field workers and pesticide handlers, have risk of exposure to mucosal surfaces, such as the eyes and airways. Widespread use of fumigants, with metam sodium the third most frequently used in the US, prompts strong interest in assessment of their effects on human health.

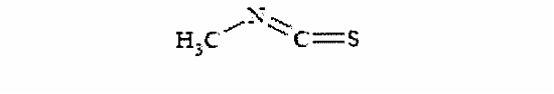

Figure 1. Chemical structure of MITC

Humans exposed to MITC have described symptoms of itchy and burning eyes, rashes and burning skin, nausea, scratchy throat, salivation, coughing, and shortness of breath. The symptoms suggest activity at the point of contact and portal of entry. Studies of oral toxicity in animals imply manifestations compatible with the human symptoms, namely activity as an irritant that produces the non-specific effects, in that case reduction in food consumption and loss of body weight, with consequent changes in hematological parameters. Acute toxicity testing with animals has led to classification of MITC as corrosive (Acute Toxicity Category 1) to skin, an eye irritant, and a skin sensitizer in guinea pigs.

1.1 Olfaction and Sensory Irritation (Chemesthesis)

Human beings can perceive the presence of most volatile organic compounds (VOCs) by one or another modality, typically olfaction at low concentrations and chemesthesis, chemically stimulated feel, including irritation, at much higher concentrations. At levels sensed as irritating, occupational exposures can distract workers and compromise their safety. For more than half of VOCs regulated in the workplace, the local effect of sensory irritation forms the basis to limit exposure (ACGIH, 2006). Protection against sensory irritation may also serve as a basis to limit exposure outside the workplace, as in homes (ASHRAE, 2006).

For the great majority of VOCs, people will sense irritation only at exposures hundreds or thousands of times the odor threshold concentration. For a few compounds, MITC among them, people may sense irritation at concentrations in the vicinity of the odor threshold. These compounds may have a recognizable odor, as MITC has a horseradish quality, but at the level where that occurs (≥1.7 ppm for MITC), the VOC may or will already have enough potency to irritate. This property belongs principally to corrosive compounds. These often stimulate via

[1] Some of this text is from the U.S. EPA Weight of Evidence Discussion for Methyl Isothiocyanate (U.S. EPA 2006)

reactions with biological nucleophiles, e.g., sulfhydryl groups of glutathione or proteins (Valentine et al., 1995).

Although the modalities of olfaction and chemesthesis share some operating characteristics, they differ in how they register chemicals over duration of exposure. Olfactory responding begins strong, then typically fades. Chemesthetic responding may begin weak, but then intensify. This will generally happen both in the eye and in the airway. Consequently, any evaluation of how humans feel airborne chemicals should include the variable of duration.

For most VOCs, chemesthetic sensitivity of the eye exceeds that of the nose or throat, though often not markedly. This outcome holds rather strongly for MITC, a fortunate occurrence because exposure to this compound poses its greatest risk to health from acute inhalation. Risk assessment for exposure to MITC can accordingly rely on studies of eye irritation and as a means to determine the point of departure (POD) for studies of acute inhalation. The eye, in effect, becomes the sentinel for the airway, both in the field and, in a manner of speaking, in the laboratory.

1.2 The Human Eye and the Chemesthetic Endpoint

Scientists have not developed convincing animal assays for ocular irritation. They have, however, developed human assays, some concerned with sensation (or "feeling"), some concerned with function, and some that link sensation and function. Regarding sensation, commonly used procedures of psychophysical methodology can quantify the magnitude of a response. Regarding function, procedures that assess interference with vision can offer means to infer debilitating irritation. A watering eye or an eye squinting from blinking, for example, will have poorer acuity, a readily measurable function. Watering and blinking mediate the link between feelings and function. Not all ocular changes subject to assay will reflect themselves in immediate functioning. Some, such as hyperemia and edema may foreshadow delayed alterations.

In a hierarchy of assays that run from the most subjective (ratings of irritation) to the least subjective (hyperemia and edema), the most subjective invariably proves the most sensitive. That is, people will feel irritated before they manifest other changes. How the assays line up in sensitivity between the extremes requires testing, but one can expect blinking to precede tearing, just as tearing will precede hyperemia. The difference between assays points up a justification, among others, for use of the term chemesthesis.

Feelings of irritation may occur without objective manifestations of irritation as a physician might define the phenomenon, i.e., no redness, no swelling, no inflammation, and so on. Although accustomed to fielding questions about subjective effects (e.g., symptoms like headache and dizziness), the physician might say, "How can one call it irritation without such signs as redness or other indicators of injury?" To modify the term and call it <u>sensory irritation</u> often gets the point across little better than to leave the word unmodified. Chemesthetic sensation, a term that can include feeling irritation, meets less resistance. It 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. The terminological distinction

should promote clarity. Like other compounds, MITC can cause chemesthetic sensations without signs of classically defined irritation. Unlike many compounds, when MITC stimulates, it apparently produces aversive sensations. This tends to hold true for most corrosive compounds.

1.3 The Russell-Rush Investigation

Russell and Rush (1996) set out to chart the course of chemesthetic responses to MITC and to measure some correlates of the responses. In their IRB-approved study, the investigators exposed human subjects via goggles to concentrations of occupational and environmental relevance and measured five types of ocular responses: perceived irritation (visual analogue scale), rate of blinking, tearing, visual acuity, and structural alterations (hyperemia, edema) evident in photos of the eye. As indicated above, these assays would inevitably differ in sensitivity, as appropriate to gauge severity of effects.

Russell and Rush studied three durations of exposure (eight hours, four hours, and 14 minutes) in an effort to chart time-dependent responses. Testing occurred 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, i.e., not to expose subjects unnecessarily. The levels ranged from 0.22 ppm for eight- and four-hour exposures up to 3.3 ppm for the 14-minute exposures.

The investigators concluded from their statistical testing that only perceived irritation and blinking held significant information about exposure at the levels explored. Using those variables, they calculated a LOEL of 0.8 ppm and a NOEL of 0.23 ppm for exposures of an hour or more, with higher levels for brief exposure.

This report re-examines the results of the Russell-Rush investigation in terms of techniques of quantitative risk assessment.

2.0 METHODS

Tables A1 to A3 of Appendix A contain the results from individual subjects for the variables of perceived magnitude of irritation, blinking, and tearing. For the variable "perceived magnitude," the tables show both the absolute rating and the increment from the rating at t = 0 min. The increment was used for all analyses, because this controlled for each individual's perception. For the variable "blinking," the tables show just incremental rate, the quantity provided in the report. (Unstimulated blinking occurs at about 12 blinks per min.) Although Russell and Rush found no significant increment in tearing with exposure, it seemed prudent to re-examine the variable by individual in the risk assessment. The data in the tables appear in the order of the age of the subjects.

In this experiment, there were three separate exposure periods: eight hours, four hours, and fourteen minutes. Each exposure duration and concentration used primarily different subjects, although a number of subjects were used for more than one duration/concentration combination; the majority of the subjects were used only once or twice, and no subject was used more than

four times. Table A1 contains results from exposures of eight hours, the duration studied in the first period of chemesthetic experimentation, where the single test concentration equaled 0.22 ppm. Table A2 contains results from exposures of four hours, the duration studied in the second period, where test concentrations equaled 0.22 and 0.8 ppm, respectively. Table A3 contains results from exposures of 14 min, the duration studied in the third period, where test concentrations were 0.6, 0.9, and 3.3 ppm, respectively.

Before the onset of exposure, the experimental and control subjects indicated little or no ocular discomfort, as shown by a modal rating for perceived irritation of 0% of full scale and a rating less than 5% for 90% of the subjects at time =0 (Fig. A1). Much the same held true for ratings obtained during the control exposures (Fig. A2). Hence, subjects generally did not find the task per se irritating to the eyes and judgments during these control conditions, whether at t = 0 or throughout the exposures to just air, left plenty of room to observe true effects.

The mean and standard deviation of responses in the control exposures permitted expression of responses during experimental exposures as normal deviates, i.e., Z-scores. Hence, if a subject's response lay two standard deviations above the mean for the control exposure at the corresponding duration, then the response received a value of 2.0. If the response lay one and a half standard deviations above that mean, then it received a value of 1.5, and so on. The procedure standardized the unit of measurement both within a variable, such as perceived magnitude, and across variables, such as perceived magnitude and blinking. It also permitted application of a uniform criterion to define a responder, $Z \geq 2$. Assuming an underlying normal distribution, a $Z \geq 2$ would occur in less than 2.5% of cases in the control exposure.

The following approach was used to identify the people with adverse responses. For the irritation and blinking endpoints, a response was identified as being adverse in any given trial if one or more of the following conditions were true:
• the person had a value of $Z \geq 2$ for the variable in question on two successive occasions; or
• the person had a value of $Z \geq 2$ for the variable in question at the end of exposure when previous responses displayed a trend toward such a value.
This approach of requiring a response at more than one time point was used to minimize false positives from variability.

These rules were applied to both perceived magnitude of irritation and blinking, but not to tearing, for which a single value of $Z \geq 2$ was sufficient to consider the response adverse. Unlike the instantaneous irritation and blinking measurements, tearing was measured infrequently during an exposure, because it required an accumulation of fluid over time, thus reducing the concern about variability across time points.

An individual was identified as a responder in a given trial if two or more endpoints were identified as adverse responses. Table 1 shows the number of responders based on the criteria for identifying adverse responses and the definition of a responder. The response rates displayed in Table 1 were used in the subsequent dose-response assessment.

Table 1. Responders by concentration in the three trials

Trial	Exposure Level (ppm)	Number of responders[2]	Total Number in Exposure Group
14-Minute Trial			
	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

2.1 Approach to Modeling

We analyzed the hazards identified in Table 1 by concentration-time-response methods, including benchmark concentrations (BMCs) and uncertainty factors (EPA, 2000a, 2000b, 2002). This analysis accounted for both the exposure level and duration in predicting the probability of a response. Such concentration-time (CxT) analyses are routinely carried out for risk assessments of short-term exposures on a variety of compounds, especially when risk estimates for various durations of exposure are needed (Zwart et al., 1990, 1992).

Those analyses typically use the following model to represent the relationships between concentration and time and response[3]

$$P(c,t) = g(b_0 + b_1*f_1(c) + b_2*f_2(t)),$$

where P(c,t) is the probability of response when the concentration is c and the duration of exposure is t. The functions g(), $f_1()$ and $f_2()$ are defined as follows.

The function g() needs to relate the linear relationship, which is its argument, to the probability scale (falling between 0 and 1). The logistic and probit functions were used for this purpose:

Logistic: $g(z) = \exp(z) / (1 + \exp(z))$
Probit: $g(z) = \Phi(z-5)$,

[2] Endpoints evaluated were perceived magnitude of irritation, blink rate, and tearing.
[3] Models with additional terms, representing other possible explanatory variables or interactions of the c and t terms are sometimes fit when needed. No other explanatory variables are proposed here. And, as shown below, no interaction terms are needed to obtain a good fitting model.

where Φ() is the cumulative standard normal distribution function. We considered both the logistic and probit functions in the following analysis.

