# Office of Environmental Health Hazard Assessment

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## MEMORANDUM

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**FROM:** Anna M. Fan, Ph.D., Chief
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**DATE:** January 31, 2002

**SUBJECT:** REVISED FINDINGS ON THE HEALTH EFFECTS OF METHYL ISOTHIOCYANATE

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Pursuant to Food and Agricultural Code Sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) provides review, consultation, and comments to the Department of Pesticide Regulation (DPR) on the evaluation of the health effects of pesticides that are candidate toxic air contaminants (TAC). As part of its statutory responsibility, OEHHA also prepares findings on the health effects of the candidate pesticide TACs. These findings are to be included as part of the final DPR report.

Attached you will find a revised version of OEHHA's draft findings on the health effects of methyl isothiocyanate. Our original findings were submitted to DPR in December 1999. Changes to the original draft findings are shown in underlined text. Revisions to our findings were necessary as a result of changes introduced into the draft TAC document by DPR and submitted to OEHHA in August 2001. Note that we have provided comments on the revised draft TAC document in addition to our previous comments on the original draft TAC document dated March 2000.

Our staff would be happy to meet with your staff to discuss these findings. If you have any questions, please contact either one of us at (510) 622-3200 or Dr. David Rice at (916) 324-1277.

Attachment

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# Office of Environmental Health Hazard Assessment's Draft Findings on the Health Effects of Methyl Isothiocyanate

Pursuant to Food and Agricultural Code Sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency provided consultation to the Department of Pesticide Regulation (DPR) on the evaluation of health effects of the chemical methyl isothiocyanate (MITC), formed as a degradation product of the pesticide active ingredient metam sodium. Furthermore, OEHHA has reviewed and commented on the draft documents on the evaluation of human health risk associated with potential exposure to MITC for consideration of the identification of MITC as a toxic air contaminant (TAC). As part of its statutory responsibility, OEHHA has prepared these findings on the health effects of MITC which are to be included as part of DPR's draft TAC document.

## Environmental Fate and Exposure

1. Metam sodium is used mainly as an agricultural fumigant. After field application in aqueous solution through sprinklers or direct shank injection, it is converted to MITC in soil within the first day. MITC diffuses through soil to produce the pesticidal effects, and a major portion is eventually lost by volatilization to air. The half-life of MITC in air by photolytic decomposition was reported as 29 to 39 hours in natural sunlight.

2. Three ambient air monitoring studies carried out in Kern and Santa Barbara Counties and seven application-site monitoring studies in Contra Costa, Kern and Madera Counties are described in the draft TAC document. Ambient air concentrations of MITC ranged from not detected (less than 0.003 ppb) to 104 ppb (131 $\mu g/m^3$), averaged over a 12-hour sampling time. Mean time-weighted average (TWA, 24-hour) concentrations of MITC in ambient air ranged from 0.1 to 8.8 ppb (0.3 to 26.4 $\mu g/m^3$). Concentrations of MITC in air at metam application sites were as high as 2,853 ppb (8,490 $\mu g/m^3$) for a one-hour sample. Mean TWA (24-hour) concentrations of MITC in application site air ranged from about 13 to 1,100 ppb (39 to 3,300 $\mu g/m^3$).

3. Two worker exposure studies (one in Washington State and one in Arizona) also provide perspective on MITC concentrations at metam sodium application sites. Mean concentrations of MITC in personal air monitors varied from 29.3 to 504 ppb (88 to 1,500 $\mu g/m^3$).

4. Breakdown of metam sodium in soil or water and MITC in air results in the formation of several other toxic chemicals including methyl isocyanate (MIC), carbon disulfide ($CS_2$), and hydrogen sulfide ($H_2S$). Conversion of MITC to MIC in laboratory experiments was about 7 percent, indicating that MIC toxicity could be a concern in areas of elevated MITC concentrations. Concentrations of these chemicals in air were not usually monitored in the metam sodium/MITC studies. However, in one study in Kern County, measured application-site levels of MIC in 12-hour collections ranged from 0.09 to 2.5 ppb (0.2 to 5.8 $\mu g/m^3$), when MITC concentrations ranged from 0.08 to 84 ppb (0.24 to 250 $\mu g/m^3$). MIC half-life in air was not reported, but is probably less than one day.

5. Human exposure to atmospheric MITC can occur by both inhalation and dermal routes, but the predominant exposure route for systemic doses is inhalation. Inhalation uptake is assumed to be 100 percent for these estimates, based on the physical properties of MITC.

