MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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October 10, 2012

TO: File for Maleic Anhydride (CAS #108-31-6)

FROM: Michael Depa, Air Quality Division, Toxics Unit

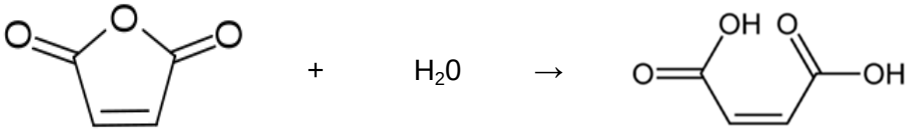
SUBJECT: Update of the Screening Level

The Initial Threshold Screening Level (ITSL) for maleic anhydride is 0.1 µg/m³ (8-hr averaging time).

The following references or databases were searched to identify data to determine the screening level for maleic anhydride (MA): United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances, the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) Online (1967- December 2010), National Library of Medicine (limited to 2009 through October, 2012), Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration (RfC) for MA. The EPA established a reference dose (RfD) of 0.1 mg/kg. Both the ACGIH and NIOSH have established Occupational Exposure Limits. The ACGIH TLV (2011) for MA is 0.01 mg/m³ (10 µg/m³) and the NIOSH REL is 1 mg/m³. The molecular weight is 98 g, and the molecular formula is C4H2O3. The molecular structure is pictured in Figure 1. The melting point is 53℃. MA is water soluble and is expected to be a white crystalline solid at 77℉ (25℃). The vapor pressure is 0.1 torr at 25℃. The odor threshold is 1.3 mg/m³ (0.32 ppm) (ACGIH, 2011). MA rapidly hydrolyzes to maleic acid in the presence of water (Figure 2).

Figure 1. Molecular Structure of Maleic Anhydride

Figure 2. Hydrolysis of Maleic Anhydride to Maleic Acid



Maleic Anhydride | Water | Maleic Acid

Animal Studies

Groups of 15 CD rats per sex were dosed with 0, 1.1, 3.3, or 9.8 mg/m³ MA for 6 hours/day, 5 days/week for 6 months (Short et al., 1988). Blood and urine were collected at 3 months from the control and high dose groups. At the 9.8 mg/m³ dose level, male rats had statistically significant decreases in body weight at months 2 through 6. Female rats had the same decrease in body weight but only during months 2 through 5. Inflammatory changes were observed in the nasal tissue of all species. Rats at all exposure levels exhibited a focal to multifocal infiltration of the nasal epithelium with neutrophils and eosinophils, which was generally graded as trace to mild. At 1.1, 3.3, and 9.8 mg/m³ MA there was an increased incidence of nasal epithelial hyperplasia and mucosal and squamous metaplasia. The lowest dose of 1.1 mg/m³ was identified as a LOAEL in rats. A no-observed-adverse-effect-level (NOAEL) was not identified for rats.

Groups of 15 Engle hamsters per sex and groups of 3 Rhesus monkeys per sex were dosed were also dosed with 0, 1.1, 3.3, or 9.8 mg/m³ MA for 6 hours/day, 5 days/week for 6 months (Short et al., 1988). The results of are previously summarized by DEQ (2002).

Basis of the ACGIH TLV

In 2010, the ACGIH established the current TLV for MA (MA) at 0.01 mg/m³ (10 µg/m³; 0.0025 ppm) for the inhalable particulate fraction and vapor. The TLV is, "…intended to minimize the potential for respiratory sensitization" (ACGIH, 2011). ACGIH (2011) states that, "MA is demonstrated to be a sensitizer by both the reported sensitization in humans and positive response in animals." In human studies, specific IgE antibodies to MA-human serum albumin conjugate were detected in workers occupationally exposed to MA (Gannon et al., 1992; Baur et al., 1995; Topping et al, 1986). In challenge studies of previously exposed workers, MA exposure provoked both early (up to one hour post-exposure) and late (3-11 hours post-exposure) asthmatic response (Lee et al, 1991; Graneek et al., 1987; Durham et al., 1987). ACGIH stated that 1 mg/m³ should prevent irritation effects, however that, "It is important to note that workers who have become sensitized to MA may not be protected by the TLV-TWA and will require attention."

