MICHIGAN DEPARTMENT OF NATURAL RESOURCES AND ENVIRONMENT

INTEROFFICE COMMUNICATION

TO: Dilantin File (CAS # 57-41-0)

FROM: Gary Butterfield

SUBJECT: Screening Level for Dilantin

DATE: October 19, 2010

Dilantin is also known as phenytoin and diphenylhydantoin. It is a solid with white crystals. The melting point is 286C, and the boiling point is estimated to be 511C. The vapor pressure is 1e-10 mmHg at 25C. The molecular formula is $C_{15}H_{12}N_2O_2$ with a molecular weight of 252.2 g/mol. It is used as a drug for the treatment of seizures.

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 Jan. 26, 2010. Little new toxicity data was found compared to the prior literature search for this chemical from 1994.

In the past (1994), the Air Quality Division (AQD) set an IRSL and SRSL for dilantin, which is based on the NTP (1993) oral dose study. A request was received from the Remediation Division (RD) to re-evaluate these cancer values and also set an ITSL so that cleanup values for Part 201 could be established. As there are no inhalation toxicity studies available for this material, it was decided by the AQD to let the RD establish oral values and then the AQD would use those oral values as the basis for setting the inhalation screening levels. As of October 2010, the RD has proposed values and public-noticed them for comment. It may be several months away from finalizing them. At this time, few significant comments have been received on the proposed values, making it unlikely that the proposed values will change. Therefore, it appears that the most expeditious way to set the new AQD values is to utilize the proposed oral values for the ITSL, and IRSL/SRSL screening levels.

For the oral non-cancer value, utilizing the therapeutic range of doses was determined to be the most appropriate basis for setting the value. The low end of the therapeutic range is 3 mg/kg. Adverse effects have been noted to occur at this dose level. This dose is considered to be a LOAEL, which will be used as the point of departure for calculating a screening level. Uncertainty factors of 10 for two factors-human sensitivity and LOAEL-to-NOAEL will be applied to obtain an oral RfD dose of 30 ug/kg. This oral dose can be converted to an inhalation RfC using a weight of 70 kg person and breathing 20 m^3, resulting in a potential ITSL of 100 ug/m^3 24-hour average. However, this material is a solid, and because the above health-based ITSL is greater than the $PM_{2.5}$ NAAQS, the AQD has decided that rather than establish a finalized ITSL the current $PM_{2.5}$ NAAQS standard should be used as the screening level for New Source Review permitting.

For the oral cancer value, the NTP bioassay was found to be the best study upon which the values could be based. The liver tumor incidence was increased in female B6C3F1 mice: 5/38, 14/40, and 30/45 at doses of 0, 50 and 160 mg/kg. The EPA BMDS cancer model was used to derive the slope factor. The oral cancer SF of 0.051 $(mg/kg)^{-1}$ based on NTP (1993) female mice liver tumors can be converted to an inhalation SF of 1.46 x 10-5 $(ug/m^3)^{-1}$ using the 70 kg body weight and breathing 20 m^3 a day. This SF results in an IRSL of 0.07 ug/m^3 and a SRSL of 0.7 ug/m^3.

References:

NTP. 1993. Toxicological and carcinogenesis studies of 5,5-diphenylhydantoin in F344 rats and B6C3F1 mice. Technical report # 404.

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APPENDIX A
Development of the Cancer Slope Factor
March 1, 2010

If the mode of action (MOA) for a carcinogenic substance is anticipated to be mutagenic, a linear (nonthreshold) approach is appropriate for risk assessment. Other MOAs may be modeled with either linear or nonlinear (threshold) approaches (U.S. EPA, 2005a).

To assess phenytoin for a mutagenic MOA, both *in vitro* and *in vivo* genetic toxicity tests have been conducted (Table 2). The following three *in vitro* tests were negative: Salmonella, mouse lymphoma, and chromosome aberrations in CHO cells. One *in vitro* test was positive: SCE in CHO. The following three *in vivo* tests were negative: bone marrow micronucleus, Drosophila, and chromosome aberrations in bone marrow. One *in vivo* test was equivocal: SCE in bone marrow.

Some evidence suggests that phenytoin may increase tumors through a promotion rather than an initiation mechanism. Specifically, an increased number of male mice exhibited hepatocarcinogenesis when phenytoin was administered orally, in addition to an intraperitoneal (ip) administration of diethylnitrosamine (DEN - a known carcinogen with a mutagenic MOA [U.S. EPA, 2005b]), compared to (1) male mice receiving ip DEN alone, and (2) male mice receiving oral phenytoin alone (Diwan *et al*., 1993). Inspection of the data reveals the possibility of a synergistic effect rather than an additive one when both phenytoin and DEN are administered; however, the paper did not include this type of data analysis. Phenytoin is structurally similar to phenobarbital (PB) (Diwan *et al*., 1993), and PB exhibits a dose-response with cytochrome P450 (P450) induction, cell proliferation, and tumor promotion (Whysner *et al*., 1996). Since phenytoin increases hepatic P450 activity (Diwan *et al*., 1993), this similarity with PB suggests that phenytoin may also be a tumor promoter; however, a mechanism of hepatocarcinogenesis by enzyme inducing agents remains unknown (Dethloff *et al*., 1996).

