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April 8, 2009

Regarding: MEMORANDUM: Response to post-RED MITC toxicology-related comments *March 2009*

Office of Prevention, Pesticides and Toxic Substances
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., N.W.
Washington, DC 20460
Reference: MITC Reference-Evaluation

Dear Ms. Santora:

We appreciate the opportunity to express our thoughts and opinions on the RED development for MITC and on EPA thoughts as stated in its March 2009 memorandum. The EPA memorandum has given us a better understanding of the basis for its proposed alternative mode of action (MOA). We see several key issues, however, for further consideration. In addition, we feel that the use of a 1-fold factor for within-human variability, that is, 1-fold for both toxicokinetic and toxicodynamic variability, is consistent with data for MITC and our understanding of its MOA. An EPA committee that estimates Acute Exposure Guideline Levels shares our choice of 1-fold factor for MITC. Furthermore, it is our understanding that retention of a full default factor of 10-fold for irritants is contrary, in general, to the spirit of data-informed decisions.

As to the choice of critical effect, EPA states that *TERA*'s judgment of eye feeling, blinking rate and tearing as the critical effect for MITC "differs conceptually from the EPA's characterization of eye irritation" (see EPA 2009, page 5, line 22). EPA suggests that eye irritation should be seen as a biomarker or surrogate for respiratory effects. This categorization unnecessarily limits analysis of the chemical and its plausible MOA. In contrast, we see sensory irritation as a precursor to an adverse effect and thus a critical effect by EPA's definition (www.epa.gov/iris. Glossary). It also remains a valid endpoint for protection against more serious respiratory effects as described by EPA, even if not used merely as a surrogate or biomarker for such effects.

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We understand the EPA position on its alternative MOA (see EPA 2009, page 12, Figure 3). However, some additional information may aid EPA regarding the sensory basis of the MOA. With respect to Temporal Association (EPA 2009, page 8, para. 2), duration of exposure increases the chemesthetic reaction to MITC. Ratings of perceived magnitude from Russell and Rush (1996) indicated the time-dependence occurs for concentrations as low as 0.8 ppm. (We note here that Russell and Rush took data as early as 1 minute into exposure.) The function for that concentration suggested that irritation may emerge in the range of tens of minutes and perhaps as long as an hour. The increase continued until about two hours when the response began to wane. A trade-off between latency and rate of increase of response characterizes TRP ion channels as well. The lower the concentration the longer the latency. In what Brône et al. (2008, see Exhibit 1 for their Fig. 2) presented as a representative case, a 32-fold increment in concentration of the agent CS reduced latency by perhaps 100-fold. A concentration between 0.03 nM (a no response concentration) and 0.1 nM (a low response concentration) might have yielded a longer latency. Since the assays lasted only 14 min, the work could never show a longer latency than that. In B of the Brône Fig. 2 (see Exhibit 1), the concentration-response relationships essentially obscure the effects of latency. The low responses had longer latencies than the high responses. (All agents showed time- and concentration-dependence responses.)

As indicated, at low levels of stimulation in humans, latency can exceed many minutes. In the chloropicrin human study (Phase 2, Chamber Exposures), the latency to the lowest level examined, 50 ppb, equaled 20 min. The latency decreased to 3 min for the level 150 ppb. Only at levels into the hundreds of ppb did latency drop below about 30 sec. Hence, the concern that a long-latency of response should lead one to question the neural (trigeminal nerve) basis for the response to MITC seems misplaced. The more important question concerns whether long latency affords further protection to the exposed person over the case where the agent has its maximum effect immediately, i.e., with no appreciable latency.

To answer the question of whether long latency affords protection, one needs to consider scenarios of exposure. Presumably, many exposures last for minutes or tens of minutes. In such cases, the person may never experience the effects of exposure. This will depend upon concentration. As the data of Russell and Rush (1996) show, higher concentrations will cause responses at shorter latencies and the responses will increase with time. Even at the higher concentrations in the study, MITC would warn with low-level sensations before these become high level. For the sensations to become intense the person needs the passage of time in contact with the agent.