ACGIH summarized a study by Barker et al., which seems to support the TLV of 10 µg/m³:

> At lower exposures (less than 10 µg/m³), negative findings are noted. In a cohort study of several factories with mixed anhydride exposures (trimellitic anhydride (TMA), phthalic anhydride (PA) and MA), sensitization was not noted in workers with recent exposures (up to an arithmetic mean of 2.8 µg/m³ for MA) but occurred in the past when acid anhydride exposures were higher (for example, past MA exposures ranged from 5 to 54 µg/m³). The authors suggested that current 'exposure to PA and MA at levels measured in the alkyd resin plants in 1992, is an uncommon cause of sensitization'. In the analysis, which included all workers and all three acid anhydrides, there was some evidence "that those employed in jobs with mean full-shift exposure ≥ 10 µg/m³ were more at risk of sensitization than those employed in jobs where the mean full-shift exposure was < 10 µg/m³ (Barker et al., 1998)."

Derivation of Screening Level

California Office of Environmental Health Hazard Assessment (Cal-OEHHA, 2008) derived a Reference Exposure Level (REL) of 0.7 µg/m³ (annual averaging time) for MA. Cal-OEHHA RELs are typically considered high quality health benchmarks, therefore, the MA REL was evaluated as a potential basis for an ITSL. Additionally, EPA (2010) published the 2005 National Air Toxics Assessment (NATA) of hazardous air pollutant impacts where Cal-OEHHA's REL was used as the health benchmark for MA. In deriving the REL, Cal-OEHHA used EPA's Benchmark Dose Software (BMDS) and the study by Short et al., (1988), which identified nasal irritation in rats at all dose

levels other than the control rats. In order to verify the REL and the method used, the raw data (see Table 1) was plugged into BMDS.

Table 1. Dose-Response Data in Rats taken from Short et al. (1988)

Dose (mg/m^3)	Number of Male and Female Rats	Incidence of Mild Epithelial Hyperplasia of Nasal Mucosa
0	30	0
1.1	30	11
3.3	30	24
9.8	30	26

Cal-OEHHA's $BMDL_{05}$ of 0.12 $\mu g/m^3$ was reproduced using the data from Short et al. (1988). However, using the Gamma model produced a poor fit according to the p-value of the chi-squared goodness of fit. US EPA (2012) recommends rejecting models that do not have p-values greater than 0.1 because of a poor fit. Using a benchmark response (BMR) of 5% (default Cal-OEHHA methodology), three of nine BMDS models provided p-values that showed adequate fits: LogLogistic, LogProbit and Multistage (data not shown). The range of the BMDLs was approximately 5, therefore it was determined that the best point of departure (POD) for a screening level would be the lowest BMDL (EPA, 2012b). In this case the LogLogistic model, with a $BMDL_{05}$ of 0.0168 $mg/m^3$was used as the POD for a potential screening level using the 5% benchmark response. Using an uncertainty factor of 30 (as Cal-OEHHA did), results in a potential screening level value of 0.1 $\mu g/m^3$. Cal-OEHHA did not adjust for subchronic to chronic duration. Typically a 24-hr averaging time would be used in this case because no adjustment for subchronic to chronic duration was used in the uncertainty analysis and the possibility of sensitization occurs in occupational settings with peaks during short-term exposures, which the animal model does not address. US EPA (2012) suggests a default BMR of 10%, however, Cal-OEHHA uses a 5% BMR as default. Using data from Short et al., (1988) and a 10% benchmark response the BMDS was employed to derive a $BMDL_{10}$ (see Table 2).

Table 2. BMDS Model Output Using BMR of 10% Extra Risk and Data from Short et al. (1988)

Model Name	AIC	P-value	Reject if P<0.1	Specified Effect	BMD (mg/m^3)	$BMDL_{10}$ (mg/m^3)
Multistage	97.7567	0.697	OK	0.1	0.199	0.144
LogLogistic	98.6963	0.4332	OK	0.1	0.246	0.047
LogProbit	**99.0545**	**0.3683**	**OK**	**0.1**	**0.241**	**0.045***
Gamma	102.679	0.0205	REJECT	0.1	0.323	0.254
Weibull	102.679	0.0205	REJECT	0.1	0.323	0.254
Quantal-Linear	102.679	0.0205	REJECT	0.1	0.323	0.254
Probit	125.827	0	REJECT	0.1	0.997	0.797
Logistic	124.355	0	REJECT	0.1	0.923	0.707

*The LogProbit model was chosen as the point of departure (POD) because it had the lowest of the BMDLs that were not rejected.

Table 2 shows BMDS model output using a 10% BMR. The LogProbit model provided the best point of departure for deriving an ITSL (see steps below). In order to calculate a potential screening level, the $BMDL_{10}$ must be adjusted for continuous exposure into the $BMDL_{ADJ}$.