The functions $f_1()$ and $f_2()$ were one of the following:

$f_i(u) =$ u (identity transformation)
$f_i(u) =$ ln(u) (logarithmic transformation).

We considered all four combinations of possible definitions for $f_1()$ and $f_2()$, based on identity and logarithmic transformations of both concentration and time, in the following analyses.

The algorithm developed by ten Berge (2007) and available as freely downloadable software was used to fit the CxT models for the various combinations of g() function and transformations of concentration and time, as well as to ,estimate the three parameters (b_0, b_1, b_2) needed to describe the relative contributions of concentration and time, and to calculate the BMCs. The BMCs that were calculated corresponded to an extra risk of 10%, a common choice for BMC analyses.

Unfortunately, the ten Berge software uses methods for confidence limit calculation (the Wald method; Fieller, 1944) that have been shown to produce erroneous confidence bounds (Crump and Howe, 1985).[4] Although it would be best practice to compute bounds using the CxT models directly, this was not feasible, and so we opted for an alternative that looked at specific durations separately and that computed well-behaved confidence bounds for the BMCs computed at those specific durations. The EPA software, BMDS version 1.4.1, was used to implement the logistic and probit models corresponding to the best-fitting CxT options. The BMCL estimates (benchmark concentration lower bounds) were defined as the 95% lower bounds on the BMC, corresponding to 10% extra risk.

3.0 RESULTS AND DISCUSSION

3.1 Mean Response

Figure 2 depicts how mean perceived magnitude of irritation (±sem), expressed in units of the normal deviate[5], varied with time in the three separate exposures. The line at Z = 0 corresponds to identity between experimental and control exposures. For exposure to the level 0.22 ppm for four or eight hours, perceived magnitude of irritation skirted along the line of identity for the entire exposure duration. For exposure to the level 0.6 ppm over 14 min, perceived magnitude lay close to the line of identity. For exposure to the level 0.8 ppm over four hours, perceived magnitude lay above the identity line at the first time that judgments were recorded, and the normal deviate tended to increase with exposure duration, reaching a maximum value of about seven units. For exposure to the levels 1.9 and 3.3 ppm, respectively, perceived magnitude

[4] For example, some BMC bound calculations in this analysis, computed using the method in the ten Berge software, gave negative concentrations.
[5] A deviate is defined as one standard deviation from the control value; thus a deviate score of 2 reflects two standard deviations away from the control.

began above the line of identity and increased sharply thereafter, with exposure to 3.3 ppm reaching Z = 15.

Based on the perceived magnitude of irritation data alone, in this representation, it can be reasoned that the NOAEL would be placed around 0.6 ppm for 14 minutes and perhaps longer. This is the same as the U.S. EPA's (2006) NOAEL for 14-minute exposures.

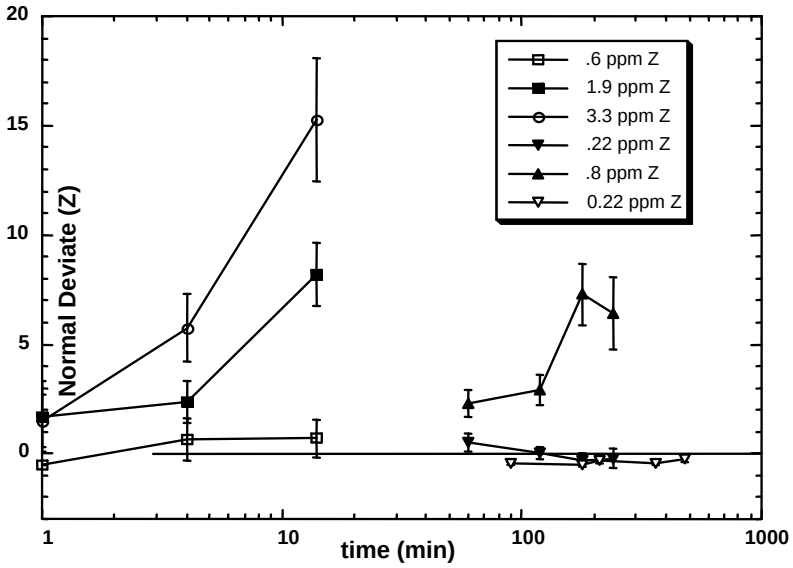

Figure 2. Mean perceived magnitude of irritation from MITC exposure (in ppm) vs. time, expressed as normal deviates (number of standard deviations from the control value of 0)

Figure 3 depicts how blinking varied with time in the three separate exposures. The general trends observed for this endpoint were similar to those seen for perceived magnitude, but blinking rate exhibited less sensitivity, with a maximum response of Z < 3. Like the variable perceived magnitude, the variable of blinking exhibited dependence on time, as well as exposure concentration. The difference in sensitivity between subjective and objective responses, properly controlled in each instance, follows the normal pattern, as indicated in the introduction (i.e., higher sensitivity for the subjective variable – perceived magnitude). Since either variable alone could qualify a person as a responder for purposes of the risk assessment, the lower sensitivity of the objective measure does not diminish the sensitivity of the result.

A visual estimate of the NOAEL based on Figure 3 would equal 0.6 ppm for 14 minutes, and perhaps longer, which is again consistent with the U.S. EPA's (2006) NOAEL for 14 minute exposures.

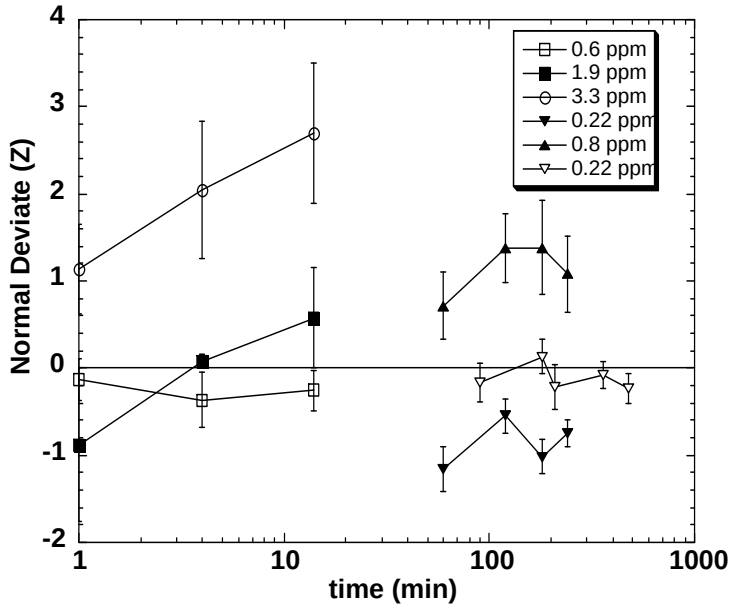

Figure 3. Mean blinks per minute from MITC exposure (in ppm) vs. time, expressed as normal deviates (number of standard deviations from the control value of 0)

3.2 BMC Modeling

Data from Table 1 were input into the CxT model described in the Methods section. As shown in Table 2, the only model configurations that gave acceptable fits to the data (i.e., p-values greater than 0.1 as per EPA's BMDS software) were either the logistic model or the probit model with the explanatory variables of "concentration" [shown in Table 2 as "c"] and the natural logarithm of time [shown in Table 2 as "ln(t)"]. These are interesting configurations because they are consistent with the following predictions: when c = 0 (air-only exposure) there is a non-zero probability of response; when t = 0 (baseline), there is zero probability of response.

Table 2. CxT Modeling results from data of Table 1 show that only the logistic and probit models with the explanatory variables of "concentration" acceptably fit the data.

Model	$f_1(c)$ =	$f_2(t)$ =	p-value for goodness-of-fit[a]
Logistic	C	t	0.006
	C	**ln(t)**	**0.12**
	ln(c)	t	< .0001
	ln(c)	ln(t)	< .0001
Probit	C	t	0.01
	C	**ln(t)**	**0.15**
	ln(c)	t	< .0001
	ln(c)	ln(t)	< .0001

[a]Smaller p-values are indicative of poorer fit. EPA typically recommends a p-value of 0.1 or greater as an indication of adequate fit.

These two predictions are appropriate for the data as we have modeled them. This is because the definition of responders (as described in the Methods section) includes the possibility of a non-zero background response. Thus an individual could present with extreme responses even with air-only exposure. Moreover, since we have used change-from-baseline for two of the three endpoints (i.e., using the incremental response for perceived magnitude and for blinking rate), the chance of having a responder (someone with two or more positive endpoint-specific responses) at t=0 should be zero. The chosen models (shown in bold in Table 2) are therefore consistent with the definitions presented in the Methods section above.

Using the maximum likelihood parameter estimates from the two chosen models, Table 3 shows CxT BMCs. As shown, very similar results were obtained for the two models.

As discussed in the Methods section, the CxT models could not be used directly to obtain reliable BMCLs. Instead, the logistic and probit models from EPA's BMDS software were separately fit to the 14-minute and 4-hour data. Results are shown in Table 4.[6] Goodness-of-fit values were all above the target p-value of 0.1.

Table 3. Combined CxT BMC estimates (ppm) at the three exposure durations

Model	14 minutes	4 hours	8 hours
Logistic	1.5	0.53	0.36
Probit	1.4	0.53	0.38

Table 4. Individual BMC and BMCL estimates by BMDS models at separate times

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]Smaller p-values are indicative of poorer fit. EPA typically recommends a p-value of 0.1 or greater as an indication of adequate fit.

The individual analyses presented in Table 4 produced BMC estimates that were comparable to or less than the preferred CxT models of Table 3. Near identical BMC results were obtained for the 14-minute duration using both approaches (Table 3 vs. Table 4) and both models. For the 4-hour duration, the BMCs of Table 4 are 62% to 70% of the corresponding BMCs estimated using the CxT approach (e.g., compare a value of 0.53 for the CxT probit model in Table 3 with the corresponding value of 0.33 found in Table 4).
The fact that the BMCs for the separate 4-hour analysis are less than the corresponding BMCs from the CxT modeling suggests that the BMCLs computed from the separate 4-hour analysis will also be less than what would have been obtained from a BMCL treatment of the combined

[6] No separate modeling was done for the 8-hour data because there were only two exposure groups (including control) for that time, and there were no responders in either group.