With respect to Other Hypotheses (EPA 2009, page 11, para. 3), we believe that our discussion at the Society of Toxicology meeting in Baltimore clarified that the ANKTM1 channel and the TRPA1 channel are identical. The name TRPA1 was adopted for uniformity with other TRP ion channel nomenclature (see Exhibit 2 for PubGene information). We introduced information about the TRPA1 channel to EPA initially to illustrate that isothiocyanates occurred in natural products and had ability to stimulate through a normal sensory mechanism, rather than through non-neural means: "TRPA1 was initially identified as a sensor for cold temperature in peripheral sensory neurons, a role that is currently debated (42–44). Subsequent studies found that TRPA1 is a receptor for plant-derived noxious deterrents, including iso-thiocyanates, the pungent ingredients in mustard, wasabi, and horseradish, and thiosulfinates in garlic and onions (24, 33,

45, 46)." (Escalera et al., 2008). We made the point that MITC occurs naturally in capers, a pungent edible material. We did not suggest that the TRPA1 mechanism is limited to, or specific for, eye irritation and have never defended it as such. The EPA memo overstates that matter.

As to the use of the experimental animal studies, we acknowledge that the Jackson et al. (1981) study has limitations for determining safe air concentrations, as it was designed to study acute lethality. We agree that more sensitive measures of eye and lung parameters would suggest more appropriate ratios with the existing eye and respiratory data in animal studies. However, more sensitive measures of lung parameters, when compared with more sensitive measures of eye parameters, may yield the same ratios as we have calculated previously (see EPA 2009, page 7, line 25). In either case, a consideration of the data shows it unlikely that lung effects would precede eye effects as concentrations increase. At low concentrations, MITC will most likely be removed by nasal and upper airways because of its high water solubility (as described more fully below).

We apologize for not having sent our complete benchmark dose (BMD) analysis of Jackson et al. (1981), since its absence may have led to some of EPA's unease with the data analysis. EPA states, for example, that the BMD models yield reliable data at only 1.5 and 2.5 hours due to an absence of dose dependence in the eye irritation data. The dose dependence for eye effects was in fact similar for all time-periods, except 3 hours and greater, when mortality occurred at higher concentrations. In contrast, the lung effects of gasping and dyspnea were unreliable except for 1.5 and 2.5 hours due to the lack of adequate dose-response.

Attached tables (exhibit 3) give more of the BMD/BMDL analysis. These show that the BMDL is stable among models, unlike the BMD. Model instability of BMDs is of less concern, since risk assessments generally focus on the BMDL. For completeness, we will send the entire BMD analysis of the Jackson et al. (1981) data under separate cover.

With the introduction of Fig. 3 (EPA 2009, page 12, para. 1), the EPA memo states, regarding eye effects, respiratory effects, and skin effects: "If each target is fairly similar in its dose-response, then this alternative interpretation of available data potentially provides a better explanation of available incidence data from Table 1 (Akanda et al., 2007) and the Arvin and Earlimart incidences" (sic). Although questions about the interpretation of those data are taken up elsewhere in this reply, we wish to note that the term "respiratory effects" fails to distinguish between upper and lower airways.

Water-soluble vapors and gases deposit themselves largely in the mucus-lined upper airways. As Medinsky & Bond (2001, p. 168) illustrated, "[e]xperimental studies and mathematical models have shown that highly water-soluble vapors such as ethanol and methanol are almost entirely scrubbed by the nose on inspiration". MITC vapor is highly water-soluble (7,600 mg/l @ 25 deg C; see www.toxnet.nlm.nih.gov). Furthermore, it is reactive, a property that favors even further its capture by the upper airways. As Medinsky & Bond also illustrate (p. 167): "Once formaldehyde contacts the mucosal surface, it dissolves because it is highly water-soluble. Because it is a reactive gas, formaldehyde and its reactive products stay in that region of deposition." These examples pertain to principles of inhalation toxicology and one needs only to know the properties for the materials of interest. The upper airways will afford protection of the

lower airways from incident airborne MITC, particularly at low concentrations, the topic of concern of the EPA memo.