$BMDL_{ADJ.}$ = $BMDL_{10}$ x hours per day x days per week

$BMDL_{ADJ.}$ = 0.045 mg/m³ x 6/24 x 5/7 x 1000 µg/mg (conversion factor)

$BMDL_{ADJ.}$ = 8.0 µg/m³

Because of differences between animal and human inhalation rates and respiratory tract surface area, the experimental animal dose is typically converted to a human equivalent dose. Gases and particulates are treated differently according to EPA (1994). When a dose conversion is used it results in what is termed the human equivalent concentration (HEC).

$Human\text{-}Dose_{HEC}$ = $Animal\text{-}Dose_{ADJ}$ x DAF

Where the DAF is the dosimetric adjustment factor (DAF).

EPA (1994) suggests a default DAF for category 1 gases (i.e., water soluble and/or highly reactive) be calculated as a regional gas dose ratio (RGDR). However, in order to calculate the $BMDL_{HEC}$ via the RGDR, it must first be determined whether MA was in the gaseous phase or particle phase during the study. Short et al., (1988), described the generation of MA as follows:

> Atmospheres containing the test material were generated by heating maleic anhydride, which has a melting point of 53°C, and by transporting vapors from the melt to the chambers with a stream of nitrogen gas.

By the time the MA reached the exposure chamber to be mixed with humidified air, it is expected that the MA would be mostly in the particle aerosol phase (the melting point is 53°C) as a liquid aerosol since the typical ambient temperature is around 27°C. However, a considerable amount of vapor may have been present in the exposure chambers. In a previous memo to the file for MA (DEQ, 2002), it was suggested that the animal exposure to MA was in the vapor phase rather than the particulate phase. A researcher familiar with the exposure conditions during the study, Gary Butterfield (2002), supported the notion that MA was in the vapor phase state. Conversely, ACGIH (2011) notes that MA physical state can vary in the ambient air:

> Because the estimated saturated vapor concentration may significantly contribute to the exposure at the TLV-TWA and evaporative losses of collected particulate may occur during sampling, both the particulate mass and vapor phase concentrations should be considered and summed to determine total airborne concentration.

Short, et al. (1988) stated that:

> Concentrations in the chambers were monitored three times a day by drawing samples through Tenax (Supelco, Bellfonte, PA) columns and by quantifying the retained material, after thermal desorption into a nitrogen steam, using a gas chromatograph…

Not knowing the physical phase of MA during the rat inhalation study adds uncertainty to the calculation of a human equivalent concentration. Cal-OEHHA did not convert the animal dose to the HEC, and assumed the animal dose equals the human dose, stating simply that:

Due to the lack of aerosol particle size data for the critical study, a human equivalent concentration could not be developed using recommended methods of inhalation dosimetry.

Support for dose equivalency also comes from a recent policy statement by EPA (2012c): *Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment*. EPA states, that for water soluble and reactive compounds which have their primary effect in the nasal region the default dosimetric adjustment factor should be 1. Given the latest EPA guidance (EPA, 2012c) and Cal-OEHHA precedence for assuming animal dose equals the human dose, it was deemed appropriate to use a DAF of 1. Using the $BMDL_{HEC}$ as the POD, a potential ITSL was determined:

$ITSL = (BMDL_{HEC})/(UF_1 \times UF_2)$

Where UF_1 = uncertainty factor of 3 for interspecies (animals to human) extrapolation
UF_2 = 10 for intraspecies (sensitive individual) extrapolation:

$ITSL = (8\ \mu g/m^3)/(3 \times 10)$

$ITSL = 0.26\ \mu g/m^3$

$ITSL = 0.3\ \mu g/m^3$ (rounding to 1 significant figure)

Since a subchronic to chronic uncertainty factor is not used, and to protect for the potential sensitization effects of MA a 24-hour averaging time would be applied to the ITSL.

Another possible method to derive the ITSL is using Rule 232(1)(c), i.e., the ITSL = OEL/100. Using the TLV as the Occupational Exposure Limit (OEL) the ITSL then becomes:

$ITSL = 0.01\ mg/m^3/100$

$ITSL = 0.1\ \mu g/m^3$ (with 8-hr averaging time).

Given that the TLV was derived using human data and accounts for sensitization, and the animal (i.e., rat) study only identified irritation effects, it was deemed more appropriate to use the TLV derived ITSL.

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