MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for o-Chloroaniline [CAS# 95-51-2]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 13, 2017

SUBJECT: o-Chloroaniline [CAS# 95-51-2] ITSL change in the averaging time from 24 hours to annual

The current initial threshold screening level (ITSL) for o-chloroaniline is 10 µg/m^3 based on an annual averaging time. The ITSL was established on November 5, 2009 based on a 90-day oral gavage study by NTP (1998) on mice and rats. The averaging time was set at 24 hours in 2009. As the study is a 90-day study, it is appropriate to set the averaging time to 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).

NTP. 1998. NTP technical report number 43 on comparative toxicity studies of o-, m-, and p-chloroaniline (CAS Nos. 95-51-2, 108-42-9, and 106-47-8) administered by gavage to F344 rats and B6C3F1 mice. NIH publication 98-3943.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: o-Chloroaniline file (CAS # 95-51-2)

FROM: Gary Butterfield

SUBJECT: Screening level for o-Chloroaniline

DATE: November 5, 2009

o-Chloroaniline is also known as 2-chloroaniline, or 2-chlorobenzenamine. It has a molecular formula of C_6H_6ClN with a molecular weight of 127.6 g/mol. The melting point is -14C, boiling point is 208C, and the vapor pressure is 0.2 mmHg at 25C.

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 - October 2009), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line literature searches for this evaluation were conducted on October 26, 2009. There were a few unpublished inhalation toxicity studies located during the literature search. There is also a 90-day oral gavage study conducted by NTP that is available. However, it usually is preferable to use inhalation studies to develop the inhalation screening levels.

Of the three chloroaniline isomers (o-, m-, and p-), the p-chloroaniline has many more studies conducted and is much better understood for possible toxic effects. However, all three isomers as well as aniline are known for causing methemoglobinemia.

In DuPont Haskell (1981), groups of 10 male rats were exposed for 4 hours (acutely) by inhalation to concentrations of 301, 452, 536, 748, 810, and 832 ppm (converts to 1571, 2359, 2798, 3904, 4228, or 4364 mg/m^3). Exposure resulted in deaths of 0/10, 0/10, 2/10, 4/10, and 9/10 being observed, respectively. An LC50 of 797 ppm or 4160 mg/m^3 was determined.

In a second acute inhalation study by DuPont Haskell (1970), groups of 6 male rats were exposed to 665, 829, 1127, 1247, 1260 ppm (or 3470, 4330, 5880, 6510, 6580, or 18110 mg/m^3). The LC50 was reported to be 1150 ppm or 6000 mg/m^3 as determined by the method of Miller and Tainter (1944).

In a two-week study by DuPont Haskell (1970), a group of 6 male rat controls and one dosed group were exposed to 237 ppm or 1230 mg/m^3, 4 hours a day for 5 days a week. Three rats of each group were sacrificed at the end of the two week exposure, while the other three were held for a 14-day recovery period. Spleens were observed to be enlarged in both exposed and control rats. Therefore, the conclusion by the authors was there was no effect from exposure.

In a 90-day gavage study (NTP 1998, Hejtmancik et al 2002), F344 rats and B6C3F1 mice 10 per species per sex were administered o-chloroaniline dissolved in water at doses of 0, 10, 20, 40, 80 or 160 mg/kg for 13 weeks on 5 days per week. The doses, when considering the dosing on 5/7 days each week, convert to a study average dose of 0, 7.1, 14.2, 28.6, 57.1, and 114.3 mg/kg. For the observed critical effect both species and both sexes had statistically increased methemoglobin with a clear dose related response in all exposed animals. The 10 mg/kg dose level is considered to be a LOAEL for this effect. Other effects also occurred at the higher dose levels – increased organ weight of spleen and heart, altered erythrocyte counts, reticulocyte count, hematocrit, reduced hemoglobin concentration.

There does not appear to be a significant difference between oral exposure and inhalation exposure systemic effects. The limited available toxicity data indicate that both exposure scenarios lead to increased methemoglobin formation and spleen changes. Therefore, it has been decided that the 90-day oral gavage study is much better quality and of sufficient duration for RfD/RfC type calculation of the screening level, over use of the 1981 inhalation LC50 or the limited 1970 two week inhalation studies. The RfD type calculation was conducted using the EPA Bench Mark Dose Software (BMDS) to determine the BMDL, with the point of departure for calculation of the reference dose (RfD) based on the methemoglobin data. The three BMDS models for continuous data were run for mice and rats of both sexes. The group mean and standard errors of methemoglobin were given by authors, but the SE must be changed to standard deviation for the BMDS software by using SD = SE x $(n)^{1/2}$. The model runs that were found to be poor fits were omitted from the attached Table 1 of results. Among the Table 1. listed results, the female rat modeled results had the lowest AIC values indicating the best fit. The lowest BMDL of 2.849 mg/kg from the three female rat values was selected as the best point of departure for RfD calculation. It should be noted that all three of the female rat BMDLs were similar with values from 2.8 to 3.9 mg/kg. It should also be noted that the female rat polynomial model having dropped the two highest dose groups also had one of the higher P values for the Test of Interest ,Test 4 (see the attached BMDS output in Appendix A).

BMDL = 2.849 mg/kg

Uncertainty factors applied to the BMDL include the standard 10 fold factors for each of the three factors: sensitive individuals, animal-to-human, and subchronic-to-chronic, to obtain a total uncertainty factor of 1000.