Human incident reports range from highly suspect to quite useful. For example, several of the MITC incident reports are from skin exposures, and in some cases from skin exposures involving people wearing goggles. Such exposures do not help in determining a safe air concentration, but instead may confound the determination of the critical effect from inhalation exposures. In contrast, other MITC incident reports allow some quantification and, more importantly, a higher degree of confidence in the estimated relative exposures. For example, the Arvin incident included medical reports and surveys of the residents with the residents' addresses. Since this exposure occurred in the late evening, when residents were likely to be at home, the medical reports can be categorized by distance from the epicenter of contamination, providing a confident measure of relative exposure.[1] Use of distance from the site of fumigation as a surrogate for concentration is a well-accepted epidemiological technique.[2]

EPA is correct in its observation that the sensitivity between eye and lung irritation appears to be smaller in the incident data than in the animal data (see EPA 2009, page 10).[3] Figures 8 and 9 of our last report (*TERA,* 2008, see Exhibit 4) showed a relative difference of about 1 to 2-fold between the presence of eye and eye-and-other effects in people closest to the site of the Arvin exposure (in Figure 9 compare distance code 2 with an estimated concentration of about 0.6 ppm to distance code 3 with an estimated concentration of about 0.4 ppm). This 1 to 2-fold difference agrees with the EPA statement on page 12 (see para. 2). However, since eye irritation occurred

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[1] We agree with the EPA that the incident data for the Arvin and Earlimart exposures are not consistent with each other (see EPA 2009, page 10). We feel that one likely reason for this inconsistency is that the Arvin and Earlimart exposures occurred at different periods during the day. The Earlimart exposure occurred during late afternoon where people were more likely at work or in different areas of the town, rendering residence-based distance codes inadequate for quantifying exposures. In contrast, the Arvin incident occurred in the late evening where people were more likely to be at home, and, thus distance codes are more likely to be an accurate measure of relative exposure. In addition, one of the distance codes (distance code 3) corresponds to a factory where all of the 3rd-shift workers who reported symptoms were exposed to the same relative concentration and their location in relation to the contamination site is known. We have repeatedly acknowledged that the Earlimart incident cannot be used to make definitive statements about the temporality or dose-response of effects due to the uncertainties of the data; for this reason, it also should not be used to discount the analysis of the data gathered for the Arvin incident.

[2] For example, ongoing research on the effects of radiation on Hiroshima and Nagasaki survivors bases their dosimetry estimates on distance from the center of the explosion (see the Radiation Effects Research Foundation (RERF). A description of the exposure estimation protocol for the RERF studies can be found at http://www.rerf.or.jp/general/research_e/raditiondose.html

[3] The difference between effects in the animal data of Jackson et al. (1981) is large because the study was designed to have a large range of concentrations (282-1640 ppm) in order to show a dose-response relationship between effect and exposure. The human incident data, however, generally have a smaller range of estimated concentrations; Earlimart- residents were exposed to a concentration between 0.5 and 1.5 ppm (only agricultural workers were likely exposed to concentrations greater than 1.5ppm) and Arvin residents were exposed to average concentrations between about 0.4 and 0.9 ppm.

at 100% incidence at this low concentration, yet lower concentrations would also evoke eye irritation until the NOAEL/BMDL of 0.2 ppm from the Russell and Rush (1996) study is reached. This would result in a difference of about 2 to 3 between the MITC concentrations that cause only eye irritation and a combination of eye and other effects.

As to the choice of uncertainty factors, a toxicokinetic factor of 1-fold is supported with either the EPA or *TERA* MOA. Both MOAs propose the same underlying receptor response at the portal of entry. Since the response does not depend on kinetics to move the active chemical to the target tissue, variability in toxicokinetics among individuals is not likely to be relevant with either MOA.