6. Dermal uptake of MITC has not been quantitatively estimated in these studies; it would be likely to provide less than 1 percent of the systemic dose received by inhalation. However, the direct effect of MITC on sensitive tissues of the eye is the predominant acute hazard. Eye irritation and odor complaints from agricultural applications of metam were responsible for designation of metam as a restricted use pesticide (CCR Titles 3 and 26, Section 6400).

7. Concentrations of MITC in air are somewhat uncertain because of the possible loss of MITC on the silica gel drying tubes placed in front of the charcoal trapping tubes in most of the exposure studies. Losses of MITC to the silica gel tubes were reported to be 58 to 100 percent for one sampling interval and 0 to 4 percent for another.

**Health Effects**

Humans

8. From a human exposure study designed to determine the eye irritation level for MITC (using special goggles to provide selective exposure to the eye region) a lowest-observed-adverse-effect-level (LOAEL) for eye irritation of 800 ppb was identified (Russell and Rush, 1996). The no-observed-adverse-effect-level (NOAEL) for eye irritation identified from this study was 220 ppb.

9. Other signs and symptoms of human acute and subacute exposure to MITC reported most frequently following the 1991 train derailment at the Cantara Loop that resulted in a large metam sodium spill in the Sacramento river included nausea, headache, throat irritation, dizziness, vomiting, and shortness of breath. Some patients also complained of chest tightness, cough, abdominal pain, diarrhea, and skin rash. Hyperventilation or anxiety-like symptoms including rapid breathing, tremulousness, and perioral and acrodigital paresthesias (tingling around the mouth and of the fingertips) were also noted.

10. Following an incident of agricultural drift over populated areas, residents of Earlimart, California were exposed to levels of MITC estimated to be in the range of 0.5 to 1.0 ppm (one-hour TWA). Odor complaints were received two hours after the initiation of the second day's application. Evacuation orders for residents located 0.45 to 0.6 miles away from the field were given based on "reports of symptoms," but the timing of the onset of symptoms or for the evacuation orders cannot be determined from the draft TAC. The following profile of symptomotology was compiled from: 1) interviews conducted six days after the incident, 2) complaints to the Tulare County Agriculture Department and Emergency Services, and 3) pesticide illness reports and medical records. Of 171 exposed individuals, nearly 80 percent experienced symptoms of eye or upper respiratory irritation (burning of the eyes, nose and/or throat). Non-specific systemic symptoms of headache, nausea, dizziness, shortness of breath, abdominal pain, vomiting, and weakness were present in approximately 60 percent of

the cases. Sixteen percent had other respiratory complaints, including dyspnea, cough and/or exacerbation of pre-existing asthma.

11. Some exposures to MITC have exceeded the acute respiratory irritation level. Exposure to respiratory irritants can result in the development of prolonged adverse effects such as reactive airways dysfunction syndrome (RADS). In this condition, subsequent exposures to far lower levels of the same or another irritant gas will then trigger respiratory distress symptoms. This may be a hazard for MITC or combined MITC/MIC exposures.

Animals

12. Acute toxicity of MITC was studied in a variety of animal species including rats, mice, rabbits, dogs, cats, guinea pigs, and monkeys. Acute effects produced in laboratory animals following inhalation exposure included excitement, eye irritation, and dyspnea. Cats appear to be the most sensitive laboratory species. The NOAEL for irritation of the ocular mucosa in a four-hour exposure in this species was identified as 35 ppb (Nesterova, 1969). In rabbits, MITC was shown to be a severe skin and eye irritant. Studies in guinea pigs demonstrated that MITC is a strong dermal sensitizer.

13. Subchronic toxicity studies of MITC in laboratory animals provide information on adverse effects following inhalation, dietary, gavage, and dermal administration. In rats, adverse effects from inhalation exposure included mortality (at 467 ppm, or 1,400 mg/m$^3$ in a 24-day study), decreased body weight gain (at 84 ppm in a 24-day study), vascular effects in the lungs (at 0.37 ppm in a four-month study), and nasal discharge (at 45 ppm in a 12 to13 week nose only inhalation study). From the key 28-day inhalation study with Wistar rats, a LOAEL of 1.7 ppm was identified in the draft TAC document based on increased incidence of atrophy of the nasal olfactory epithelium in both sexes. MITC administered orally resulted in decreased feed consumption and body weight (in mice at 44 ppm in a three-week drinking water study and in a three-month gavage study), inactivity and abnormal feces (at 25 ppm in a ten-day gavage study in rats), forestomach acanthosis, hyperkeratosis, and submucosal cyst formation (at 3 ppm in an eight-month gavage study in rats), increased liver weight and liver inflammation, altered ovary and adrenal weight, and spermatogenic disorder (at 1 ppm in a three-month gavage study in mice), and blood changes (at 10 ppm in a three-month gavage study in mice). Subchronic dermal application of MITC produced skin ulceration, crust formation, neutrophil infiltration, enlarged peribronchial lymph nodes (at 120 ppm in a one-month dermal study in rats), and erythema and decreases in serum albumin and plasma cholinesterase activity (at 1 ppm in a 31-day dermal study in rats).