CxT data set. In addition, the lower bounds depend on the number of observations; the greater the number the observations, the tighter the bounds will be, all else being equal. Thus, because the the individual analyses of Table 4 were restricted to one duration at a time, the sample size was smaller; this also suggests that the BMCLs from the individual analyses would tend to be lower than would be obtained when the combined data set was analyzed together as in Table 3. These two facts make it likely that the reported BMCLs, especially for the 4-hour duration, are "conservative" in the sense that they are lower than would be obtained from a preferred analysis (were it possible to do that preferred analysis). Therefore, use of the individual BMCLs as a starting point for the estimation of a safe concentration would be health protective.

Both Figures 2 and 3 are consistent with the BMCs found in Tables 3 and 4. The figures show a NOAEL of 0.6 ppm for MITC exposures of 14 minutes and perhaps longer, and a NOAEL of 0.22 ppm at longer exposures to MITC. Table 4 suggests a BMCL of 0.22 ppm based on the logistic model for a 4-hour exposure; a BMCL of 0.83 ppm was estimated from that same model for a 14-minute exposure.

3.3 Choice of Uncertainty Factors

Because these BMCs are based on human data, no uncertainty factor (UF) for extrapolation from experimental animals is needed. 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. Nor is an uncertainty factor for insufficient database needed, since the critical effect, irritation, is considered to be more sensitive than other endpoints. However, an uncertainty factor for protecting sensitive populations should be considered in this risk assessment, as described below.

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 there is minimal variability for direct contact effects, and that only dynamic, not kinetic variability, is relevant for such effects. The standard operating procedures for developing Acute Exposure Guideline Levels (AEGLs) (NRC, 2001**)** state that a UF of 3 is generally used for human variability when the mechanisms of action is such that the response to the chemical is unlikely to differ in different subpopulations. The procedures further note that this response typically involves a direct-acting mechanism of toxicity in which metabolic or physiologic differences are unlikely to play a major role, and a steep dose-response curve may also indicate little population variability. Based solely on this initial consideration, and the fact that the critical effects are irritation endpoints, a default UF of 3 would be considered as adequate for MITC. This default 3-fold factor would represent the potential toxicodynamic variability.

Studies of ocular irritation show minor variation in sensitivity among subjects aged 18 to 35 years and screened for ocular health (Cain et al., 2005, 2007). The chemesthetic studies also show quite steep stimulus-response (psychometric) functions at threshold. To illustrate the point, the span of concentrations between a barely detectable sensation (e.g., 10% detectability) and a consistently detected sensation (e.g., 90% detectability) normally equals about sixfold. Similarly, the span between the least and most sensitive person, as measured at a given criterion

of performance, such as the point of 50% detection, is normally less than tenfold[7]. Essentially the same holds for chemesthetic sensitivity in the nose among subjects screened for health of the airways.

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. This is in contrast to the threshold for olfaction, which may increase by more than one hundredfold between early adulthood and old age. Since (1) the age of the majority (58%) of subjects in Russell and Rush's tests lay below 35 years (a common cut-off for participants in chemosensory experiments to avoid effects of age), (2) the majority of subjects were from the sensitive age range, and (3) the effect of age on chemesthetic sensitivity is small, age should have had little or no influence on the results. (Only three exposures included a person of aged 60 or above.) Rather, the sensitive portion of the distribution was well-represented in the sample population, since young adults constituted the majority of the sample. As shown in Appendix A, the younger study subjects appear to have been more sensitive to MITC exposure on average than the older ones.

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). Boys and girls did not differ significantly. Among adult subjects, however, women have sometimes exhibited slightly better sensitivity than men by criteria other than threshold (Garcia Medina and Cain, 1982; Dunn et al., 1982). Lack of consistency across studies suggests at most a small underlying effect, easily obscured by random intersubject variability. Russell and Rush included approximately included half females and half males in their study.

Aside from age and sex as systematic demographic variables with possible effects on sensitivity, most other variables would likely have a desensitizing influence. This includes smoking and chronic exposure to chemicals (Cometto-Muñiz and Cain, 1982; Dunn et al. 1982; Smeets and Dalton, 2002). Russell and Rush apparently did not exclude smokers or subjects with chronic chemical exposure.

Russell and Rush did allow persons with respiratory allergies to participate, but they excluded persons who "evinced current symptoms of cold or allergy" (p. 12) or "recent asthma attacks" (p. 27). People with chronic allergies have shown a less than twofold gain in sensitivity in nasal chemesthesis, even though the testing took place in dormant phases of the allergies (Shusterman et al., 2003). As Kjaergaard et al. (1992) discovered, however, some effects evident in the nose fail to hold for the eye. In general, the eye seems less affected by variables such as sex, smoking, and allergies. With respect to the investigation of Russell and Rush, inclusion of both males and females, younger and older subjects, smokers and nonsmokers, allergic and non-allergic subjects, and perhaps those exposed and not exposed to chemicals in the workplace suggests that there was enough diversity in the sample to represent the range in the population,

[7] Note that the intraspecies UF is not intended to cover the full range of human variability. Instead, it extrapolates from the low end of the dose-response curve, corresponding to the NOAEL in the tested population. Thus, total population variability of a factor of less than 10 is consistent with an intraspecies UF of less than 10.

with the more sensitive portion of the population generally being well-represented. If so, then estimates of BMCLs would seem already to have dealt with most of the uncertainty that might have come from systematic variables. It is noted that the study sample did not include hypersensitive individuals, but these people are also excluded from UF consideration using standard approaches (EPA, 2002).

One concern noted in an analysis on chloropicrin (*TERA*, 2005) was the potential for effects on asthmatics. The documentation for several AEGLs noted this concern for respiratory irritant effects in asthmatics, and asthmatics were often described as sensitive (or presumed sensitive) populations because of dynamic differences in the development of AEGLs for sensory irritants, sometimes using a full factor of 10, but more often using smaller factors. Unfortunately, there are relatively few and inconsistent data on this issue and the relative sensitivity of asthmatics vs. healthy individuals to the respiratory irritant effects of sensory irritants is not generally known. No respiratory effects were monitored in the Russel 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 UF 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 free nerve endings, a point that was discussed in the chloropicrin report, and available information from MITC exposure incidents generally support the inference that ocular irritation is a more sensitive indicator than respiratory irritation for MITC (Manley, personal communication), as appears the case for chloropicrin. All of this analysis mollifies 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 BMCL10 and the uncertainty factor for human variability. The BMCL10 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 (see the Appendices B and C for Logistic or Probit model Figures), the best estimate of the response at the BMCL10 for overall effects can be estimated at 1-3%. Thus, the response at the BMCL10 is very near a true threshold in the test population. The choice of the uncertainty factor would still need to consider the remaining population variability, the uncertainty in response in the test population, and the remaining distance between a 1-3% response and the population threshold. However, additional bounding information is provided by the observation that no responders were found at 0.22 ppm for 8 hours, the presumed threshold concentration. Moreover, the chosen BMCLs are from the individual time trials found in Table 4, and are expected to be lower than BMCLs that might be projected from the BMCs calculated using the preferred approach, and found in Table 3. This added conservatism argues for a reduced uncertainty factor

Overall, based on the use of a BMCL10 for a sensitive endpoint for which human variability is generally considered to be relatively small (eye irritation without lingering effects) from the sensitive end of the general population, an UF of 10 for human variability is inappropriately large. A factor of 3 or smaller is clearly supported, and consistent with the recommendations of NRC (2001**)**. Note, however, that the NRC recommendations are generally applied to animal data, or human data on the general population, rather than data from the sensitive end of the general population, and thus an uncertainty factor of less than 3 might be appropriate. Further support for a UF smaller than 3 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 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 current 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 BMCL10 seems reasonable.

Thus, an UF in the order of 1, as used by EPA for chloropicrin, is our best judgment of the appropriate human variability UF. This is a health-protective value. A value of 1-fold would be consistent with the low estimated response at the conservative point of departure.

3.4 Health Protective Concentrations

The best estimate of a health protective concentration for a 4-hour exposure is 0.2. This is determined by dividing the average of the BMCLs of either 0.20 or 0.22 ppm of the 4-hour trial found in Table 4 by an uncertainty factor of 1, 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 BMCLs of either 0.83 or 0.78 ppm for the 14-minute trial found in Table 4 by an uncertainty factor of 1, as discussed above.

The current assessment has considered the human data in sufficient depth that an uncertainty factor can be derived based on the entirety of the data, and additional conservatism is unwarranted. The fact that the study demonstrated the use of sensitive individuals by an analysis of differences in responses among ages further supports a safe concentration of up to 0.2 ppm for 4 hours and up to 0.8 ppm for 14 minutes as health protective values.

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APPENDIX A

Data from the Russell & Rush (1996) Eye Irritation Study

Table A 1. Perceived magnitude of irritation (recorded as % of full scale), blink rate, and tearing data recorded for each subject during the 8 hour exposure duration
Time: 8 hours

air

ID			Perceived Magnitude					Increment from t = 0 min						Blinking (counts per minute)						Tearing (mg)					
s-e#	ISN	age	0 hour	1.5hr	3hr	3.5hr	6hr	8hr	0 hour	1.5hr	3hr	3.5hr	6hr	8hr	0 hour	1.5hr	3hr	3.5hr	6hr	8hr	0 hour	1.5hr	3hr	3.5hr	6hr	8hr
31-T	65	19	3	3	3	1	6	2	0	0	0	-2	3	-1	0	7	7	8	8	8		8	2			7
25-S	3	20	3	2	22	2	50	2	0	-1	19	-1	47	-1	0	-10	-9	-4	-4	-6		6	1		4	4
21-R	25	22	1	6	5	9	9	4	0	5	4	8	8	3	0	1	-2	-3	-2	-3		14	7		10	4
13-S	52	24	1	7	4	2	3	3	0	6	3	1	2	2	0	-5	2	-4	-8	-7		1	3		6	1
6-S	13	26	0	10	33	0	24	2	0	10	33	0	24	2	0	2	-7	-2	-2	-7		9	9		4	1
19-S	54	27	0	2	1	0	1	0	0	2	1	0	1	0	0	-2	-10	-3	-4	1		2	4		7	2
3-R	34	31	0	0	0	0	0	7	0	0	0	0	0	7	0	6	8	9	12	8			8			7
27-S	36	31	2	39	44	34	56	39	0	37	42	32	54	37	0	10	6	2	3	9		5	1		3	3
9-R	56	34	3	6	4	3	13	3	0	3	1	0	10	0	0	-6	-9	-9	0	-6		19	4		5	6
15-R	59	38	0	15	1	1	3	2	0	15	1	1	3	2	0	-14	-9	-5	-11	0		9	8		10	4
37-T	1	46	3	12	22	15	14	31	0	9	19	12	11	28	0	-9	-6	1	-6	-6		4	3		6	1
34-T	46	52	2	3	3	1	3	2	0	1	1	-1	1	0	0	-2	-6	-3	0	9		4	4		6	4
>30 average			2	13	12	9	15	14	0						0	-3	-3	-1	0	2	na	8	5	na	6	4
<30 average			1	5	11	2	16	2	0						0	-1	-3	-1	-2	-2	na	6	7	na	6	2
<25 average			2	5	9	4	17	3	0						0	-2	-1	-1	-2	-2	na	7	3	na	7	4
					Average					7.25	10.33	4.17	13.67	6.58		-1.83	-2.92	-1.08	-1.17	0.00		7.36	4.50		6.10	3.67
					Standard Deviation					10.53	14.53	9.68	18.51	12.45		7.36	6.87	5.26	6.48	6.78		5.33	2.81		2.38	2.19
					Average (excluding subject 27-S)					4.55	7.45	1.64	10.00	3.82												
					Standard Deviation (excluding subject 27-S)					5.05	11.08	4.32	14.12	8.34												