Likewise, the most probative study supports a dynamic uncertainty factor of 1-fold because the critical effect is eye irritation, sensitive individuals were tested, and irritation is not expected to be greater in children (Hummel et al., 2007). MITC is a known lachrymator (which is why the Russell and Rush study used only eye exposures), and highly water-soluble. At low ambient concentrations, the upper airways should strongly attenuate the dose to the lung and may even prevent exposure to the lung. The effect of MITC on sensitive subpopulations, such as asthmatics, is an important consideration in this assessment. Although asthmatics might react more strongly than normals to MITC at higher concentrations, the available data do not indicate their airways are more sensitive than their eyes.[4]

Again, we thank the EPA for the opportunity to share our thoughts on the development of a safe concentration for MITC after short-term exposures.

Sincerely,

Michael Dourson, Ph.D., DABT, ATS
Toxicology Excellence for Risk Assessment

Melissa Kohrman, B.A.
Toxicology Excellence for Risk Assessment

for William S. Cain, Ph.D.
University of California, San Diego

[4] Out of the approximately 800 incident reports on MITC we previously summarized, 13 were known to be asthmatics (*TERA*, 2008, Table 7). This response of ~2% (13/~800) is much less than the identified percentage of asthmatics in the background population of Kern County (EPA, 2007), and Tulare County (ALA, 2007), the sites of many incidents. Furthermore, as described in *TERA* (2008), 4 (we mistakenly stated this as 5) had symptoms other than eye effects. These symptoms are likely to have been due to MITC exposures above the level needed to cause eye irritation, since all 4 described symptoms at the portal of entry in addition to other sites.

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Exhibit 1

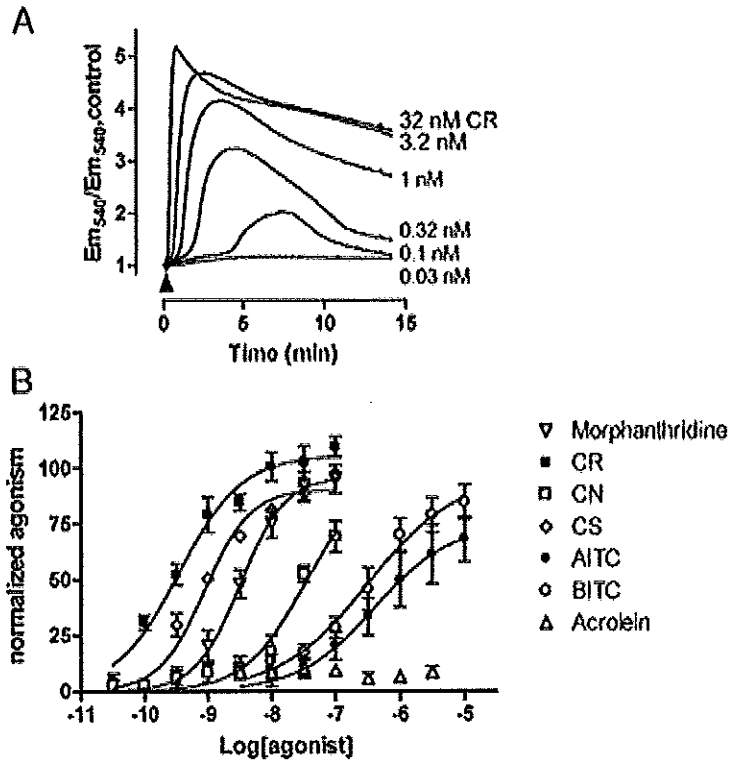

Fig. 2 from Brône et al. (2008). "Fluorometric measurement of the intracellular Ca^{2+} concentration as a measure for hTRPA1 activation by tear gasses and other agonists. A. As a representative example the effect of different concentrations of the tear gas CR on the hTRPA1 expressed in HEK 293 cells is shown. The arrowhead indicates the application of CR. The emission signal Em_{540} was divided by the signal of the first control measurement (Em_{540}, control) to compensate for background. B. Concentration–response relationship of agonists on intracellular Ca^{2+} in hTRPA1-HEK cells. Every data point corresponds with 4 measurements ($n = 4$). The calculation of the normalized agonism is explained in the Methods. The data were fitted and the obtained EC50 values are listed in Table 1."

