MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Hydroquinone (CAS # 123-31-9)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: August 29, 2016

SUBJECT: Screening Level for Hydroquinone (CAS # 123-31-9)

The initial threshold screening level (ITSL) for hydroquinone (CAS # 123-31-9) is 140 µg/m^3 based on an annual averaging time. The initial risk screening level (IRSL) is 0.058 µg/m^3 with an annual averaging time, and the secondary risk screening level (SRSL) is 0.58 µg/m^3 with an annual averaging time.

Hydroquinone (also known as benzene-1,4-diol, 1-4 dihydroxy benzene, or quinol) is an aromatic organic phenolic compound that is a white needle-like crystal or crystalline powder that is light and air sensitive and darkens to brown in the air due to oxidation. It is miscible in water and has a molecular weight of 110.11 g/mol. Hydroquinone is used: as a photographic reducer and developer; as a reagent in the determination of small quantities of phosphate; as an antioxidant for fats and oils; as a polymerization inhibitor for acrylates; as an stabilizer in paints, varnishes, dyes, motor fuels, and oils; and as a skin bleaching agent to lighten areas of darkened skin for reducing the signs of age (NTP, 2009; Pubchem 2016). Hydroquinone has been found in the leaves, bark, and fruit of the shrubs in the ericaceae family such as cranberry cowberry, bearberry, and blueberry (IARC, 1999).

Figure 1. Structure of hydroquinone.

A literature review was conducted to determine the screening levels for hydroquinone. The following references and databases were searched to derive the above screening levels: Chemical Criteria Database (CCD), United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental

Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2014 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 5/27/16), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, U.S. EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

ITSL Derivation:

The EPA (2009) established a Provisional Peer Reviewed Toxicity Value for Superfund (PPRTV) reference dose for chronic oral exposure (RfD) for hydroquinone of 4E-2 mg/kg/day (0.04 mg/kg/day). This value is based on a NOAEL of 4.3 mg/kg/day from a study by Carlson and Brewer (1953) for hematological effects from a 3 – 5 month study in humans with an uncertainty factor (UF) of 100 (UF of 10 for variation of human sensitivity and UF of 10 for extrapolation subchronic to chronic exposure). "The oral toxicity of hydroquinone was assessed in two men who ingested 500 mg/day for 5 months and 17 men and women (number/sex not reported) who ingested 300 mg/day for 3 – 5 months (Carlson and Brewer, 1953). Total daily chemical intake was consumed with meals in three divided doses. Assuming an average human body weight of 70 kg (U.S. EPA, 1987), the estimated daily doses on a per-kg basis were 7.1and 4.3 mg/kg-day. Hematology indices (red blood cell [RBC] count, hematocrit, percent hemoglobin, differential white blood cell count, sedimentation rate, platelet count, coagulation time, and iteric index) and urine indices (albumin, reducing sugars, white and red cell counts, cases, and urobilinogen) were evaluated during a control period for 1 month prior to exposure and again while the experiment was in progress, enabling each subject to serve as his/her own control. Results of the blood analyses and urinalyses revealed no abnormal findings. No additional information was reported on the design or results of this study. Because the high dose was administered to only two subjects, the low dose is used to identify a NOAEL of 4.3 mg/kg-day for hematological and renal effects in humans" (EPA, 2009).

Under Rule 232(1)(b) an ITSL can be determined with an oral reference dose using the equation below:

$$ITSL = Oral\ RfD\ \times \frac{70\ kg}{20\ m^3} = 0.04\ {}^{mg}/_{kg/day}\ \times \frac{70\ kg}{20\ m^3} = 0.14\ {}^{mg}/_{m^3} = 140\ {}^{\mu g}/_{m^3}$$

According to Rule 232(2)(b) a 24-hour averaging time period should be used, but this ITSL is based on a 3 - 5 month study in humans and EPA (2009) applied an UF = 10, for subchronicity of the study in deriving the chronic RfD. Therefore, it is appropriate to utilize a longer averaging time, which would be an annual averaging time. Therefore, the ITSL for hydroquinone is 140 µg/m^3 based on an annual averaging time.