0.22ppm

ID			Perceived Magnitude						Increment from t = 0 min						Blinking (counts per minute)						Tearing (mg)					
s-e#	ISN	age	0 hour	1.5hr	3hr	3.5hr	6hr	8hr	0 hour	1.5hr	3hr	3.5hr	6hr	8hr	0 hour	1.5hr	3hr	3.5hr	6hr	8hr	0 hour	1.5hr	3hr	3.5hr	6hr	8hr
14-T	14	19	0	2	2	0	0	1	0	2	2	0	0	1	0	-10	-5	-6	-7	-11		5	4		6	9
24-R	4	20	3	5	3	5	32	11	0	2	0	2	29	8	0	-6	-7	-6	0	-5		2	9		7	2
26-R	70	20	1	7	0	0	0	0	0	6	-1	-1	-1	-1	0	0	4	5	2	5		3	4		8	5
28-T	11	22	0	5	7	4	6	5	0	5	7	4	6	5	0	-1	1	1	-1	3		7	2		3	2
23-T	20	23	6	7	7	3	12	11	0	1	1	-3	6	5	0	-2	3	6	4	0		2	2		1	2
4-T	50	24	3	13	10	3	9	13	0	10	7	0	6	10	0	-1	-3	-5	-4	-2			5			1
5-S	16	25	5	8	7	8	14	12	0	3	2	3	9	7	0	-13	-1	-2	2	-6			5			6
20-T	49	27	3	3	8	13	8	2	0	0	5	10	5	-1	0	0	-7	-1	-5	-2		4	0		1	2
18-R	26	28	2	10	11	9	7	7	0	8	9	7	5	5	0	-10	-8	-12	-10	-8		3	8		5	7
10-T	35	28	8	5	13	2	14	9	0	-3	5	-6	6	1	0	8	10	8	4	0		9	2		9	8
33-S	42	31	0	0	0	1	3	0	0	0	0	1	3	0	0	-3	-4	-5	-7	2		3	2		4	3
36-S	5	39	3	5	6	4	7	8	0	2	3	1	4	5	0	-8	-8	-8	-2	-5		6	2		5	3
35-R	23	39	5	6	7	2	9	8	0	1	2	-3	4	3	0	12	5	-6	1	2		7	3		3	2
32-R	48	43	0	0	0	0	0	0	0	0	0	0	0	0	0	-2	-8	-1	0	4		5	2		4	2
12-R	61	48	0	0	0	0	0	0	0	0	0	0	0	0	0	-5	-3	0	-2	-4		6	3		6	2
11-S	7	60	1	1	1	2	3	2	0	0	0	1	2	1	0	-8	-1	-4	-2	2		6	0		7	4
>30average			2	2	2	2	4	3	0						0	-2	-3	-4	-2	0	na	6	2	na	5	3
<30 average			3	7	7	5	10	7	0						0	-4	-1	-1	-2	-3	na	5	4	na	5	6
<25 average			2	7	5	3	10	7	0						0	-3	-1	-1	-1	-2	na	4	4	na	5	4

Table A 1. Perceived magnitude of irritation (recorded as % of full scale), blink rate, and tearing data recorded for each subject during the 4 hour exposure duration
Time: 4 hours

Air only

ID			Perceived Magnitude					Increment from t = 0 min					Blinking (counts per minute)					Tearing (mg)				
s-e#	ISN	age	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr
13a	12	19	1	2	2	2	1	0	1	1	1	0	0	2	8	14	5		5			4
27a	67	19	0	5	4	2	1	0	5	4	2	1	0	9	26	6	12		3			8
46a	9	21	4	14	28	18	15	0	10	24	14	11	0	2	3	-1	5		5			7
37a	25	22	5	13	12	13	12	0	8	7	8	7	0	-3	3	7	4		8			9
23a	63	26	0	0	0	0	0	0	0	0	0	0	0	3	-1	7	-2		5			2
3a	42	31	1	1	1	0	1	0	0	0	-1	0	0	-6	-9	-10	-10		2			4
18a	2	35	0	29	9	5	16	0	29	9	5	16	0	3	7	10	10		6			6
30a	17	40	0	0	0	0	0	0	0	0	0	0	0	16	7	12	14		3			7
42a	31	43	0	2	2	8	3	0	2	2	8	3	0	8	0	0	5		4			4
50a	69	51	1	1	1	1	1	0	0	0	0	0	0	1	1	-2	4		9			6
34a	33	52	1	2	2	7	1	0	1	1	6	0	0	-6	-8	-8	-13		4			8
8a	8	67	1	1	1	1	1	0	0	0	0	0	0	6	3	-2	6		5			7
>30 average			1	5	2	3	3	0					0	3	0	0	2	na	5	na	na	6
<30 average			2	7	9	7	6	0					0	3	8	7	5	na	5	na	na	2
<25 average			3	9	12	9	7	0					0	3	10	7	7	na	5	na	na	7
					Average				4.67	4.00	3.58	3.17		2.92	3.33	2.75	3.33		4.92			6.00
					Standard Deviation				8.39	6.98	4.64	5.36		6.35	8.94	7.72	8.11		2.02			2.09

0.22ppm																					
ID			**Perceived Magnitude**					**Increment from t = 0 min**					**Blinking (counts per minute)**					**Tearing (mg)**				
s-e#	ISN	age	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr
47a	66	18	0	5	1	0	0	0	5	1	0	0	0	-2	-6	-1	-6		3			5
44a	15	19	0	17	0	0	0	0	17	0	0	0	0	-8	-2	-4	-6		3			4
51a	27	19	2	1	3	2	23	0	-1	1	0	21	0	-8	1	-4	2		2			2
49a	45	19	2	15	8	5	4	0	13	6	3	2	0	-5	6	-9	2		13			7
41a	10	21	1	2	2	2	2	0	1	1	1	1	0	-5	4	4	-5		7			6
38a	53	21	3	25	8	8	8	0	22	5	5	5	0	-11	-2	-8	-1		4			9
40a	28	22	9	42	29	23	10	0	33	20	14	1	0	-5	2	-9	-1		9			7
39a	40	22	28	40	28	22	13	0	12	0	-6	-15	0	-3	0	-10	-7		8			5
45a	26	28	1	5	14	10	6	0	4	13	9	5	0	-14	-6	-14	-10		4			5
48a	23	39	3	3	3	3	6	0	0	0	0	3	0	6	-13	1	-2		5			5
52a	18	46	0	1	2	1	1	0	1	2	1	1	0	4	6	-2	4		6			10
43a	46	52	0	0	0	0	0	0	0	0	0	0	0	-2	-9	-5	-3		7			9
>30 average			1	1	2	1	2	0					0	3	-5	-2	0	na	6	na	na	8
<30 average			5	17	10	8	7	0					0	-7	0	-6	-4	na	4	na	na	5
<25 average			6	18	10	8	8	0					0	-6	0	-5	-3	na	6	na	na	6
					Average														7.00			7.00
					Standard Deviation														2.83			1.94

0.8ppm

ID			Perceived Magnitude					Increment from t = 0 min					Blinking (counts per minute)					Tearing (mg)				
s-e#	ISN	age	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr	0 hour	1 hr	2 hr	3hr	4hr
29a	6	19	2	3	3	34	34	0	1	1	32	32	0	6	23	12	19		0			6
28a	27	19	5	39	38	66	66	0	34	33	61	61	0	7	18	22	28		2			3
26a	55	19	1	16	17	51	32	0	15	16	50	31	0	1	16	30	22		3			6
21a	58	19	0	30	41	20	19	0	30	41	20	19	0	10	18	12	6		6			6
20a	62	22	0	16	12	13	16	0	16	12	13	16	0	0	0	-4	0		9			6
19a	26	28	0	48	28	28	16	0	48	28	28	16	0	2	-4	-6	-4		3			4
2a	44	29	1	37	44	67	94	0	36	43	66	93	0	14	25	21	12		2			12
5a	1	46	0	24	25	40	42	0	24	25	40	42	0	4	19	9	7		7			6
4a	69	51	6	15	27	32	34	0	9	21	26	28	0	23	26	25	19		11			10
>30 average			3	20	26	36	38	0					0	14	23	17	13	na	9	na	na	8
<30 average			1	27	26	40	40	0					0	6	14	12	12	na	3	na	na	8
<25 average			2	21	22	37	33	0					0	5	15	14	15	na	4	na	na	5
					Average														4.78			6.56
					Standard Deviation														3.67			2.79

Table A3. Perceived magnitude of irritation (recorded as % of full scale), blink rate, and tearing data recorded for each subject during the 14 minute exposure duration

Time: 14 min

Air only

ID			Perceived Magnitude				Increment from t = 0 min				Blinking (counts per minute)				Tearing (mg)			
s-e#	ISN	age	0 min	1 min	4 min	14 min	0min	1min	4min	14 min	0min	1min	4min	14 min	0 min	1 min	4 min	14 min
45b	66	18	0	8	6	3	0	8	6	3	0	4	4	2				1
41b	58	19	0	4	6	12	0	4	6	12	0	-2	-7	-12				2
8b	29	22	0	0	0	0	0	0	0	0	0	12	17	24				1
25b	44	29	0	0	0	0	0	0	0	0	0	-7	0	6				1
32b	17	40	0	0	3	1	0	0	3	1	0	0	1	-4				1
29b	18	46	0	0	0	0	0	0	0	0	0	7	7	-6				4
16b	69	51	2	2	3	2	0	0	1	0	0	7	-1	13				5
13b	46	52	0	0	0	0	0	0	0	0	0	-5	-5	7				2
38b	21	55	0	1	1	3	0	1	1	3	0	10	0	2				2
21b	57	55	3	4	5	10	0	1	2	7	0	-7	-4	4				2
>30 average			1	1	2	3					0	2	0	3	na	na	na	3
<30 average			0	3	3	4					0	2	4	5	na	na	na	1
<25 average			0	4	4	5					0	5	5	5	na	na	na	1
				Average			1.40	1.90	2.60		1.90	1.20	3.60					2.10
				Standard Deviation			2.63	2.38	4.01		7.06	6.92	10.11					1.37