Exhibit 2

Summary from Entre Gene

1: TRPA1 transient receptor potential cation channel, subfamily A, member 1 [*Homo sapiens*]

GeneID: 8989
updated 01Mar-2009

Summary

Official Symbol

TRPA1 provided by HGNC

Official Full Name

transient receptor potential cation channel, subfamily A, member 1 provided by HGNC

Primary source

HGNC:497

See related

Ensembl:ENSG00000104321; HPRD:09208; MIM:604775

Gene type

protein coding

RefSeq status

REVIEWED

Organism

Homo sapiens

Lineage

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as

ANKTM1; TRPA1

Exhibit 3: MITC BMD results - Jackson et al. (1981) and BASF (1987)

Eye effects: lacrimation and eye closure (NOTE: 1640 was included & death was counted as a response)					
0.25 hrs					
model	BMD	BMDL	P	AIC	
gamma (restrict)	48	6.06	1	2	
gamma (unrestrict)	56.6	6.06	1	2	
log (nonlog)		p-value < 0.10			
log (log)	46.2	6.13	1	4	
MS	8.03	3.24	0.99	4.75	D.F. =1
probit (nonlog)	115	6.32	1	4	
probit (log)		p-value < 0.10			
QL	163	6.1	1	4	
Weibull(restrict)	163	6.1	1	4	
Weibull (unrestrict)	161	6.1	1	4	
0.5 hrs					
model	BMD	BMDL	P	AIC	
gamma (restrict)	48	6.06	1	2	
gamma (unrestrict)	56.6	6.06	1	2	
log (nonlog)		p-value < 0.10			
log (log)	46.2	6.13	1	4	
MS	8.03	3.24	0.99	4.75	D.F. =1
probit (nonlog)	115	6.32	1	4	
probit (log)		p-value < 0.10			
QL	163	6.1	1	4	
Weibull(restrict)	163	6.1	1	4	
Weibull (unrestrict)	161	6.1	1	4	
1 hr					
model	BMD	BMDL	P	AIC	
gamma (restrict)	48	6.06	1	2	
gamma (unrestrict)	56.6	6.06	1	2	
log (nonlog)		p-value < 0.10			
log (log)	46.2	6.13	1	4	
MS	8.03	3.24	0.99	4.75	D.F. =1
probit (nonlog)	115	6.32	1	4	
probit (log)		p-value < 0.10			
QL	163	6.1	1	4	
Weibull(restrict)	163	6.1	1	4	
Weibull (unrestrict)	161	6.1	1	4	
1.5 hrs					
model	BMD	BMDL	P	AIC	
gamma (restrict)	48	6.06	1	2	

Eye effects: lacrimation and eye closure (NOTE: 1640 was included & death was counted as a response)					
gamma (unrestrict)	56.6	6.06	1	2	
log (nonlog)		p-value < 0.10			
log (log)	46.2	6.13	1	4	
MS	8.03	3.24	0.99	4.75	D.F. =1
probit (nonlog)	115	6.32	1	4	
probit (log)		p-value < 0.10			
QL	163	6.1	1	4	
Weibull(restrict)	163	6.1	1	4	
Weibull (unrestrict)	161	6.1	1	4	

2 hours					
model	BMD	BMDL	P	AIC	
gamma (restrict)	48	6.06	1	2	
gamma (unrestrict)	56.6	6.06	1	2	
log (nonlog)		p-value < 0.10			
log (log)	46.2	6.13	1	4	
MS	8.03	3.24	0.99	4.75	D.F. =1
probit (nonlog)	115	6.32	1	4	
probit (log)		p-value < 0.10			
QL	163	6.1	1	4	
Weibull(restrict)	163	6.1	1	4	
Weibull (unrestrict)	161	6.1	1	4	