IRSL Derivation:

Hydroquinone is listed on the EPA's HAPs list. EPA (NATA 2011) does not apply cancer benchmarks. IARC (1999) has listed hydroquinone as not classifiable as to its carcinogenicity to humans (Group 3). "Inadequate information is available on the carcinogenicity of hydroquinone in humans from two occupational studies. Standardized mortality ratios for total cancer and site-specific cancers were not elevated in a cohort of 879 workers who were exposed in a plant in which hydroquinone was manufactured and used (Pifer et al., 1995). This study is limited by a weak power to detect effects, due to the relatively small cohort size and small numbers of deaths from site-specific cancers. An increased number of malignant melanoma cases were observed in a cohort of 836 lithographers – about 200 of whom had worked regularly by hand with photographic chemicals and were exposed to hydroquinone (Nielsen et al., 1996). This study is limited by a small number of cases (the excess of malignant melanoma was based on 5 cases, only 2 of which had reported exposure to hydroquinone), as well as mixed chemical exposures to various pigments, dyes, and organic solvents used in lithography printing processes" (EPA, 2009).

"Chronic toxicology/carcinogenesis studies were performed in which groups of 65 F344/N rats of each sex were treated with 0, 25, or 50 mg/kg-day doses of hydroquinone (>99% pure) by gavage in deionized water for 5 days/week for up to 103 weeks (NTP, 1989). Groups of 64 or 65 B6C3F1 mice of each sex were similarly exposed to doses of 0, 50, or 100 mg/kg-day. Clinical signs and body weight were evaluated throughout the studies. Hematology exams (total red and white blood cell counts, differential white cell counts, hematocrit, hemoglobin concentration, and reticulocyte counts) and clinical chemistry exams (6 indices including blood urea nitrogen) were performed on 10 animals from each group after 65 weeks of exposure. Necropsies, organ weight measurements (liver, kidney, brain), and histological examinations were performed on all rats after 65 or 103 weeks of exposure. The histological exams were comprehensive in all rats (except that preputial gland and thyroid were not examined in low-dose males) and vehicle control and high-dose mice; tissues examined in low-dose mice were limited to gross lesions, liver, spleen, thyroid, and adrenal glands in males, and gross lesions, liver, lungs, ovaries, salivary glands, and thyroid in females" (EPA, 2009).

"The NTP (1989) concluded that there was some evidence of carcinogenic activity of hydroquinone in male and female rats based on increases in renal tubular adenomas in male rats and mononuclear cell leukemia in females" (EPA, 2009). The incidences of renal tubule cell adenomas in male rats and mononuclear cell leukemia are shown in Table 1. "There was a statistically significant trend for increased renal tumors with dose and incidence in the high dose-group was statistically increased in pairwise comparison to concurrent controls. The incidence in both dose groups exceeded the highest historical incidence of this tumor in either untreated (3/50 = 6%) or water gavage (1/50 = 2%) controls, and it is markedly higher than the overall historical incidence of less than 0.5% in both types of controls" (EPA, 2009). "There was a statistically significant trend for increased mononuclear cell leukemia with dose and the incidence in the high-dose

group was statistically increased in pair-wise comparison to concurrent controls. The historical incidence of mononuclear cell leukemia for water gavage vehicle control female F344/N rats was 25±15% (*n* = 299), while that for untreated controls was 19% ± 7% (*n* = 1983). The incidence of leukemia in the high-dose females was just within the historical control range" (EPA, 2009).

"The researchers graded the severity of the observed leukemia as three stages. Features of Stage 1 include limited distortion of splenic architecture, no infiltration of other organs that are not likely to cause death. Stage 2 effects include an effacement of splenic architecture, limited infiltration of the liver, and possibly other organs that may [have] contributed to mortality. Stage 3 effects include a marked effacement of splenic architecture and advanced infiltration of the liver and other organs that were the most probable cause of death in affected animals. The severity of the observed leukemia was increased in the high-dose group relative to controls. Of the leukemias observed in each group, 5/9 (56%), 8/15 (52%), and 14/22 (64%) were classified as Stage 3 in the control, low- and high-dose groups, respectively" (EPA, 2009).

Table 1. Incidences of Neoplastic Lesions in Male and Female F344/N Rats Given Gavage Doses of Hydroquinone for 103 Weeks[a].

Tumor Type	0 mg/kg-day	25 mg/kg-day	50 mg/kg-day
Males			
Renal Tubule cell adenoma	0/55[b] (0%)	4/55 (7%)	8/55[c] (14%)
Females			
Mononuclear cell leukemia	9/55[b] (16%)	15/55 (27%)	22/55[d] (40%)

[a]NTP, 1989.
[b]$p \leq 0.005$ by logistic regression trend test.
[c]$p \leq 0.005$ by logistic regression pairwise test.
[d]$p \leq 0.01$ by logistic regression pairwise test.