NOTE: PREVIOUS #14 WAS DELETED

14. Because of the small number of animals (five/sex/dose) and the high incidence of atrophy of the nasal olfactory epithelium in the controls (30 percent), the response at the two lowest dose groups (60 percent in either group) is not statistically significantly different from the controls. Therefore, it is difficult to definitively identify a LOAEL or NOAEL from the subchronic inhalation rat study. Accordingly, we applied benchmark dose methodology (BMD) to the data and identified the benchmark concentration at a response rate of five

percent ($BMC_{05}$) for use as a point of departure. Applying this methodology to the combined incidence data (total; focal plus non-focal atrophy), we derived a lower confidence limit on the $BMC_{05}$ of 1.2 mg/m$^3$. Converting to ppm and adjusting for discontinuous exposure (experimental exposure was six hours/day, five days/week) a $BMC_{05}$ of 70 ppb is calculated. We would adopt the adjusted $BMC_{05}$ of 70 ppb as the reference point for the calculation of RELs and MOEs.

15. In long-term toxicity studies, MITC was administered via gavage (dogs) or drinking water (rats and mice). Adverse effects included decreased feed consumption and body weight along with poor condition in dogs (LOAEL of 2 mg/kg-day), and decreased water consumption and body weight in rats (LOAEL of 2.1 mg/kg-day) and mice (LOAEL of 9.82 mg/kg-day). Some blood and liver effects were observed in mice and dogs at higher doses (changes in blood platelets, total serum protein, hematocrit, and ratios of lymphocytes and neutrophils at 21.34 mg/kg-day in female mice and at 24.09 mg/kg-day in male mice and decrease of liver weights at 2 mg/kg-day in dogs). There is insufficient evidence of oncogenicity in any of the studies. No long-term study via inhalation is available.

16. There are two reproductive toxicity studies, one two-generation drinking water and one three-generation oral gavage study in rats. No reproductive effects were identified. Systemic effects observed at the mid and highest doses tested included decreased water consumption and weight loss at 10 and 50 ppm in the two-generation study and decrease of body weights in $F_0$ males at 3 and 10 mg/kg-day in the three-generation study.

17. Three developmental toxicity studies are available, one using rats and two using rabbits. These studies showed decreased fetal body weight and size at doses that also produced maternal adverse effects such as decreased feed consumption and body weight gain (at 25 mg/kg-day in rats, 5 mg/kg-day in New Zealand White rabbits, and at 3 and 10 mg/kg-day in albino rabbits). The maternal effects were noted in both species.

18. Most MITC genotoxicity data are negative. Evaluation of chromosomal effects in Chinese hamster V79 cells indicated a weakly positive response. There was no evidence for gene mutation in a mammalian cell assay. The results of microbial cell assays were considered not useful for hazard identification by DPR due to various deviations from Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. Tests for sister-chromatid exchange (SCE) and DNA damage were negative.

19. Studies are available that were designed to evaluate MITC effects on the immune system, cardiovascular system, blood coagulation, hemolysis, and central nervous system. However, little can be concluded from these studies because only summary information was available for evaluation.

20. MIC is known to be highly reactive and acutely toxic to humans and animals. Acute symptoms following exposure to high air concentrations of MIC include skin and eye injuries, myelotoxicity, asthma, chest pain, pulmonary edema, dyspnea, respiratory failure, and death.

21. Positive genotoxicity data exist for MIC. Increased mutation frequencies were seen in L5178Y mouse lymphoma cells and SCEs and chromosomal aberrations were increased in Chinese hamster ovary cells exposed to MIC *in vitro*. Increases in SCEs and chromosomal aberrations were observed in bone marrow cells from $B6C3F_1$ mice exposed *in vivo*, and a dose-related increase in SCEs occurred in lung cells but not in peripheral blood lymphocytes. A significant increase in micronucleated polychromatic erythrocytes in the peripheral blood was also observed in male mice in one experiment. These data suggest that MIC could have carcinogenic potential.