2.5 hours					
model	BMD	BMDL	P	AIC	
gamma (restrict)	48	6.06	1	2	
gamma (unrestrict)	56.6	6.06	1	2	
log (nonlog)		p-value < 0.10			
log (log)	46.2	6.13	1	4	
MS	8.03	3.24	0.99	4.75	D.F. =1
probit (nonlog)	115	6.32	1	4	
probit (log)		p-value < 0.10			
QL	163	6.1	1	4	
Weibull(restrict)	163	6.1	1	4	
Weibull (unrestrict)	161	6.1	1	4	

3 hours	All models had a p-value < 0.10

3.5 hours	All models had a p-value < 0.10

4 hours	All models had a p-value <

Eye effects: lacrimation and eye closure (NOTE: 1640 was included & death was counted as a response)
0.10

Dyspnea and Gasping (NOTE: 1640 ppm was included & death was measured as a response)	
0.25 hrs	All models had a p-value < 0.10
0.5 hrs	All models had a p-value < 0.10
1 hr	All models had a p-value < 0.10

1.5 hrs				
model	BMD	BMDL	P	AIC
gamma	636	529	0.31	30
logistic (non-log)	657	529	0.37	29
logistic (log)	647	539	0.24	30
MS	647	431	0.33	31
Probit (non-log)	645	516	0.39	29
QL	645	515	0.42	29
Weibull (non-log)	645	515	0.42	29

2 hrs	All models had a p-value < 0.10

2.5 hrs				
model	BMD	BMDL	P	AIC
gamma (unrestrict)	247	89	0.62	71
gamma (restrict)	247	95	0.62	71
logistic (log)	261	111	0.49	72
logistic	294	214	0.67	71
MS	143	96	0.96	67
probit	277	201	0.72	70
probit (log)	266	123	0.49	72
QL	248	110	0.67	70

Dyspnea and Gasping (NOTE: 1640 ppm was included & death was measured as a response)				
Weibull	248	110	0.67	70

3 hours				
model	BMD	BMDL	P	AIC
gamma (unrestrict)	124	7.76	0.32	78
gamma (restrict)	124	68	0.32	78
log(nonlog)	230	170	0.26	78
log (log-unrestrict)	140	13.7	0.24	79
log (log-restrict)	140	45.2	0.24	79
MS	108	76.2	0.59	74
probit (nonlog)	216	162	0.29	78
probit (log-unrestrict)	153	19	0.24	79
probit (log-restrict)	164	124	0.33	77
QL	138	69	0.31	78
Weibull (unrestrict)	138	20.5	0.31	78
Weibull (restrict)	138	69.2	0.31	78

3.5 hrs				
model	BMD	BMDL	P	AIC
gamma (unrestrict)	133	14.7	0.63	70
gamma (restrict)	133	49.6	0.63	70
log(nonlog)	184	128	0.44	72
log (log)	163	42	0.56	71
MS	69.8	50.4	0.57	71
probit (nonlog)	174	123	0.47	72
probit (log-unrestrict)	172	50.1	0.58	71
probit (log-restrict)	172	91.1	0.58	71
QL	124	50.1	0.65	70
Weibull (unrestrict)	124	25.4	0.65	70
Weibull (restrict)	124	50.1	0.65	70

4 hours				
model	BMD	BMDL	P	AIC
gamma (unrestrict)	125	11.1	0.28	62
gamma (restrict)	125	38.5	0.28	62
log(nonlog)	165	106	0.21	64
log (log)	153	41	0.21	63
MS	62	39.9	0.39	61
probit (nonlog)	156	103	0.23	63
probit (log-unrestrict)	159	45.8	0.23	63
probit (log-restrict)	159	71.1	0.23	63
QL	114	38.9	0.29	62
Weibull (unrestrict)	114	20.5	0.29	62
Weibull (restrict)	114	38.9	0.29	62