Since the eight genotoxicity tests resulted in six negatives, one positive, and one equivocal, a mutagenic MOA for phenytoin can neither be ruled out nor accepted. Elevation of hepatic P450 activity caused by phenytoin is promising for support of a threshold phenytoin MOA, but not definitive. Therefore, the MOA for phenytoin has not been established and the default linear (nonthreshold) extrapolation (U.S. EPA, 2005a) is used for the cancer evaluation.

As described earlier in this Toxicological Assessment, two chronic feed experiments in F344/N or Wistar rats and B6C3F1 mice identified combined liver tumors in female mice as the critical effect for cancer following phenytoin administration. The liver tumor data is summarized, as follows, in Table A1.

Table A1. Liver tumors in B6C3F1 female mice.

Dataset #1 (NTP, 1993)	Dose mg phenytoin/ kg BW-d	# of female mice	Incidence of combined liver tumors	Incidence percentage
	0	38	5	13.158
	50	40	14	35.000
	160	45	30	66.667
Dataset #2 (Dethloff *et al*., 1996)	Dose mg phenytoin/ kg BW-d	# of female mice	Incidence of combined liver tumors	Incidence percentage
	0	50	8	16.000
	10	50	5	10.000
	25	50	10	20.000
	45	50	25	50.000
Dataset #3 (Dethloff *et al*., 1996)	Dose mg phenytoin/ kg BW-d	# of female mice	Incidence of liver adenoma	Incidence percentage
	0	50	5	10.000
	10	50	4	8.000
	25	50	7	14.000
	45	50	24	48.000

Datasets #1, #2, and #3 were analyzed individually by the U.S. EPA BenchMark Dose Software (BMDS), Version 2.0.0.33, Multistage Cancer Version 1.7 (May 16, 2008). Also, Datasets #1 and #2 were combined, as appropriate (U.S. EPA, 2005a), for additional analysis. Combining Datasets #1 and #2, and combining them with elimination of the highest dose, as detailed in Table A2, are possible since one experiment from each study included identical characteristics: species (mouse), strain (B6C3F1), sex (female), feed (Purina Certified Rodent Chow 5002), dose initiation (age 7 to 8 weeks), dose duration (104 to 107 weeks), and endpoint (combined liver tumors). Elimination of the highest dose in the combined data set is justified because when using BMDS the highest dose group(s) may be dropped as long as there are enough data left to adequately define the low dose region (U.S. EPA, 2009).

Results are, as follows, in Table A2:

Table A2. Cancer Slope Factors from Benchmark Dose Modeling.

Dataset(s)	Endpoint selection rationale	Dose-response model chosen	Rationale for model choice	Mouse Cancer Slope Factor (mg/kg-day)-1	Human Cancer Slope Factor[a] (mg/kg-day)-1
#1 (NTP, 1993)	trend test p <0.001	Multistage Cancer Version 1.7 (5/16/08), effect 0.10, degree 1, extra risk	Lower AIC (142.679) p = 0.946 Scaled Residual = 0.056	0.007770	0.05084
#2 (Dethloff et al., 1996)	trend test p <0.01	Same, with degree 3	Lowest AIC (200.79) p = 0.6195 Scaled Residual = 0.706	0.006008	0.03931
#3 (Dethloff et al., 1996)	trend test p <0.01	Same, with degree 3	Lowest AIC (174.602) p = 0.7839 Scaled Residual = 0.463	0.005493	0.03594
Combined #1 AND #2		Same, with degree (1,2,3,4,5)	(FAILED THE CURVE FIT TESTS)		
Combined #1 AND #2 (minus highest dose)		Same, with degree 2	Lowest AIC (286.366) p = 0.1742 Scaled Residual = 1.485	0.007045	0.04610

[a]SF adjustment: (70 human kg/.03820 mouse kg)0.25 power = 6.543 adjustment.

Given the above results, there are four slope factors from which to choose. Dataset #1 appears to best fit the model overall; this dataset produced the lowest Akaike Information Criterion (AIC), highest Chi squared p value, and smallest (maximum) scaled residual when compared to those from the other datasets. Therefore, the slope factor calculated from Dataset #1 (0.050842) is the best choice based on the best model fit and is used as 0.051 $(mg/kg\text{-}d)^{-1}$ for the calculation of environmental cleanup criteria for phenytoin.