Pseudo RfD = 2.849 mg/kg / 1000 = 2.849 ug/kg

It should also be noted that other DEQ Divisions, have set criteria values for o-chloroaniline, including Water Bureau, and RRD. Those Divisions used the lowest dose, 10 mg/kg from NTP 1998, as the LOAEL in their calculations. An UF of 3000 was applied to obtain the RfD of 3 ug/kg. The RfD type values set by those divisions are at 3 ug/kg, similar to the pseudo RfD established here.

R232(1)(b) allows the calculation of the screening level from the RfD or 'pseudo RfD' as follows.

(Pseudo RfD) x 70 kg/20 m^3 = ITSL

ITSL = (2.849 ug/kg) x (70kg/20m^3) = 9.97 rounded to 10 ug/m^3 with 24-hour averaging.

References

DuPont Haskell Laboratory. 1970. Acute inhalation toxicity, and Subacute inhalation toxicity. Laboratory Report No. 218-70. EPA OTS 0571672.

DuPont Haskell Laboratory. 1981. Inhalation median lethal concentration of benzenamine, 2-chloro in rats. Laboratory Report No. 326-81. EPA OTS 0571625.

Hejtmancik et al. 2002. Comparative gavage subchronic toxicity studies of o-chloroaniline and m-chloroaniline in F344 and B6C3F1 mice. Toxicol Sci 69:234-243. A published journal article of NTP 1998 study.

NTP. 1998. NTP technical report number 43 on comparative toxicity studies of o-, m-, and p-chloroaniline (CAS Nos. 95-51-2, 108-42-9, and 106-47-8) administered by gavage to F344 rats and B6C3F1 mice. NIH publication 98-3943.

Appendix A

BMDS output for Female Rat Polynomial model with dropping two highest doses

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  Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
  Input Data File: C:\USEPA\BMDS21\Data\ply95512_FratSetting.(d)
  Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\ply95512_FratSetting.plt
                                Tue Nov 03 10:45:16 2009
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 BMDS Model Run
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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

   Dependent variable = Col3
   Independent variable = Col1
   Signs of the polynomial coefficients are not restricted
  The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 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

              Default Initial Parameter Values
                   lalpha =     -3.92728
                     rho =            0
                   beta_0 =     0.363109
                   beta_1 =    0.0230772
                   beta_2 =  0.000622434

         Asymptotic Correlation Matrix of Parameter Estimates
              lalpha         rho      beta_0      beta_1      beta_2
  lalpha           1        0.49         0.1       -0.18        0.18
    rho         0.49           1       0.038       -0.13        0.15
  beta_0         0.1       0.038           1       -0.66         0.5
  beta_1       -0.18       -0.13       -0.66           1       -0.95
  beta_2        0.18        0.15         0.5       -0.95           1

                        Parameter Estimates

                                          95.0% Wald Confid Int
     Variable        Estimate       Std. Err.     Lower CL    Upper CL
      lalpha       -3.88057        0.261236     -4.39258   -3.36855
        rho        0.798046        0.356186     0.0999344    1.49616
      beta_0        0.371797       0.0299089      0.313176     0.430417
      beta_1       0.0203714       0.0063753    0.00787604   0.0328668
      beta_2     0.000713816     0.000226504    0.000269877 0.00115776
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scal Res.
0	10	0.37	0.372	0.13	0.0968	-0.0587
7.1	10	0.54	0.552	0.09	0.113	-0.346
14.2	9	0.83	0.805	0.06	0.132	0.569
28.6	10	1.53	1.54	0.22	0.171	-0.154

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	59.192158	5	-108.384316
A2	67.554070	8	-119.108139
A3	61.751866	6	-111.503731
fitted	61.547478	5	-113.094956
R	10.116636	2	-16.233272

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	114.875	6	<.0001
Test 2	16.7238	3	0.0008054
Test 3	11.6044	2	0.003021
Test 4	0.408775	1	0.5226

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels. It seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data.

Benchmark Dose Computation
Specified effect = 1
Risk Type = Estimated standard deviations from the control mean
Confidence level = 0.95
BMD = 4.14878
BMDL = 2.84975

Table 1. BMDS output results for the NTP 1998 methemoglobin data

	Dose levels included	Model	Scaled Resid	Test 4 P	AIC fitted	BMD	BMDL
Mice female	All doses	Hill	1.68	0.1089	-165.8	10.34	6.030
	All doses	Power	1.26	0.1077	-166.1	7.431	5.221
	Drop high	Power	1.56	0.1498	-164.4	9.560	5.974
	Drop high	Polynomial	1.56	0.1498	-164.4	9.560	5.974
Mice male	Drop high	Hill	0.958	0.1874	-170.0	7.803	4.641
	Drop 2 highest	Hill	0.723	0.2411	-140.5	6.731	---
	All doses	Polynomial	0.997	0.2217	-151.8	8.403	5.188
	Drop high	Polynomial	0.84	0.4963	-172.3	7.377	4.663
	Drop 2 highest	Polynomial	0.775	0.2442	-140.5	7.083	3.588
	Drop 2 highest	Power	0.724	0.5032	-142.5	6.736	4.547
	Drop 3 highest	Power	0.786	0.2667	-108.0	6.718	3.850
Rat female	Drop high	Hill	0.39	0.6439	-135.4	5.623	3.984
	Drop 2 high	Polynomial	-0.346	0.5226	-113.0	4.148	2.849
	Drop 2 high	Power	-0.0871	0.7792	-113.4	4.744	3.298
Rat male	All doses	Hill	-0.0495	0.1532	-178.9	4.257	2.729
	Drop high	Polynomial	-0.893	0.1863	-164.9	3.482	2.457
	All doses	Power	-1	0.1467	-179.3	3.349	2.408
	Drop high	Power	-0.632	0.184	-164.9	3.973	2.623