Dyspnea and Gasping (NOTE: 1640 ppm was included & death was measured as a response)

Exhibit 4

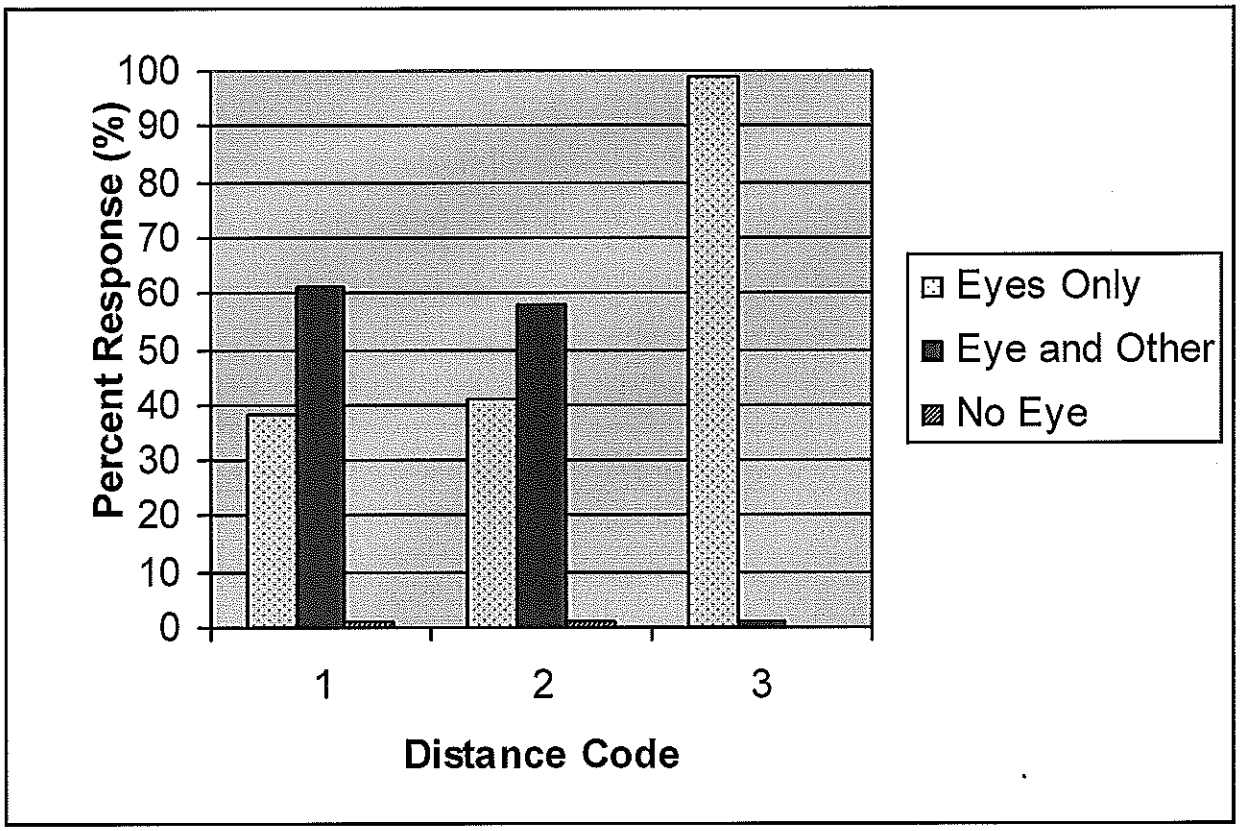

Figure 8. Percent of responders in the Arvin incident who experienced eye irritation only, eye irritation in conjunction with other symptoms, or other symptoms without eye irritation, in relation to their distance from the treated field.

