MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Methyl acrylate [CAS# 96-33-3]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 19, 2017

SUBJECT: Methyl acrylate [CAS# 96-33-3] ITSL change in the averaging time from 24 hours to annual

The current initial threshold screening level (ITSL) for methyl acrylate is 70 µg/m^3 based on an annual averaging time. The ITSL established on 4/15/2010 is based on a Reininghaus et al. (1991) inhalation study on rats, where the animals were exposed to methyl acrylate at doses of 0, 14.3, 42.4, or 128.4 ppm for 6 hours/day, 5 days/week, for 24 months. All animals exposed to methyl acrylate developed nasal mucosal changes and ocular changes. Therefore, the lowest exposure level is considered the LOAEL. When the screening level was derived in 2010 the averaging time was set at 24 hours. As the basis for the screening level used a 24-month inhalation study, the averaging time may appropriately be set at annual. Therefore, the averaging time is being changed from 24 hours to annual at this time.

References:

APCR. 2016. Air Pollution Control Rules, Promulgated pursuant to Part 55, Air Pollution Control, of the Natural Resources and Environmental Protection Act, Michigan Department of Environmental Quality. 1994. Act 451, as amended (NREPA).

Reininghaus W, Koestner A, Klimisch HJ. 1991. Chronic toxicity and oncogenicity of inhaled methyl acrylate and *n*-butyl acrylate in Sprague-Dawley rats. Food Chem Toxicol 29:329-339.

MICHIGAN DEPARTMENT OF NATURAL RESOURCES AND ENVIRONMENT

INTEROFFICE COMMUNICATION

TO: Methyl Acrylate File (CAS # 96-33-3)

FROM: Gary Butterfield

SUBJECT: Screening Level for Methyl acrylate

DATE: April 15, 2010

Methyl acrylate is also known as methyl propenoate, or acrylic acid methyl ester. It is a liquid. The melting point is -76C, and the boiling point is 80C. The vapor pressure is 69 mmHg at 20C. The molecular formula is $C_4H_6O_2$ with a molecular weight of 86.1 g/mol. It is used in the manufacture of acrylic and modacrylic fibers, resins and coatings.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Environmental Quality (DEQ) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1968 - Jan 2010), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line literature searches were conducted on 01-26-10.

In the past, the AQD had an interim ITSL based on the old (1989) ACGIH TLV of 10 ppm. There was a newer TLV of 2 ppm (or 7 mg/m^3) set in 1997; however, the interim ITSL wasn't adjusted to the newer TLV basis. At this time a full review was conducted of available literature to set an up-to-date ITSL based on best available data.

The literature search located a chronic inhalation study with Sprague-Dawley rats, Reininghaus et al (1991), where animals were exposed for 6 hours a day, 5 days a week for 24 months to average doses of 0, 14.3, 42.4, and 128.4 ppm. The lifetime study adjusted doses (considering the 6/24 and 5/7) are 0, 8.9, 26.6, and 80.7 mg/m^3. No oncogenic effects were found in this study. All of the exposed groups of rats had nasal mucosal changes, as well as, ocular changes that were attributed to the irritant effects of methyl acrylate. There was a dose related increase in severity and incidence of these effects with an increasing dosage. The lowest dose level (8.9 mg/m^3) can be considered to be the LOAEL.

The current EPA preferable method for calculation of RfC utilizes the benchmark dose software (BMDS). Use of the BMDS with the Reininghaus et al (1991) data was also attempted. The authors reported the percentage of combined male and female rats with either the nose or eye lesions. The combination of male with female data is unusual; however, that is how these authors reported the lesion incidences. The number of combined male and female rats in each dose group at the end of 24 months of exposure was reported to be 95, 98, 100, and 98 for the control to high dose groups, respectively. The percentage of those rats with eye lesions were 1, 10, 30 and 59% for the control to high dose groups, respectively. The percentage with nose lesions were 1, 6, 96, and 99%. Details on each lesion incidence for each sex were not given in this article. Thus, the combined incidences were all that could be modeled by BMDS.

BMDS Summary Table

Model	p-Value	Scaled Resid.	AIC	BMD	BMDL
Eye Lesions					
Gamma	0.7322	-0.226	333.80	9.18358	7.72195
Weibull	0.7322	-0.226	333.80	9.18358	7.72195
Quantal Linear	0.7322	-0.226	333.80	9.18358	7.72195
Nose Lesions					
Logistic Hi Dose	0.3187	-0.343	93.4613	10.362	8.74851

The data did not adequately fit many of the possible BMDS models.

The screening level can be calculated following the EPA (1994) methodology and the BMDS output as follows. The ventilation rate for a generic chronic Sprague-Dawley rat weighing 430 g is 0.28 L/min from the ventilation equation in EPA (1994) RfC methodology. Methyl acrylate is considered to be a category 1 gas as it is reactive and causes extrathoracic effects with nose and eye irritation due to its high reactivity.

$$RGDR = \frac{(Ve/SA)a}{(Ve/SA)h} = \frac{(0.28/15)}{(13.8/200)} = 0.27$$

The selected point of departure is 8 mg/m^3 based on the BMDL for the eye lesions from the three models that adequately fit the data as they had the greatest Chi squared P-value, and lowest scaled residual value. The uncertainty factors that were applied include: a factor of 10 for sensitive individuals, and a factor of 3 for the adjustment of animal-to-human because use of the RGDR accounts for part of the

interspecies factor. The total uncertainty factor of 30 was used, see the ITSL calculation below.

