MICHIGAN DEPARTMENT OF NATURAL RESOURCES AND ENVIRONMENT

INTEROFFICE COMMUNICATION

TO: Cumene File (CAS # 98-82-8)

FROM: Gary Butterfield
              Doreen Lehner

SUBJECT: Screening level re-evaluation for Cumene

DATE: March 1, 2010

The Department was requested to re-evaluate the cancer screening levels that were developed in Autumn 2009 for cumene. The NTP released a report in early 2009 that showed chronic inhalation of cumene caused increased incidences of neoplastic lesions in rats and mice.

Only two of the tumor types identified by NTP had clear dose-related increases. Those included the female mice lung alveolar/bronchiolar adenoma and carcinoma, and the male rats nose respiratory epithelium adenomas. The adjusted incidence of female mice lung alveolar/bronchiolar adenoma was 1/43, 26/46, 36/48, and 38/49 for the lifetime adjusted mice exposure concentrations of 0, 110, 219, and 437 mg/m^3. The combined incidence of female mice lung alveolar/bronchiolar adenoma and carcinoma was 4/45, 31/46, 42/49 and 46/50. The male rats nose respiratory epithelium adenomas incidences was 0/50, 7/40, 18/42, and 10/43 at the lifetime adjusted rat exposure concentrations of 0, 219, 437, and 877 mg/m^3.

The female mice tumors occurred in the lung alveolar/bronchiolar area; i.e., the pulmonary region. The RGDR(pu) for a category 3 gas as the adjustment for animal exposure to human exposure was evaluated. The blood:air partition coefficients are not known for either the mice or humans. Therefore, the RGDR(pu) is default value of 1. Thus, the animal adjusted concentrations are the same as the human equivalent concentrations.

The BMDS multistage cancer model was run for each of the three possible tumor types. The following table lists the key data.

Table 1. Summary of BMDS runs - dropped high dose in all cases to improve the modeled goodness-of-fit, per EPA BMDS guidance.

	P value	Scaled Resid	AIC	SF (mg/m^3)$^{-1}$
male rat nasal Adenomas	1.0000	0.0000	98.4624	0.00140904
Female mice Adenom-Carcn	0.7244	0.260	129.398	0.0105437
Female mice Adenomas	0.6467	0.348	142.543	0.00712794

All three of these data sets adequately fit the multistage model. Althought the male rat data fit the model most precisely, the female mice combined adenoma and carcinomas yields a greater slope factor (most potent), which will be used for calculation of the screening level (per R231(3)(b)) with the SF of 0.0105 $(mg/m^3)^{-1}$ or 1.05e-5 $(ug/m^3)^{-1}$.

The resultant IRSL is calculated from the equation IRSL = 1e-6/1.05e-5 $(ug/m^3)^{-1}$. Thus the the IRSL is 0.1 ug/m^3 with annual averaging, and the SRSL is 1 ug/m^3 with annual averaging.

It should be noted that the above screening level values are different from the 2009 values due to the current approach selecting the female mice tumors over the more precise model fitting male rat nose tumors, correction of decimal place errors, and using the category 3 gas RGDR adjustment rather than category 1 gas adjustment.

<u>References</u>

NTP. 2009. Toxicology and carcinogenesis studies of cumene in F344 rat and B6C3F1 mice. NTP TR-542

GB:lh

Appendix - BMDS output

female mice lung alveolar/bronchiolar adenoma or carcinoma - drop high dose
the time to tumor incidence is 4/45, 31/46, 42/49, 46/50 - control to high
===
 Multistage Cancer Model. (Version: 1.7; Date: 05/16/2008)
 Input Data File: C:\USEPA\BMDS21\Data\msc98828fmile2adjustSetting.(d)
 Gnuplot Plotting File c:\USEPA\BMDS21\Data\msc98828fmile2adjustSetting.plt
                        Tue Feb 16 15:15:44 2010
===
BMDS Model Run
~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive

   Dependent variable = Col3
   Independent variable = Col1

Total number of observations = 3
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2   (***is the default degree***)

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 =   0.117706
                  Beta(1) = 0.00846171
                  Beta(2) =   0

       Asymptotic Correlation Matrix of Parameter Estimates

       (*** The model parameter(s) -Beta(2)
             have been estimated at a boundary point, or have been specified by the user,
             and do not appear in the correlation matrix)

           Background   Beta(1)
Background   1   -0.57
   Beta(1)   -0.57   1

                   Parameter Estimates

                                        95.0% Wald CI
      Variable   Estimate   Std. Err.   LC Limit   UC Limit
      Background   0.0901649   *   *   *

3

```
Beta(1)        0.00883343         *       *       *
Beta(2)        0                  *       *       *
```

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-62.637	3			
Fitted model	-62.6989	2	0.123648	1	0.7251
Reduced model	-96.3394	1	67.4048	2	<.0001

AIC: 129.398

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0902	4.057	4.000	45	-0.030
110.0000	0.6557	30.161	31.000	46	0.260
219.0000	0.8685	42.558	42.000	49	-0.236

$Chi^2 = 0.12$ d.f. = 1   P-value = 0.7244

Benchmark Dose Computation

```
Specified effect =       0.1
Risk Type        =    Extra risk
Confidence level =       0.95
       BMD =    11.9275
      BMDL =     9.4843
      BMDU =    24.6434
```

Taken together, (9.4843 , 24.6434) is a 90   % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor =   0.0105437