0.6ppm

ID			Perceived Magnitude				Increment from t = 0 min				Blinking (counts per minute)				Tearing (mg)			
s-e#	ISN	age	0 min	1 min	4 min	14 min	0 min	1 min	4min	14min	0min	1 min	4min	14 min	0min	1 min	4 min	14 min
36b	44	29	0	0	0	0	0	0	0	0	0	-6	1	8				3
44b	43	31	0	0	3	3	0	0	3	3	0	-3	-8	-6				2
37b	22	35	0	0	0	0	0	0	0	0	0	2	14	14				2
43b	24	35	0	0	0	1	0	0	0	1	0	2	-7	-7				7
40b	1	46	0	0	0	2	0	0	0	2	0	10	0	7				-1
47b	18	46	0	0	0	0	0	0	0	0	0	-5	-2	-2				5
46b	19	49	0	0	18	31	0	0	18	31	0	2	0	0				2
39b	69	51	3	3	3	6	0	0	0	3	0	5	-5	0				3
42b	46	52	0	0	10	8	0	0	10	8	0	2	-5	-5				0
>30 average			0	0	4	6					0	2	-2	0	na	na	na	3
<30 average			na	na	na	Na					na	na	na	na	na	na	na	3
<25 average			na	na	na	na					na	na	na	na	na	na	na	na
					Average							1.00	-1.33	1.00				2.56
					Standard Deviation							5.02	6.60	7.19				2.40

1.9ppm

ID			Perceived Magnitude				Increment from t = 0 min				Blinking (counts per minute)				Tearing (mg)			
s-e#	ISN	age	0 min	1 min	4 min	14 min	0min	1min	4min	14 min	0 min	1 min	4 min	14 min	0min	1 min	4min	14 min
19b	66	18	0	37	8	27	0	37	8	27	0	-13	4	0				2
26b	15	19	0	0	0	21	0	0	0	2	0	-5	2	-1				5
20b	39	19	18	17	31	79	0	-1	13	61	0	-4	0	22				2
24b	43	31	0	6	9	50	0	6	9	50	0	-1	5	14				2
17b	68	33	2	9	14	29	0	7	12	27	0	-12	-4	-14				0
27b	23	39	3	6	22	50	0	3	19	47	0	10	17	24				7
23b	17	40	0	0	0	19	0	0	0	19	0	4	6	17				0
18b	32	47	0	0	5	17	0	0	5	17	0	-30	-30	-26				3
22b	21	55	0	1	2	49	0	1	2	49	0	12	16	49				3
>30 average			1	4	9	36					0	-3	2	11	na	na	na	3
<30 average			6	18	13	42					0	-7	2	7	na	na	na	3
<25 average			same as <30 average												na	na	na	na
						Average						-4.33	1.78	9.44				2.67
												12.9	13.7	22.4				
						Standard Deviation						7	5	1				2.24

3.3ppm

ID			Perceived Magnitude				Increment from t = 0 min				Blinking (counts per minute)				Tearing (mg)			
s-e#	ISN	age	0 min	1 min	4 min	14 min	0min	1min	4min	14 min	0 min	1 min	4 min	14 min	0 min	1 min	4 min	14 min
10b	13	26	0	16	24	100	0	16	24	100	0	30	26	44				53
11b	63	26	0	25	30	86	0	25	30	86	0	11	14	44				2
9b	64	30	0	0	7	58	0	0	7	58	0	18	38	68				1
7b	38	44	0	1	28	86	0	1	28	86	0	4	1	38				7
14b	18	46	0	0	5	16	0	0	5	16	0	10	38	55				4
12b	61	48	0	0	19	96	0	0	19	96	0	5	20	4				8
15b	19	49	10	10	18	68	0	0	8	58	0	-10	0	2				76
6b	7	60	0	6	16	58	0	6	16	58	0	14	8	22				9
5b	8	67	0	0	3	16	0	0	3	16	0	7	-7	1				1
>30 average			1	2	14	57					0	7	14	27	na	na	na	15
<30 average			0	21	27	93					0	21	20	44	na	na	na	28
<25 average			na	Na	na	na					na	na	na	na	na	na	na	na
													15.3	30.8				17.8
					Average							9.89	3	9				9
												10.9	16.4	24.7				27.2
					Standard Deviation							0	2	1				0

Table A 2. Perceived magnitude of irritation data (recorded as % of full scale) collected from trials involving only air and no MITC [8]

	Time: 14 min				Time: 4 hours			Time: 8 hours		
ISN	air	0.6ppm	1.9ppm	3.3ppm	air	0.22	0.8	Air	0.22	Average
1		0					0	3		1.00
2					0					0.00
3								3		3.00
4									3	3.00
5									3	3.00
6							2			2.00
7				0					1	0.50
8				0	1					0.50
9					4					4.00
10						1				1.00
11									0	0.00
12					1	0				0.50
13				0				0		0.00
14									0	0.00
15			0							0.00
16									5	5.00
17	0		0		0					0.00
18	0	0		0		0				0.00
19		0		10						5.00
20									6	6.00
21	0		0							0.00
22		0								0.00
23			3			3			5	3.67
24		0								0.00
25					5			1		3.00
26						1	0		2	1.00
27						2	5			3.50
28						9				9.00
29	0									0.00
31					0					0.00
32			0							0.00
33					1					1.00
34								0		0.00
35									8	8.00
36								2		2.00
38				0						0.00
39			18							18.00
40						28				28.00
42					1				0	0.50

[8]

43		0	0						0.00
44	0	0				1			0.33
45					2				2.00
46	0	0			0		2		0.50
48								0	0.00
49								3	3.00
50								3	3.00
52							1		1.00
53					3				3.00
54							0		0.00
55						1			1.00
56							3		3.00
57	3								3.00
58	0					0			0.00
59							0		0.00
61				0				0	0.00
62						0			0.00
63				0	0				0.00
64				0					0.00
65							3		3.00
66	0		0		0				0.00
67					0				0.00
68			2						2.00
69	2	3			1	6			3.00
70								1	1.00
95th percentile									7.70

Table A 3. Perceived magnitude of irritation data (recorded as % of full scale) from all trials where MITC concentrations are at 0ppm (air only studies and at t=0)

Air					T=0											4hr study	8hr study					
ISN	air	0.6ppm	1.9ppm	3.3ppm	air	0.22	0.8	air	0.22	1min	4min	14min	1hr	1.5hr	2hr	3hr	3hr	3.5hr	4hr	6hr	8hr	Average	Standard Dev
1		0					0	3						12			22	15		14	31	12.1	10.97
2					0								29		9	5			16			11.8	11.26
3								3						2			22	2		50	2	13.5	19.55
4									3													3.0	
5									3													3.0	
6							2															2.0	
7				0					1													0.5	0.71
8				0	1								1		1	1			1			0.8	0.41
9					4								14		28	18			15			15.8	8.61
10						1																1.0	
11									0													0.0	
12					1	0							2		2	2			1			1.3	0.82
13				0				0						10			33	0		24	2	9.9	13.47
14									0													0.0	
15			0																			0.0	
16									5													5.0	
17	0		0		0					0	3	1	0		0	0			0			0.4	0.97
18	0	0		0		0				0	0	0										0.0	0.00
19		0		10																		5.0	7.07
20									6													6.0	
21	0		0							1	1	3										1.0	1.22
22		0																				0.0	
23			3			3			5													3.7	1.15
24		0																				0.0	
25					5			1					13	6	12	13	5	9	12	9	4	8.1	4.13

26						1	0		2													1.0	1.00
27						2	5															3.5	2.12
28						9																9.0	
29	0									0	0	0										0.0	0.00
31					0								2		2	8			3			3.0	3.00
32			0																			0.0	
33					1								2		2	7			1			2.6	2.51
34								0						0			0	0		0	7	1.2	2.86
35									8													8.0	
36								2						39			44	34		56	39	35.7	18.12
38				0																		0.0	
39			18																			18.0	
40						28																28.0	
42					1				0				1		1	0			1			0.7	0.52
43		0	0																			0.0	0.00
44	0	0					1			0	0	0										0.2	0.41
45						2																2.0	
46	0	0				0		2		0	0	0		3			3	1		3	2	1.2	1.34
48									0													0.0	
49									3													3.0	
50									3													3.0	
52								1						7			4	2		3	3	3.3	2.07
53						3																3.0	
54								0						2			1	0		1	0	0.7	0.82
55							1															1.0	
56								3						6			4	3		13	3	5.3	3.93
57	3									4	5	10										5.5	3.11
58	0						0			4	6	12										4.4	4.98
59								0						15			1	1		3	2	3.7	5.65
61				0					0													0.0	0.00
62							0															0.0	

63				0	0								0	0	0		0			0.0	0.00
64				0																0.0	
65								3					3	3		3		6	2	3.3	1.37
66	0		0			0				8	6	3								2.8	3.49
67					0								5	4	2		1			2.4	2.07
68			2																	2.0	
69	2	3			1		6			2	3	2	1	1	1		1			2.1	1.51
70									1											1.0	
95th percentile																				15.455	

Table A 4. Changes from baseline expressed as standard normal deviates, using Air-only at corresponding time as basis for normal distribution mean and std, for the 14 minute exposure trialsdurations