**Basis, Potency, and Range of Health Risks to Humans**

22. The draft TAC document includes an assessment of risks from potential acute or short-term human exposures and from seasonal exposures to the airborne MITC following agricultural use of metam sodium, dazomet and/or metam potassium. The draft TAC document does not include an assessment of chronic health risks from potential chronic human exposures.

23. Human health risks are estimated in the draft TAC document from the acute or short-term exposures based on the eight-hour NOAEL of 220 ppb for eye irritation (Russell and Rush, 1996). This NOAEL was identified in an acute study with human volunteers and was used for calculating reference exposure levels (RELs) and margins of exposure (MOEs) for various groups. The NOAEL of 35 ppb for irritation of the ocular mucosa in a four-hour exposure in cats (Nesterova, 1969) was used in 1992 by OEHHA to calculate an acute REL for MITC following the Cantara Incident.

24. Both the human volunteer study (Russell and Rush, 1996) and the laboratory study in cats (Nesterova, 1969) have limitations for use in quantitative risk assessment. These limitations are listed in Table 1. While the use of the human study for eye irritation might be justified, it should be noted that an REL based on the NOAEL from the Nesterova (1969) study would be significantly lower, and the MOEs significantly less, than those calculated in the draft TAC document using Russell and Rush (1996).

25. The eye irritation endpoint used for evaluating acute human exposures to MITC was from a human volunteer study (Russell and Rush, 1996) where only the eyes were exposed (using goggles) to the material. In an actual exposure situation, in addition to the eyes, the nose and mouth would be simultaneously exposed, which may effectively lower the NOAEL for this endpoint. Uncertainty exists as to what degree the NOAEL would be affected.

26. RELs calculated in the draft TAC document for acute, seasonal and chronic exposures to MITC are presented in Table 2. The acute REL calculated from the human exposure study (Russell and Rush, 1996) is based on an eight-hour exposure. In the draft TAC document it is noted that because the level of eye irritation was unchanged at one, four and eight hours, the one, four, and eight-hour REL values are equivalent. Using the Russell and Rush (1996) study, the NOAEL for human eye irritation was 220 ppb after eight hours of exposure, based on subjective symptoms of eye discomfort at the next higher level of 800 ppb MITC. This NOAEL of 220 ppb is then divided by an uncertainty factor of ten (accounting for intra-species variability), resulting in an acute REL of 22 ppb (66 $\mu g/m^3$).

**Table 1. Limitations of the Two Critical Experimental Studies for Acute MITC Exposure**

| Nesterova, 1969 | Russell and Rush, 1996 |
|---|---|
| 1. Report lacks essential information on experimental conditions and parameters:<br>• There is no information about the number of animals, sex, weight, or age of the three species reportedly used in the inhalation experiment.<br>• No control groups were specified. | 1. This study attempted to determine the human eye irritation threshold using an eye mask. It did not address MITC effects on the upper respiratory tract or other parts of the human body. |
| 2. It is not possible to determine whether the toxic effects seen in experimental animals were based solely on MITC exposure:<br>• The experimental method specified that MITC was generated from the decomposition of metam sodium promoted by heated soils.<br>• Measurements of airborne MITC were undertaken, but no measurements were made of other volatile degradation products of metam sodium.<br>• It is possible that toxic effects were due to the additive/synergistic effects of degradation products with MITC, or to MITC itself. | 2. The recruitment questionnaire asked about medical history including eye infection/irritation, asthma, allergies, medication, smoking, and pregnancy. Subjects wearing contact lenses or pregnant and lactating women were excluded. However, the interim report did not indicate the number of subjects with these conditions who were included in the study. For example, the study may have excluded subjects with asthma or hay fever, as they may not have wanted to participate in a study involving chemical irritants. Therefore, only healthy, young adults may have been represented. |
| 3. The quality or accuracy of the MITC assay method is not described. No information was provided about the nature of the airborne concentrations, whether they were consistent or variable, or when the measurements were undertaken. | 3. The study included 138 human subjects (69 of each gender) recruited from the campus community, with a mean age of 32 (range of 18 to 67). These subjects did not represent the full age range nor, probably, the racial make-up of the California population. |
| 4. The effects reported were primarily clinical observations. There was no evidence for an extensive toxicity evaluation as would be conducted under FIFRA guidelines. No organ weights or histology was reported, but some clinical chemistry and hematology apparently were done (no specific tests were identified and only the results were reported). | 4. Lacrimation (tearing) may occur via the trigemino-facial reflex from either a direct (eye) or indirect (nasal) stimulation. By isolation of ocular from nasal exposure with the eye mask, the origin of the reaction can be differentiated. However, most individuals would experience full-face exposure to MITC with combined effects on nasal, eye, and upper respiratory nerve endings, and the skin. The study does not provide data to assess this likely exposure scenario. |
| | 5. In animals, the Draize eye irritation test is evaluated using "irritation scores." In the human study, a non-invasive, subjective approach is used. Each test subject is asked to report on perceived eye irritation. Eye photographic analysis was found "not of value" because the more sensitive individuals "tended to be canceled out by others who displayed some native edema and redness in the early morning." It is unclear why this would not be useful, with each person acting as his or her own control, as stated. If this measure were applied properly, the results should have been more comparable to the animal irritation study method. |