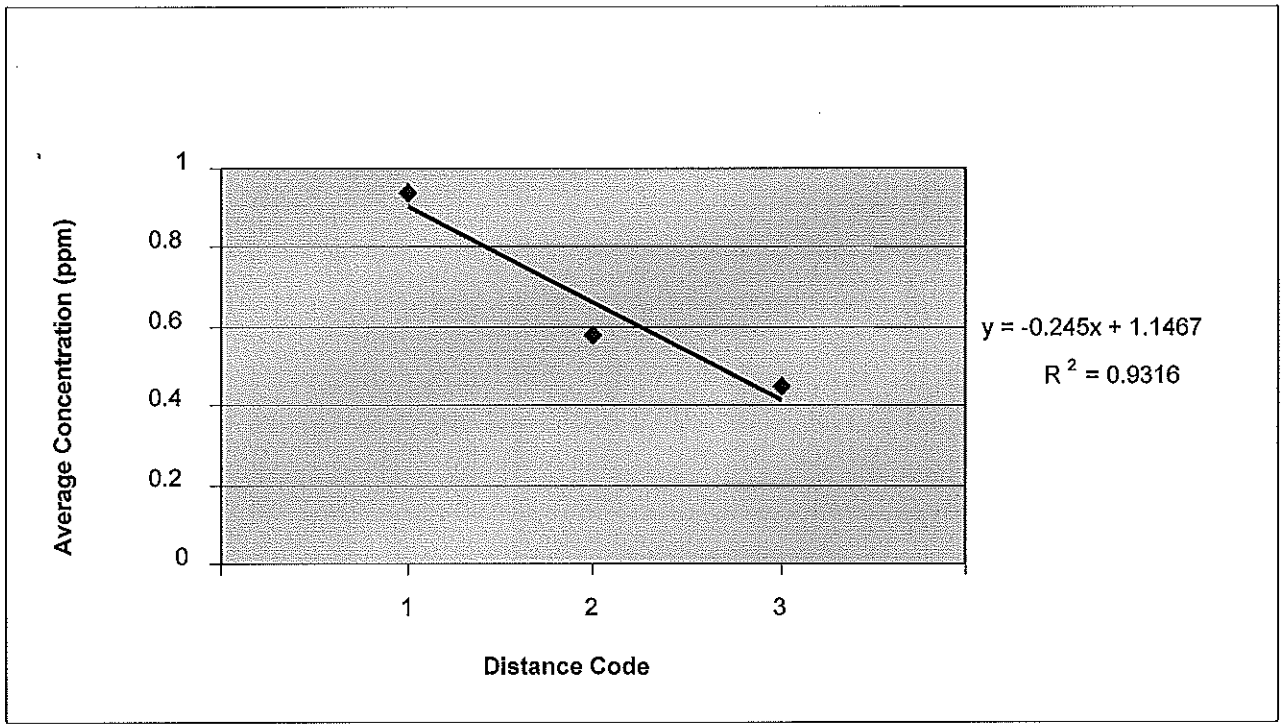

Figure 9. Average MITC concentration estimates (obtained from O'Malley et al., 2005) are shown in relation to the distance codes provided by the CDPR. Distance code 3 represents the farthest distance from the treated fields

TERA Statement of Purpose

Toxicology Excellence for Risk Assessment (***TERA***) is a non-profit, 501(c)(3) corporation organized for scientific and educational purposes. Our mission is to protect public health by developing and communicating risk assessment information, improving risk methods through research, and educating the public on risk assessment issues. Some specific activities of ***TERA*** are listed below.

- Establish high-quality risk assessment values based on the latest scientific data and methods through the **Verifiable Estimates for Risk Assessment** (***VERA***) program
- Provide a unique side-by-side comparison of hazard values, information and dose response from organizations and independent parties worldwide through the **International Toxicity Estimates for Risk** (***ITER***) Database
- Conduct **research** to improve the underlying methods for human and ecological risk assessment
- **Peer Review and Consultation** of risk information, methods and study designs through an independent and public process
- **Educate** diverse groups on risk assessment issues, through training courses, scientific support and the State Hazard Evaluation Lending Program (**State HELP**)
- Improve the practice of **risk assessment** through independent and objective guidance and advice

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