	Perceived Magnitude			Blinking (counts per minute)			Tearing
Air Only	*1min*	*4min*	*14min*	*1min*	*4min*	*14min*	*14min*
	2.507	1.724	0.100	0.297	0.404	-0.158	-0.803
	0.987	1.724	2.347	-0.552	-1.184	-1.543	-0.073
	-0.532	-0.799	-0.649	1.430	2.282	2.017	-0.803
	-0.532	-0.799	-0.649	-1.260	-0.173	0.237	-0.803
	-0.532	0.463	-0.399	-0.269	-0.029	-0.752	-0.803
	-0.532	-0.799	-0.649	0.722	0.838	-0.949	1.387
	-0.532	-0.378	-0.649	0.722	-0.318	0.930	2.116
	-0.532	-0.799	-0.649	-0.977	-0.895	0.336	-0.073
	-0.152	-0.378	0.100	1.147	-0.173	-0.158	-0.073
	-0.152	0.042	1.098	-1.260	-0.751	0.040	-0.073
10							
mean	0.00	0.00	0.00	0.00	0.00	0.00	0.00
std	1	1	1	1	1	1	1
sem	0.316228	0.316228	0.316228	0.316228	0.316228	0.316228	0.316228
median	-0.532	-0.378	-0.524	0.014	-0.173	-0.059	-0.073
0.6 ppm	*1min*	*4min*	*14min*	*1min*	*4min*	*14min*	*14min*
	-0.532	-0.799	-0.649	-1.119	-0.029	0.435	0.657
	-0.532	0.463	0.100	-0.694	-1.329	-0.949	-0.073
	-0.532	-0.799	-0.649	0.014	1.848	1.028	-0.073
	-0.532	-0.799	-0.399	0.014	-1.184	-1.048	3.576
	-0.532	-0.799	-0.150	1.147	-0.173	0.336	-2.262
	-0.532	-0.799	-0.649	-0.977	-0.462	-0.554	2.116
	-0.532	6.770	7.090	0.014	-0.173	-0.356	-0.073
	-0.532	-0.799	0.100	0.439	-0.895	-0.356	0.657
	-0.532	3.406	1.348	0.014	-0.895	-0.850	-1.532
9							
mean	-0.53	0.65	0.68	-0.13	-0.37	-0.26	0.33
std	1.18E-16	2.685185	2.484021	0.711504	0.952413	0.711358	1.754116
sem	3.93E-17	0.895062	0.828007	0.237168	0.317471	0.237119	0.584705
median	-0.532	-0.799	-0.150	0.014	-0.462	-0.356	-0.073
1.9ppm	*1min*	*4min*	*14min*	*1min*	*4min*	*14min*	*14min*
	13.520	2.565	6.092	-2.110	0.404	-0.356	-0.073
?	-0.532	-0.799	4.594	-0.977	0.116	-0.455	2.116
	-0.911	4.668	14.580	-0.835	-0.173	1.819	-0.073
	1.747	2.986	11.834	-0.411	0.549	1.028	-0.073
	2.127	4.247	6.092	-1.968	-0.751	-1.740	-1.532

resp	0.608	7.190	11.085	1.147	2.282	2.017	3.576
	-0.532	-0.799	4.094	0.297	0.693	1.325	-1.532
	-0.532	1.304	3.595	-4.517	-4.505	-2.927	0.657
resp	-0.152	0.042	11.584	1.430	2.137	4.489	0.657
9							
mean	1.70	2.38	8.17	-0.88	0.08	0.58	0.41
std	4.559085	2.71791	4.087004	1.83664	1.986254	2.215628	1.631785
sem	1.519695	0.90597	1.362335	0.612213	0.662085	0.738543	0.543928
median	-0.152	2.565	6.092	-0.835	0.404	1.028	-0.073

3.3 ppm	*1min*	*4min*	*14min*	*1min*	*4min*	*14min*	*14min*
resp	5.545	9.293	24.316	3.979	3.581	3.995	37.145
resp	8.963	11.816	20.821	1.289	1.848	3.995	-0.073
resp	-0.532	2.145	13.831	2.280	5.314	6.368	-0.803
resp	-0.152	10.975	20.821	0.297	-0.029	3.402	3.576
resp	-0.532	1.304	3.345	1.147	5.314	5.083	1.387
resp	-0.532	7.190	23.318	0.439	2.715	0.040	4.306
resp	-0.532	2.565	13.831	-1.685	-0.173	-0.158	53.929
resp	1.747	5.929	13.831	1.713	0.982	1.819	5.035
	-0.532	0.463	3.345	0.722	-1.184	-0.257	-0.803
9							
mean	1.49	5.74	15.27	1.13	2.04	2.70	11.52
std	3.454721	4.324736	7.896491	1.543712	2.371708	2.443016	19.85301
sem	1.151574	1.441579	2.632164	0.514571	0.790569	0.814339	6.61767
median	-0.532	5.929	13.831	1.147	1.848	3.402	3.576

Table A 5. Changes from baseline expressed as standard normal deviates, using Air-only at corresponding time as basis for normal distribution mean and std, for the 4 hour exposure durations

	Perceived Magnitude				Blinking (counts per minute)				Tearing	
	1 hr	*2 hr*	*3hr*	*4hr*	*1 hr*	*2 hr*	*3hr*	*4hr*	*1 hr*	*4hr*
	-0.437	-0.430	-0.557	-0.591	-0.144	0.522	1.457	0.206	0.041	-0.957
	0.040	0.000	-0.341	-0.404	0.959	2.536	0.421	1.069	-0.949	0.957
	0.636	2.865	2.245	1.462	-0.144	-0.037	-0.486	0.206	0.041	0.479
	0.397	0.430	0.952	0.716	-0.932	-0.037	0.550	0.082	1.526	1.436
	-0.556	-0.573	-0.772	-0.591	0.013	-0.485	0.550	-0.658	0.041	-1.915
	-0.556	-0.573	-0.988	-0.591	-1.405	-1.380	-1.651	-1.645	-1.443	-0.957
	2.900	0.716	0.305	2.396	0.013	0.410	0.939	0.823	0.536	0.000
	-0.556	-0.573	-0.772	-0.591	2.062	0.410	1.198	1.316	-0.949	0.479
	-0.318	-0.287	0.952	-0.031	0.801	-0.373	-0.356	0.206	-0.454	-0.957
	-0.556	-0.573	-0.772	-0.591	-0.302	-0.261	-0.615	0.082	2.021	0.000
	-0.437	-0.430	0.521	-0.591	-1.405	-1.268	-1.392	-2.015	-0.454	0.957
	-0.556	-0.573	-0.772	-0.591	0.486	-0.037	-0.615	0.329	0.041	0.479
12										
mean	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
std	1	1	1	1	1	1	1	1	1	1
sem	0.288675	0.288675	0.288675	0.288675	0.288675	0.288675	0.288675	0.288675	0.288675	0.288675
median	-0.437	-0.430	-0.449	-0.591	-0.066	-0.037	0.032	0.206	0.041	0.239
	1 hr	*2 hr*	*3hr*	*4hr*	*1 hr*	*2 hr*	*3hr*	*4hr*	*1 hr*	*4hr*
	0.040	-0.430	-0.772	-0.591	-0.775	-1.044	-0.486	-1.152	-0.949	-0.479
	1.470	-0.573	-0.772	-0.591	-1.720	-0.597	-0.874	-1.152	-0.949	-0.957
	-0.675	-0.430	-0.772	3.329	-1.720	-0.261	-0.874	-0.165	-1.443	-1.915
	0.993	0.287	-0.126	-0.218	-1.248	0.298	-1.521	-0.165	4.000	0.479
	-0.437	-0.430	-0.557	-0.404	-1.248	0.075	0.162	-1.028	1.031	0.000
	2.065	0.143	0.305	0.342	-2.193	-0.597	-1.392	-0.535	-0.454	1.436
resp	3.376	2.292	2.245	-0.404	-1.248	-0.149	-1.521	-0.535	2.021	0.479

	0.874	-0.573	-2.065	-3.391	-0.932	-0.373	-1.651	-1.275	1.526	-0.479
	-0.079	1.289	1.167	0.342	-2.666	-1.044	-2.169	-1.645	-0.454	-0.479
	-0.556	-0.573	-0.772	-0.031	0.486	-1.828	-0.227	-0.658	0.041	-0.479
	-0.437	-0.287	-0.557	-0.404	0.171	0.298	-0.615	0.082	0.536	1.915
	-0.556	-0.573	-0.772	-0.591	-0.775	-1.380	-1.003	-0.781	1.031	1.436
12										
mean	0.51	0.01	-0.29	-0.22	-1.16	-0.55	-1.01	-0.75	0.49	0.08
std	1.277831	0.902853	1.103029	1.47202	0.895163	0.668711	0.665809	0.518456	1.542833	1.114924
sem	0.368878	0.260631	0.318417	0.424936	0.258411	0.19304	0.192202	0.149665	0.445378	0.321851
median	-0.020	-0.430	-0.664	-0.404	-1.248	-0.485	-0.939	-0.720	0.289	-0.239

	1 hr	*2 hr*	*3hr*	*4hr*	*1 hr*	*2 hr*	*3hr*	*4hr*	*1 hr*	*4hr*
	-0.437	-0.430	6.123	5.382	0.486	2.200	1.198	1.933	-2.433	0.000
resp	3.495	4.154	12.372	10.796	0.644	1.641	2.492	3.043	-1.443	-1.436
resp	1.231	1.719	10.002	5.196	-0.302	1.417	3.528	2.303	-0.949	0.000
	3.019	5.300	3.537	2.956	1.116	1.641	1.198	0.329	0.536	0.000
resp	1.351	1.146	2.029	2.396	-0.460	-0.373	-0.874	-0.411	2.021	0.000
	5.164	3.438	5.261	2.396	-0.144	-0.821	-1.133	-0.905	-0.949	-0.957
resp	3.734	5.587	13.449	16.769	1.747	2.424	2.363	1.069	-1.443	2.872
	2.304	3.008	7.847	7.249	0.171	1.753	0.809	0.452	1.031	0.000
resp	0.516	2.435	4.830	4.636	3.165	2.536	2.881	1.933	3.010	1.915
9										
mean	2.26	2.93	7.27	6.42	0.71	1.38	1.38	1.08	-0.07	0.27
std	1.764447	1.956526	3.948267	4.705045	1.158361	1.188071	1.614603	1.31937	1.814529	1.335068
sem	0.588149	0.652175	1.316089	1.568348	0.38612	0.396024	0.538201	0.43979	0.604843	0.445023
median	2.304	3.008	6.123	5.196	0.486	1.641	1.198	1.069	-0.949	0.000

Table A 6. Changes from baseline expressed as standard normal deviates, using Air-only at corresponding time as basis for normal distribution mean and std, for the 8 hour exposure durations