$NOAEL_{(HEC)}$ = POD x RGDR = 8 mg/m^3 x 0.27 = 2.1 mg/m^3

$$ITSL = \frac{2.1\ mg/m^3}{(10 \times 3)} = 70\ ug/m^3 \quad 24\text{-hour average}$$

In support of this ITSL, it should be noted that this calculated screening level is comparable in size to a possible screening level based on the ACGIH TLV, which would be 70 ug/m^3 with an 8-hour averaging time. As well as, an ITSL calculated by the old EPA RfC method using the LOAEL from Reininghaus data, which also results in a similar value of 80 ug/m^3 with 24-hour averaging.

The ITSL for methyl acrylate is being set at 70 ug/m^3 with 24-hour averaging time.

References:

ACGIH. 2001. Documentation of the Threshold Limit Values and Biological Exposure Index. Methyl acrylate.

EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F

NIOSH. 2005. NIOSH Pocket guide to chemical hazards. NIOSH publication 2005-149.

Reininghaus et al. 1991. Chronic toxicity and oncogenicity of inhaled methyl acrylate and n-butyl acrylate in Sprague-Dawley rats. Food Chem Toxicol 29: 329-39.

GB:lh

Appendix - BMDS printouts

---- A summary table ----

eye lesions -

	p-value	scaled resid	AIC	BMD	BMDL
Gamma	0.7322	-0.226	333.80	9.18358	7.72195
Gamma -Hi	NA	0.000	202.52	9.7597	6.58508
Weibull	0.7322	-0.226	333.80	9.18358	7.72195
Weibull -Hi	NA	0.00	202.52	9.77002	6.58508
Quantal Lin	0.7322	-0.226	333.80	9.18358	7.72195
Quantal L -Hi	0.6093	-0.434	200.79	8.470	6.5017

nose lesions -

	p-value	scaled resid	AIC	BMD	BMDL
Gamma	0.000	-1.38			
Gamma -Hi	NA				
Logistic -Hi	0.3187	-0.343	93.4613	10.362	8.74851

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rat - eye lesions - all doses

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Gamma Model. (Version: 2.13; Date: 05/16/2008)
Input Data File: C:\USEPA\BMDS21\Data\gam98828_rat-eyeSetting.(d) Gnuplot Plotting File: C:\USEPA\BMDS21\Data\gam98828_rat-eyeSetting.plt
Tue Feb 23 12:45:05 2010

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BMDS Model Run

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The form of the probability function is:

P[response]= background+(1-background)*CumGamma[slope*dose,power],
where CumGamma(.) is the cummulative Gamma distribution function

Dependent variable = Col3
Independent variable = Col1
Power parameter is restricted as power >=1

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
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Default Initial (and Specified) Parameter Values
Background = 0.0151042
Slope = 0.0203008
Power = 1.3

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Slope
Background	1	-0.24
Slope	-0.24	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald CI LC Limit	UC Limit
Background	0.0101674	0.0100845	-0.00959793	0.0299327
Slope	0.0114727	0.00125527	0.00901241	0.013933
Power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-164.597	4			
Fitted model	-164.904	2	0.614177	2	0.7356
Reduced model	-220.769	1	112.345	3	<.0001

AIC: 333.808

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0102	0.966	0.950	95	-0.016
8.9800	0.1071	10.493	9.800	98	-0.226
26.6000	0.2705	27.050	30.000	100	0.664
80.7000	0.6078	59.568	57.820	98	-0.362

Chi^2 = 0.62 d.f. = 2 P-value = 0.7322

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 9.18359
BMDL = 7.72195

Nose lesions – drop high dose

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Logistic Model. (Version: 2.12; Date: 05/16/2008)
Input Data File: C:\USEPA\BMDS21\Data\log96333_rat-noseSetting.(d)
Gnuplot Plotting File: C:\USEPA\BMDS21\Data\log96333_rat-noseSetting.plt
Tue Feb 23 12:51:46 2010

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BMDS Model Run

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The form of the probability function is:
P[response] = 1/[1+EXP(-intercept-slope*dose)]
Dependent variable = Col3
Independent variable = Col1
Slope parameter is not restricted
Total number of observations = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
background = 0 Specified
intercept = -4.57984
slope = 0.27971

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.86
slope	-0.86	1

Parameter Estimates

95.0% Wald CI
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Variable	Estimate	Std. Err.	LC Limit	UC Limit
intercept	-5.51613	0.605859	-6.70359	-4.32867
slope	0.324102	0.0340278	0.257408	0.390795

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-44.3574	3			
Fitted model	-44.7307	2	0.746586	1	0.3876
Reduced model	-189.875	1	291.034	2	<.0001

AIC: 93.4613

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0040	0.381	0.950	95	0.925
8.9800	0.0688	6.740	5.880	98	-0.343
26.6000	0.9571	95.710	96.000	100	0.143

Chi^2 = 0.99 d.f. = 1 P-value = 0.3187

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 10.362
BMDL = 8.74851