**Table 2. Reference Exposure Levels for Acute, Seasonal and Chronic Exposures Calculated in the Draft TAC Document**

| Species | "NOEL" | REL |
|---|---|---|
| **Acute Exposure (1, 4 or 8-hour)** | | |
| Human (adult) | 220 ppb | 22 ppb; 66 $\mu g/m^3$ |
| **Seasonal Exposure (24-hour)** | | |
| Rat | 100 ppb | |
| Human | | 1 ppb; 3 $\mu g/m^3$ |
| **Chronic Exposure (24-hour)** | | |
| Rat | 100 ppb | |
| Human | | 0.1 ppb; 0. 9 $\mu g/m^3$ |

27. In the draft TAC document both seasonal (subchronic) and chronic RELs were calculated (see Table 2). The seasonal REL of 1 ppb was calculated from the estimated subchronic NOAEL of 100 ppb. This estimated NOAEL was derived in the draft TAC document from the 28-day inhalation study LOAEL of 1.7 ppm (based on clinical signs and decreased polymorphonuclear granulocytes in Wistar rats at the next highest dose) by adjusting for discontinuous exposure by multiplying the LOAEL by an appropriate adjustment factor [1,700 ppb × (6/24 hours)] × (5/7 days) = 304 ppb]. This adjusted LOAEL was then divided by an uncertainty factor of 300 (a factor of three for LOAEL to NOAEL extrapolation, a factor of ten for inter-species, and a factor of ten for intra-species variability) to arrive at the seasonal REL of 1 ppb. A chronic REL of 0.1 ppb was derived by applying an additional uncertainty factor of ten to the subchronic NOAEL for subchronic to chronic exposure extrapolation.

NOTE: THE previous # 29 WAS REMOVED

28. Using the $BMC_{05}$ of 70 ppb to calculate RELs would result in values of 0.7 ppb and 0.07 ppb for the subchronic and chronic RELs, respectively. The subchronic REL is calculated by applying a combined uncertainty factor of 100 (ten for inter-species extrapolation and ten for intra-species extrapolation) to the $BMC_{05}$ of 70 ppb. The chronic REL is calculated similarly, with the application of an additional uncertainty factor of ten (total uncertainty factor of 1,000) to account for subchronic to chronic exposure extrapolation. Given the uncertainty in identifying a NOAEL or LOAEL from this study, the REL calculated using the

benchmark concentration might be more scientifically defensible than the REL calculated using the LOAEL.

29. The highest measured mean acute application site air concentration (one-hour exposure) was 2,853 ppb, resulting in a mean MOE of less than one. Nearly all (90 percent) of the MOEs for acute exposure to application site air were less than one. These estimates are well below an MOE of ten, which is generally considered by DPR to be protective of human health for adverse effects observed in human studies. Based on these considerations, acute exposures to MITC at application sites represent a public health concern and exposure to MITC in ambient air may pose a public health concern.

30. MOEs for acute exposure to average ambient air concentrations of MITC range from 15 to 2,200. MOEs of this magnitude are generally considered by DPR to be protective of human health for adverse effects observed in human studies. Based on these considerations, acute exposures to MITC at application sites represent a public health concern and exposure to MITC in ambient air may pose a public health concern.