	Perceived Magnitude					Alternative w/o ISN 36 in calc of mean and stdev changes **Perceived Magnitude**					**Blinking (counts per minute)**					**Tearing**			
	1.5hr	*3hr*	*3.5hr*	*6hr*	*8hr*	*1.5hr*	*3hr*	*3.5hr*	*6hr*	*8hr*	*1.5hr*	*3hr*	*3.5hr*	*6hr*	*8hr*	*1.5hr*	*3hr*	*6hr*	*8hr*
	-0.688	-0.711	-0.637	-0.576	-0.609	-0.901	-0.673	-0.842	-0.496	-0.578	1.200	1.444	1.725	1.415	1.180	0.119	-0.889		1.523
	-0.783	0.596	-0.534	1.801	-0.609	-1.099	1.042	-0.610	2.620	-0.578	-1.110	-0.886	-0.554	-0.437	-0.885	-0.256	-1.245	-0.883	0.152
	-0.214	-0.436	0.396	-0.306	-0.288	0.090	-0.312	1.473	-0.142	-0.098	0.385	0.133	-0.364	-0.129	-0.442	1.244	0.889	1.640	0.152
	-0.119	-0.505	-0.327	-0.630	-0.368	0.288	-0.402	-0.147	-0.567	-0.218	-0.430	0.716	-0.554	-1.055	-1.032	-1.193	-0.533	-0.042	-1.219
	0.261	1.560	-0.430	0.558	-0.368	1.081	2.305	-0.379	0.991	-0.218	0.521	-0.595	-0.174	-0.129	-1.032	0.307	1.600	-0.883	-1.219
	-0.498	-0.642	-0.430	-0.684	-0.529	-0.504	-0.582	-0.379	-0.637	-0.458	-0.023	-1.031	-0.364	-0.437	0.147	-1.006	-0.178	0.378	-0.762
	-0.688	-0.711	-0.430	-0.738	0.033	-0.901	-0.673	-0.379	-0.708	0.381	1.064	1.589	1.915	2.032	1.180		1.245		1.523
	2.825	2.179	2.874	2.179	2.443	6.430	3.116	7.030	3.116	3.978	1.608	1.298	0.586	0.643	1.327	-0.443	-1.245	-1.304	-0.305
	-0.404	-0.642	-0.430	-0.198	-0.529	-0.306	-0.582	-0.379	0.000	-0.458	-0.566	-0.886	-1.504	0.180	-0.885	2.181	-0.178	-0.463	1.066
	0.736	-0.642	-0.327	-0.576	-0.368	2.071	-0.582	-0.147	-0.496	-0.218	-1.653	-0.886	-0.744	-1.518	0.000	0.307	1.245	1.640	0.152
	0.166	0.596	0.809	-0.144	1.720	0.883	1.042	2.399	0.071	2.899	-0.974	-0.449	0.396	-0.746	-0.885	-0.631	-0.533	-0.042	-1.219
	-0.593	-0.642	-0.534	-0.684	-0.529	-0.702	-0.582	-0.610	-0.637	-0.458	-0.023	-0.449	-0.364	0.180	1.327	-0.631	-0.178	-0.042	0.152
12																			
mean	0.00	0.00	0.00	0.00	0.00	0.54	0.26	0.59	0.26	0.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
std	1	1	1	1	1	2.086846	1.310899	2.242234	1.310796	1.492671	1	1	1	1	1	1	1	1	1
sem	0.288675	0.288675	0.288675	0.288675	0.288675	0.60242	0.378424	0.647277	0.378394	0.430897	0.288675	0.288675	0.288675	0.288675	0.288675	0.301511	0.288675	0.316228	0.288675
median	-0.309	-0.573	-0.430	-0.441	-0.368	-0.108	-0.492	-0.379	-0.319	-0.218	-0.023	-0.449	-0.364	-0.129	-0.221	-0.256	-0.178	-0.042	0.152
						probably do not want to use these													

	1.5hr	*3hr*	*3.5hr*	*6hr*	*8hr*	*1.5hr*	*3hr*	*3.5hr*	*6hr*	*8hr*	*1.5hr*	*3hr*	*3.5hr*	*6hr*	*8hr*	*1.5hr*	*3hr*	*6hr*	*8hr*
	-0.498	-0.573	-0.430	-0.738	-0.448	-0.504	-0.492	-0.379	-0.708	-0.338	-1.110	-0.303	-0.934	-0.900	-1.622	-0.443	-0.178	-0.042	2.437
	-0.498	-0.711	-0.224	0.828	0.114	-0.504	-0.673	0.084	1.346	0.501	-0.566	-0.595	-0.934	0.180	-0.737	-1.006	1.600	0.378	-0.762
	-0.119	-0.780	-0.534	-0.792	-0.609	0.288	-0.763	-0.610	-0.779	-0.578	0.249	1.007	1.155	0.489	0.737	-0.818	-0.178	0.799	0.609
	-0.214	-0.229	-0.017	-0.414	-0.127	0.090	-0.041	0.547	-0.283	0.142	0.113	0.570	0.396	0.026	0.442	-0.068	-0.889	-1.304	-0.762
	-0.593	-0.642	-0.740	-0.414	-0.127	-0.702	-0.582	-1.073	-0.283	0.142	-0.023	0.861	1.345	0.798	0.000	-1.006	-0.889	-2.145	-0.762
	0.261	-0.229	-0.430	-0.414	0.274	1.081	-0.041	-0.379	-0.283	0.741	0.113	-0.012	-0.744	-0.437	-0.295		0.178		-1.219
	-0.404	-0.573	-0.120	-0.252	0.033	-0.306	-0.492	0.316	-0.071	0.381	-1.517	0.279	-0.174	0.489	-0.885		0.178		1.066
	-0.688	-0.367	0.602	-0.468	-0.609	-0.901	-0.221	1.936	-0.354	-0.578	0.249	-0.595	0.016	-0.592	-0.295	-0.631	-1.600	-2.145	-0.762
	0.071	-0.092	0.293	-0.468	-0.127	0.684	0.139	1.242	-0.354	0.142	-1.110	-0.740	-2.073	-1.364	-1.180	-0.818	1.245	-0.463	1.523
	-0.973	-0.367	-1.050	-0.414	-0.448	-1.495	-0.221	-1.768	-0.283	-0.338	1.336	1.881	1.725	0.798	0.000	0.307	-0.889	1.219	1.980
	-0.688	-0.711	-0.327	-0.576	-0.529	-0.901	-0.673	-0.147	-0.496	-0.458	-0.159	-0.158	-0.744	-0.900	0.295	-0.818	-0.889	-0.883	-0.305
	-0.498	-0.505	-0.327	-0.522	-0.127	-0.504	-0.402	-0.147	-0.425	0.142	-0.838	-0.740	-1.314	-0.129	-0.737	-0.256	-0.889	-0.463	-0.305
	-0.593	-0.573	-0.740	-0.522	-0.288	-0.702	-0.492	-1.073	-0.425	-0.098	1.880	1.153	-0.934	0.334	0.295	-0.068	-0.533	-1.304	-0.762
	-0.688	-0.711	-0.430	-0.738	-0.529	-0.901	-0.673	-0.379	-0.708	-0.458	-0.023	-0.740	0.016	0.180	0.590	-0.443	-0.889	-0.883	-0.762
	-0.688	-0.711	-0.430	-0.738	-0.529	-0.901	-0.673	-0.379	-0.708	-0.458	-0.430	-0.012	0.206	-0.129	-0.590	-0.256	-0.533	-0.042	-0.762
	-0.688	-0.711	-0.327	-0.630	-0.448	-0.901	-0.673	-0.147	-0.567	-0.338	-0.838	0.279	-0.554	-0.129	0.295	-0.256	-1.600	0.378	0.152
16																			
mean	-0.47	-0.53	-0.33	-0.45	-0.28	-0.44	-0.44	-0.15	-0.34	-0.09	-0.17	0.13	-0.22	-0.08	-0.23	-0.47	-0.42	-0.49	0.04
std	0.320981	0.211553	0.395451	0.374563	0.275873	0.669838	0.277324	0.886693	0.490975	0.411788	0.884127	0.786754	1.020479	0.62693	0.678807	0.394997	0.887466	1.022903	1.137953
sem	0.080245	0.052888	0.098863	0.093641	0.068968	0.167459	0.069331	0.221673	0.122744	0.102947	0.221032	0.196688	0.25512	0.156733	0.169702	0.105567	0.221866	0.273382	0.284488
median	-0.546	-0.573	-0.379	-0.495	-0.368	-0.603	-0.492	-0.263	-0.389	-0.218	-0.091	-0.012	-0.364	-0.051	-0.147	-0.443	-0.711	-0.463	-0.533

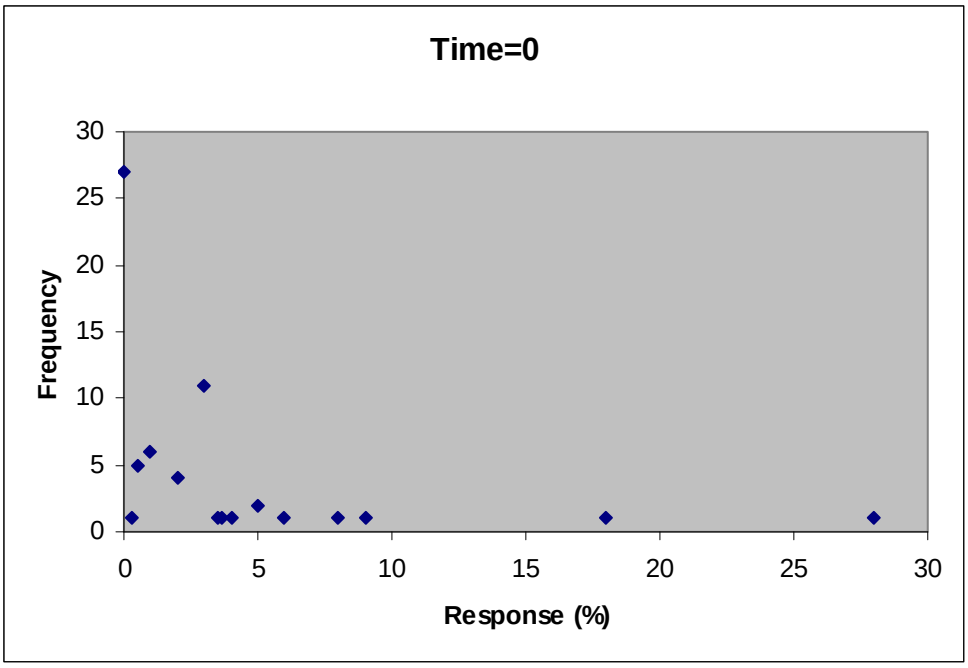

Figure A 1. Distribution of responses of *percent of full scale* at t = 0 irrespective of condition. When a subject participated in more than one session, as about one-third did, the number entered into the distribution equaled the average of the replicates. Hence, a subject entered the distribution only once.

