MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Carbazole file (CAS # 86-74-8)

FROM: Gary Butterfield

SUBJECT: Screening level for Carbazole

DATE: September 3, 2009

Carbazole is also known as diphenyleneimine, and dibenzopyrrole. Carbazole has molecular formula of $C_{12}H_9N$ with a molecular weight of 167.2 g/mol. It is a solid of white crystals or plates. The melting point is 247C, and the boiling point is 335C.

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

The AQD worked on developing an IRSL for carbazole in 2006. At that time the chronic oral B6C3F1 mouse study by Tsuda et al (1982) was used to set screening levels. This is the same study that was used by EPA (1986) to develop an oral potency factor. There is no other chronic data available for this chemical. The EPA oral potency is based on the male liver hepatocellular carcinoma incidence of 9/46, 12/42, 20/42, 37/48 for the 0, .15, .3 and .6% diet (or daily doses for males of 0, 192, 398, 863 mg/kg) over the 104 week study.

In the 2006 review, combining tumors (liver carcinomas and liver neoplastic nodules) was attempted. However, the marginally written study does not give enough details to combine tumors without the possibility of double counting animals. This is evident in the middle dose females who had 43 animals in the group, with a combined incidence of 45 animals having either liver carcinomas (24) and liver neoplastic nodules (21), see table 2 in Tsuda et al (1982). The 2006 review assumed there was a typo, and attempted to say 43/43 had the combined lesions. At this time, it is considered in appropriate to combine these lesions. Another problem becomes evident if combining is tried – the cancer model goodness of fit will only work if the higher two dose levels are dropped. The necessity of dropping multiple groups to get the model to run correctly makes the combining tumors attempt questionable.

Therefore, it is currently being determined that the male mice hepatocellular incidence (as was used by EPA 1986, at doses of 0, 192, 398, 863 mg/kg and incidence of 9/46, 12/42, 20/42, 37/48) is the best and most appropriate data set to model the cancer slope factor. The BMDS multistage cancer model is EPA's current model for this type evaluation – as opposed to the old Global82 model that was used in 1986 – was used to model the cancer slope factor. Calculation of the inhalation SF of 2.8e-6 $(ug/m^3)^{-1}$ and the corresponding IRSL of 0.4 ug/m^3 annual average is detailed in appendix B.

References:

EPA. 1986. Health and Environmental Effects Profile for Carbazole. EPA/600/X-86/334

EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. EPA-600/6-87-008

Tsuda et al. 1982. Carcinogenic effect of carbazole in the liver of F1 mice. JNCI 69: 1383-1387.

GB:lh

- - - Appendix A: Global 82 method as used by EPA 1986 - - -

Tsuda et el (1982)
Liver Incidences (in animals who lasted in study at least 51 weeks):
- female -
neoplastic nodules 2/45, 13/49, 21/43, 16/46
hepatocellular carcinomas 2/45, 35/49, 24/43, 30/46
- male -
neoplastic nodules 13/46, 30/42, 22/42, 10/48
hepatocellular carcinomas 9/46, 12/42, 20/42, 37/48 **** selected data set for model

cumulative doses female 0, 153, 366, 747 g/kg
male 0, 139, 290, 628
daily dose (CD/728) = female 0, 210, 503, 1026 mg/kg/d
male 0, 192, 398, 863 **** selected data set for model

Global82
Q_1* from the 95% UCL/MLE of the 10^{-6} dose

EPA HEEP slope factor = 0.001566 $(mg/kg)^{-1}$

Human SF = 0.001566 $(mg/kg)^{-1}$ x $(70kg/0.03kg)^{1/3}$ = 0.001487 $(mg/kg)^{-1}$ x 13.2635
= 0.0208 $(mg/kg)^{-1}$
EPA 1986 calculation used the old scaling ratio to the 2/3 power ie. $(70kg/0.03kg)^{1/3}$
EPA 1986 used the old assumed body weight for mice of 30 grams

Convert oral to inhalation SF – use 70 kg person breathing 20 m^3 a day, and 1 mg=1000ug

- - - Appendix B: BMDS method - - -

Tsuda et el (1982)
Liver Incidences (in animals who lasted in study at least 51 weeks):
- female -
neoplastic nodules 2/45, 13/49, 21/43, 16/46
hepatocellular carcinomas 2/45, 35/49, 24/43, 30/46
- male -
neoplastic nodules 13/46, 30/42, 22/42, 10/48
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male 0, 192, 398, 863 **** selected data set for model

Using BMDS v2.1
Degree of polynomial = 2
The default 90% two-sided confidence interval for the BMD was used

BMDS slope factor = 0.001487 $(mg/kg)^{-1}$ = mouse SF

Human SF = 0.001487 $(mg/kg)^{-1}$ x $(70kg/0.037kg)^{1/4}$ = 0.001487 $(mg/kg)^{-1}$ x 6.5951
= 0.009807 $(mg/kg)^{-1}$
This review calculation used the new scaling ratio to the 3/4 power ie. $(70kg/0.037kg)^{1/4}$
This review used EPA 1988 assumed body weight for mice of 37 grams

Convert oral to inhalation SF – use 70 kg person breathing 20 m^3 a day, and 1 mg=1000ug
Inhalation SF = 0.009807 $(mg/kg)^{-1}$ x 1 /3500 = 2.8e-6 $(ug/m^3)^{-1}$

IRSL = [1e-6]/[2.8e-6 $(ug/m^3)^{-1}$] = 0.36 ug/m^3 rounded to 0.4 ug/m^3
SRSL = [1e-5]/[2.8e-6 $(ug/m^3)^{-1}$] = 3.6 ug/m^3 rounded to 4 ug/m^3

The Global82 method used the 95% lower confidence limit of dose to obtain the SF. The BMDS method uses a default 90% confidence interval for BMD.
As an alternative method the 95% interval was entered into the BMDS – the out put SF was 0.00159249 $(mg/kg)^{-1}$ This value is closer to the Global82 SF of 0.001566 $(mg/kg)^{-1}$ It was decided to use the default BMDS 90% value for this screening level calculation.