31. MIC has been observed to cause reproductive toxicity (increased dead fetuses at birth) in Swiss mice after exposures to concentrations of 1 or 3 ppm for six hours/day during days 14 to 17 of gestation. A NOAEL was not observed in this study. DPR derived a NOAEL of 100 ppb from the LOAEL of 1 ppm using a LOAEL to NOAEL extrapolation uncertainty factor of ten; DPR considered this to be a six-hour ENOEL (estimated NOEL). DPR then calculated one-hour and 24-hour ENOELs of 600 ppb and 25 ppb, respectively, using a time extrapolation based on Haber's Law ($C^n \times T = K$, where C = concentration, T = time, K = a constant level or severity of response and n = an empirically-derived chemical-specific parameter greater than zero). The resulting ENOELs were then divided by an uncertainty factor of 100 to account for inter-species and intra-species variation, and corrected for the breathing rate of a child (0.76 $m^3$/kg-day) compared to that of a rat (0.96 $m^3$/kg-day). The resulting one-hour, six-hour and 24-hour acute RELs calculated for MIC by DPR were 7.6 ppb, 1.3 ppb and 0.3 ppb, respectively. OEHHA does not use time extrapolation in calculating acute RELs when the critical toxic effect is developmental toxicity (OEHHA, 1998). Using OEHHA methodology, an acute one-hour REL of 1 ppb (2.4 $\mu g/m^3$) can be calculated by dividing the NOAEL of 100 ppb by an uncertainty factor of 100 to account for inter-species and intra-species variation. Estimated air concentrations of MIC generated from the photolysis of MITC can be compared to this REL.

32. The estimated NOAEL used in the draft TAC document for evaluation of potential adverse health effects from seasonal exposures was 100 ppb based on increased incidence of atrophy of the nasal olfactory epithelium in both sexes in a 28-day rat inhalation toxicity study. The highest estimated mean seasonal ambient air concentration was 3.5 ppb in Weedpatch, Kern County during the summer of 1993. The corresponding MOE is 28. Three of fourteen MOEs for ambient exposure were less than 100, and, therefore, below the level generally accepted by DPR to be protective of human health for adverse effects observed in animal studies. Most MOEs for ambient exposures, however, were greater than 100, a level generally considered by DPR to be protective of human health for adverse effects observed in animal studies. Estimated mean seasonal application site air concentrations ranged from 2 to 80 ppb,

with corresponding MOEs ranging from 1 to 50. All MOEs for seasonal exposure to application site air were less than 100, and, therefore, below the level generally accepted by DPR to be protective of human health for adverse effects observed in animal studies. Based on these considerations, seasonal exposures to MITC at application sites represent a public health concern.

NOTE: PREVIOUS #35 WAS DELETED

33. Using the $BMC_{05}$ to assess seasonal exposures, all seasonal MOEs for application-site exposures would be less than 100. MOEs for ambient air exposures would be less than 100 for 6 of 14 scenarios evaluated in the draft TAC document. Note that MOEs for 3 of 14 ambient air exposure scenarios were less than 100 using the estimated NOAEL (100 ppb) in the draft TAC document. Twice as many scenarios for exposure to MITC in ambient air have MOEs below the level generally considered by DPR to be protective of human health for adverse effects observed in animal studies when calculated based on the $BMC_{05}$ instead of the estimated NOAEL used in the draft TAC document.

34. Based on the available information, seasonal exposure to MITC presents a public health concern. Because of the small numbers of animals used in the experiment and the uncertainties introduced into the risk assessment by estimating a NOAEL, the most scientifically defensible approach is to use BMD methodology to calculate the point of departure for assessing risks from seasonal exposures to MITC.

**Uncertainties and Other Relevant Findings**

35. Health risk assessment for acute inhalation exposure to MITC was based on a study involving human volunteers with their eyes exposed to air concentrations of MITC in a laboratory setting. In practice, people are most frequently exposed to airborne MITC following agricultural metam sodium applications. Under such conditions, inhalation exposure is not limited to MITC but also may include other degradation products such as $CS_2$, $H_2S$, and MIC. Uncertainty exists as to the degree of contribution of these products to the overall potential toxicity.

36. Potential health risks from chronic exposures to MITC have not been assessed because no chronic exposure data exist. The potential significance of repeated seasonal exposures to MITC is uncertain.

37. Uncertainty also exists as to the potency of MITC as a human dermal and pulmonary sensitizer. Potential sensitization properties of airborne MITC following metam sodium applications might also be enhanced due to MIC co-exposures.

38. No sensitive subpopulations have been specifically identified, although it has been observed that people with pre-existing respiratory conditions can be especially vulnerable to chemicals with respiratory irritant and sensitization properties (see finding above regarding RADS).