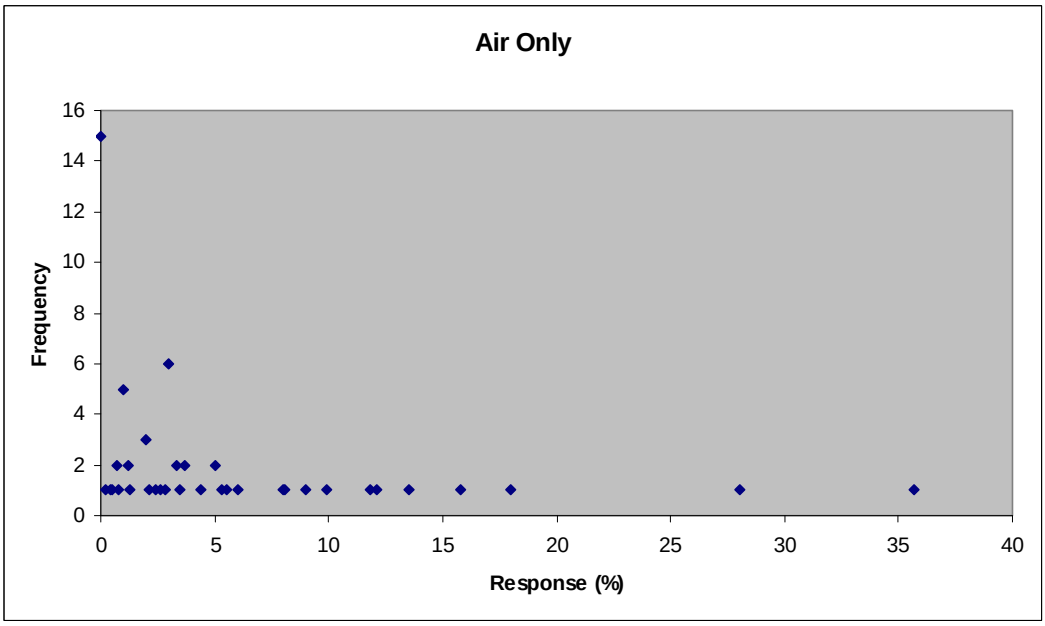

Figure A 2. Distribution of responses of *percent of full scale* at both t = 0, irrespective of condition, and t > 0, irrespective of the time of a judgment, during exposures to air (control). To illustrate, if a subject served in a control exposure of 14 min and an experimental exposure of 4 hr, all four judgments (t = 0, 1, 4, and 14 min) from the 14-min exposure and the first judgment from the four-hour exposure (t = 0) would become the basis for the subject's entry into the distribution. Before entry, the values would be averaged, so that the subject would appear only once.

APPENDIX B

Plots of BMC and BMCL Models Fit to 14-Minute Trial Dose-Response Data
(note in these plots that BMD/L is equivalent to BMC/L)

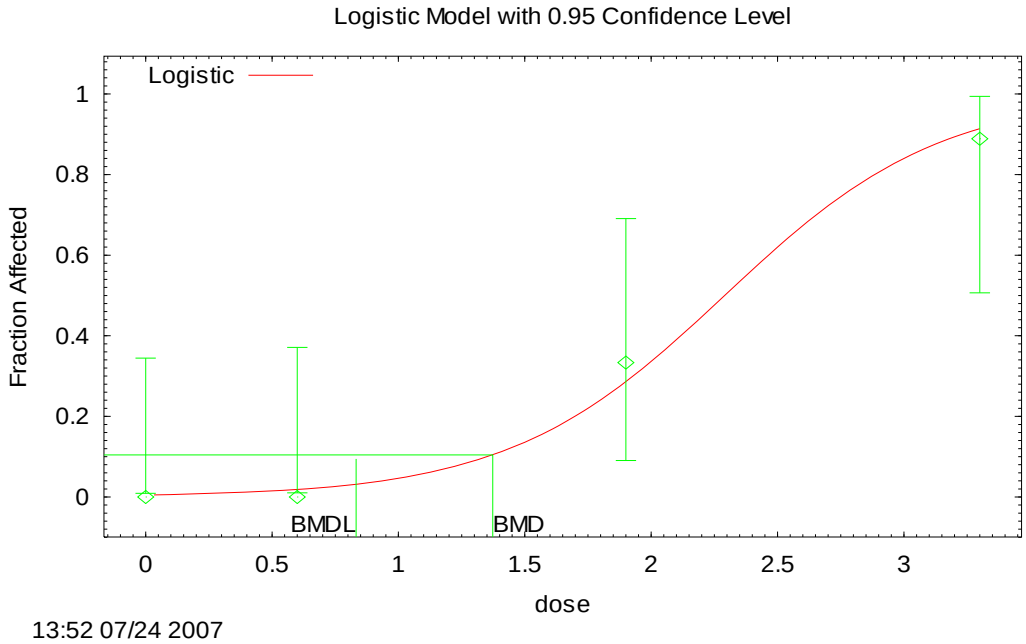

Figure B 1. Logistic model with a 0.95 confidence level for the 14-minute trial dose-response data

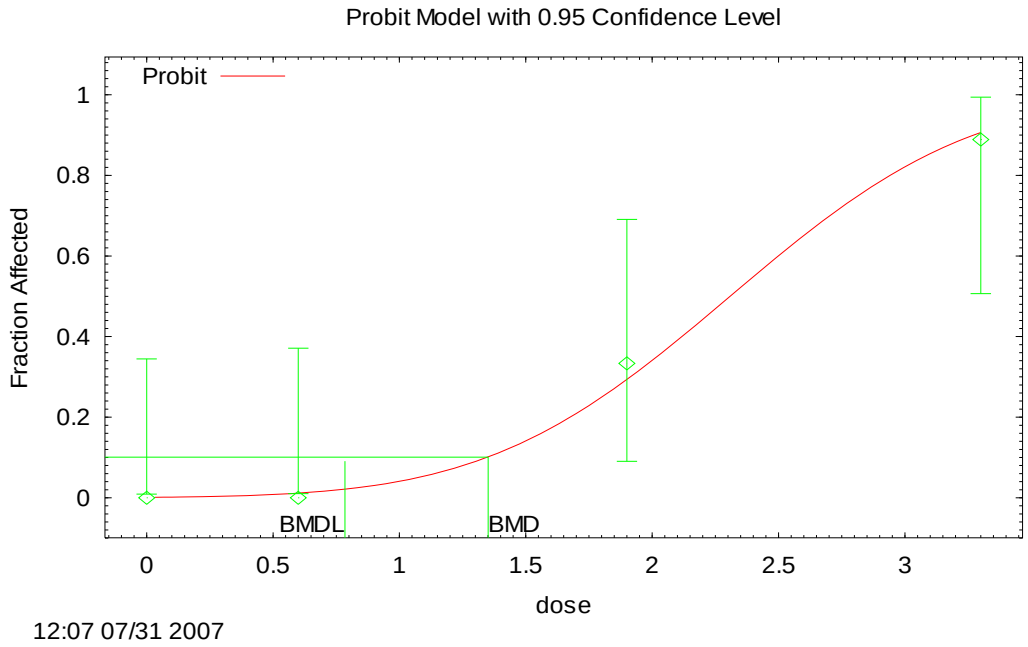

Figure B 2. Probit model with a 0.95 confidence level for the 14-minute dose-response data

APPENDIX C

Plots of BMC and BMCL Models Fit to 4-Hour Trial Dose-Response Data
(note in these plots that BMD/L is equivalent to BMC/L)

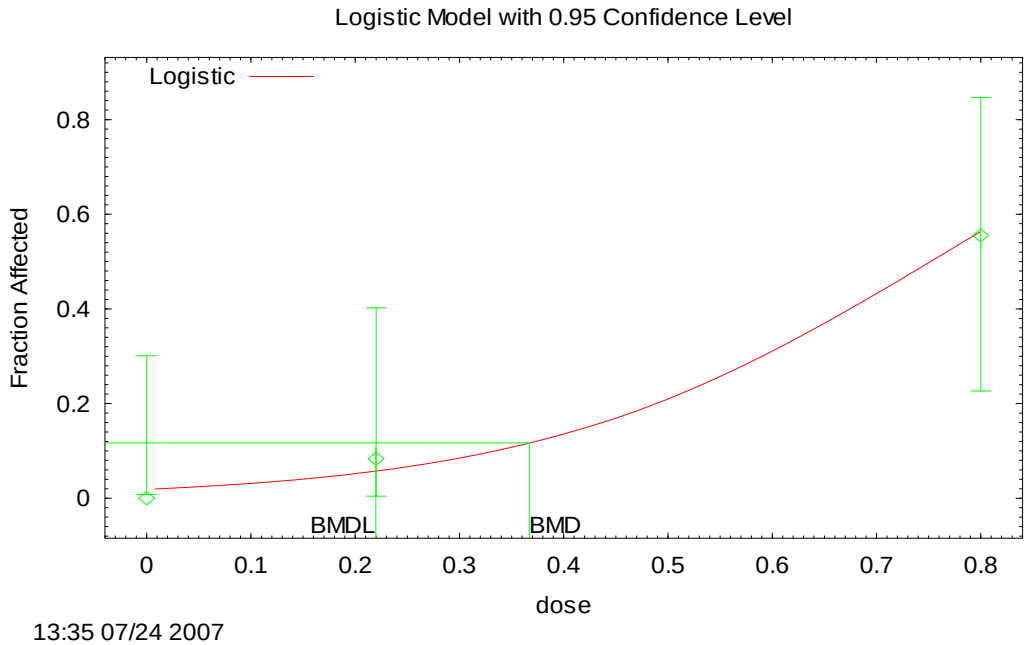

Figure C 1. Logistic model with a 0.95 confidence level for the 4-hour trial dose-response data

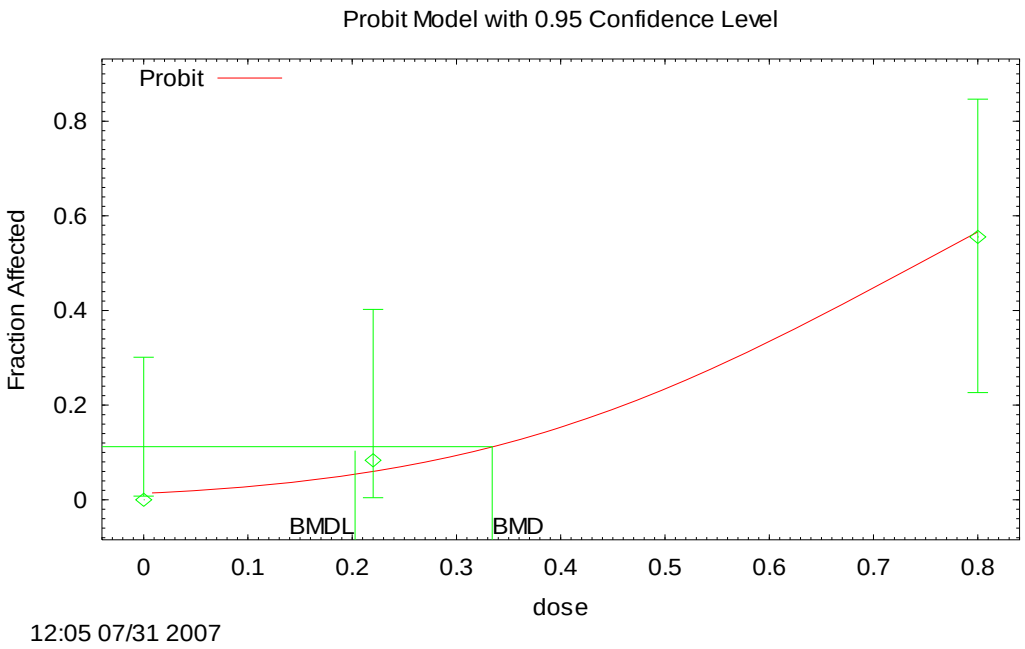

Figure C 2. Probit model with a 0.95 confidence level for the 4-hour trial dose-response data