The EPA (2009) used Benchmark Dose Software (BMDS) [version 1.3.2] using dichotomous data models to analyze the incidences of renal tubule adenomas in male rats and mononuclear cell leukemia in female rats. "Confidence bounds were automatically calculated by the BMDS using a maximum likelihood profile method" (EPA, 2009). "Output from the BMDS programs was evaluated using the criteria described in U.S. EPA (2000). Goodness-of-fit was evaluated using the chi-square statistic calculated by the BMDS program. Acceptable goodness-of-fit is indicated by a *p*-value greater than or equal to 0.1. Models that did not meet these criteria were eliminated from consideration. Local fit is evaluated visually on a graphic output by comparing the observed and estimated results at each data point. $BMDL_{10}$ estimates that are within a factor of three are considered to show no model dependence and are ranked using the AIC reported by the BMDS program. The model with the lowest AIC is considered a superior fit" (EPA, 2009).

Table 2. Multistage Benchmark Dose Modeling Results for Rats Exposed to Hydroquinone by Gavage for 2 Years[a].

Incidence	Sex	AIC	*p*-Value[b]	$BMDL_{10}$ (mg/kg/day)	$BMDL_{10\ HED}$[c] (mg/kg/day)
Renal tubule adenomas[d]	Male	76.2961	0.9979	15.7456	4.4
Mononuclear cell leukemia[d]	Female	191.571	0.8016	7.3221	1.8

[a]NTP, 1989.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Human cancer equivalent dose of the $BMDL_{10}$ calculated as animal $BMDL_{10}$ x $(W_{animal}/W_{human})^{1/4}$ where W_{human} = 70 kg (human reference body weight) and W_{animal} = 0.416 kg for male rats and 0.273 kg for female rats (time weighted average body weights in the study).
[d]Betas restricted to ≥ 0; polydegree = 1 (lowest degree polynomial with adequate fit).

Abbreviations: AIC = Akaike Information Criterion; $BMDL_{10}$ = 95% lower confidence limit on the BMD_{10} (maximum likelihood estimate of the dose producing a 10% extra risk of effect [$BMDL_{10}$ not shown in this table]).

EPA chose mononuclear cell leukemia in female rats as the most sensitive endpoint because it occurs at a lower dose. "In order to linearly extrapolate cancer risks from the $BMDL_{10\ HED}$ to the origin, a cancer oral slope factor (OSF) was calculated as the ratio $0.1/BMDL_{10\ HED}$. Taking the $BMDL_{10\ HED}$ of 1.8 mg/kg-day for mononuclear cell leukemia in female rats as the POD, a provisional OSF of 0.06 $(mg/kg\text{-}day)^{-1}$ is calculated as follows" (EPA, 2009):

$$\begin{aligned} p-OSF &= 0.1 \div BMDL_{10\,HED} \\ &= 0.1 \div 1.8\ {}^{mg}/_{kg-day} \\ &= 0.06\ ({}^{mg}/_{kg-day})^{-1} \end{aligned}$$

Rule 231(1) states that the IRSL is calculated using the following equation:

$$IRSL = \frac{1 \times 10^{-6}}{unit\ risk}$$

Where the unit risk is (q_1^*), the equation for calculating q_1^* is below:

$$q_1^*\ ({}^{\mu g}/_{m^3})^{-1} = q_1^*({}^{mg}/_{kg/day})^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{a}{b}$$

Where:
a = absorption efficiency by the inhalation route of exposure.
b = absorption efficiency by the oral route of exposure.

In the absence of absorption efficiency data, the value for a/b = 1.

The oral human cancer slope factor is in $(mg/kg/day)^{-1}$ units which needs to be converted to $(\mu g/m^3)^{-1}$. Inserting the human cancer slope factor (q_1^*) to the equation above gives:

$$q_1^* \left({}^{\mu g}/_{m^3}\right)^{-1} = 0.06 \left({}^{mg}/_{kg/day}\right)^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{1}{1}$$
$$= 0.000017143 \left({}^{\mu g}/_{m^3}\right)^{-1}$$

Using Rule 231(1) equation above to derive the IRSL:

$$IRSL = \frac{1 \times 10^{-6}}{0.000017143 \left({}^{\mu g}/_{m^3}\right)^{-1}} = 0.058332847\ {}^{\mu g}/_{m^3} \approx 0.058\ {}^{\mu g}/_{m^3}$$

According to Rule 231(4) the averaging time for an IRSL or SRSL is annual. Therefore, the IRSL for hydroquinone is 0.058 $\mu g/m^3$ with an annual averaging time and the SRSL is 0.58 $\mu g/m^3$ with an annual averaging time.

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