Michigan Department of Environmental Quality

Interoffice Communication

TO: File for biphenyl (CAS # 92-52-4)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Memo to the file for biphenyl (CAS # 92-54-4)

DATE: September 30, 2013

The initial threshold screening level (ITSL) for biphenyl (CAS # 92-52-4) will remain 13 µg/m^3 based on an 8-hour averaging time. The IRSL for biphenyl is 0.43 µg/m^3 and the SRSL is 4.3 µg/m^3 based on an annual averaging time.

ITSL Derivation:

The EPA (2013) did not derive a reference concentration for chronic inhalation exposure (RfC) due to the lack of chronic or subchronic biphenyl inhalation studies. The EPA (2013) issued an RfD of 0.5 mg/kg/day based on renal papillary mineralization in male F344 rats in a 2-year dietary study by Umeda et al., (2002). Umeda et al. (2002) exposed F344 rats (50/sex/group) to concentrations of 0, 500, 1,500, or 4,500 ppm (0, 36.4, 110, or 378 mg/kg/day for males and 0, 42.7, 128, or 438 mg/kg/day for females) biphenyl in the diet for 2 years. A decrease in mean body weight was observed in high dose male and female rats when compared to controls. A statistically significant decrease in survival occurred in 378 mg/kg/day males (19/50), the first death occurring at treatment week 36; the early deaths were attributed to hematuria and bladder tumors. The 31 remaining male rats in the 378 mg/kg/day group had a statistically significant increase in urinary pH (pH of 7.97 versus 7.66 for controls; $p< 0.05$) in the final treatment week, with blood noted in the urine of 23/31 of these males. Statistically significant increases in relative kidney weights occurred in 110 and 378 mg/kg/day males and 128 and 438 mg/kg/day females and absolute kidney weights of the 378 mg/kg/day males were increased. Bladder calculi were observed in 43/50 of the 378 mg/kg/day males and 8/50 of the 438 mg/kg/day females. “Histopathological lesions of the ureter, kidney, and urinary bladder associated with biphenyl exposure were reported in male and female rats” (EPA, 2013). The incidences of transitional cell hyperplasia and dilatation in the ureter were increased in the 378 mg/kg/day rats compared to controls (EPA, 2013). “The kidney was identified as the most sensitive target of biphenyl toxicity based on data from the 2-year bioassay in F344 rats by Umeda et al. (2002). Dose-response modeling using BMDS was performed for the following non-neoplastic renal lesions: transitional cell hyperplasia (nodular and simple) and mineralization of the renal pelvis, hemosiderin deposits, and papillary mineralization” (EPA, 2013). The point of departure – human equivalent dose (POD_{HED}) = 13.9 mg/kg/day with an uncertainty factor of 30 (3 for animal to human; 10 for sensitive human individuals) giving an RfD of 0.5 mg/kg/day). A candidate ITSL based on this RfD would be calculated as follows:

$$0.5\ {}^{mg}/_{kg-day} \times \frac{70\ kg}{20\ {}^{m^3}/_{day}} \times \frac{1000\ \mu g}{1\ mg} = 1750\ {}^{\mu g}/_{m^3}$$

The American Conference of Governmental Industrial Hygienists (ACGIH) recommended a TLV-TWA of 0.2 ppm (1.3 mg/m^3) for occupational exposure to biphenyl "to minimize the potential for irritation of nasal mucosa and respiratory difficulties in rats and mice exposed by inhalation to biphenyl dust" (ACGIH, 2001). "Inhalation by rats of biphenyl dust, impregnated on diatomaceous earth, 7 hours/day for 64 days at 300 mg/m^3 caused irritation of the nasal mucosa, labored breathing with bronchopulmonary lesions, and slight toxic effects on liver and kidneys (Deichmann et al, 1947). Five rats died between the exposure days 29 and 49" (ACGIH, 2001). Rabbits and mice were also tested, while no effects were seen on rabbits, "mice exposed to 5 mg/m3 for this period showed signs of respiratory difficulty. Rats at this concentration were not affected" (ACGIH, 2001).

The available study data that EPA used to derive their RfD is based on animal feeding studies and systemic effects. The ACGIH TLV is based on inhalation portal-of-entry studies on mice, which are a susceptible animal model for this compound. The ACGIH TLV of 1.3 mg/m^3 TLV-TWA is a more appropriate basis for the ITSL than the systemic effects via oral exposure. The ITSL derived from the TLV is also protective of kidney effects, which were the critical systemic effects as determined by EPA (2013).

IRSL Derivation:

The EPA also did not derive a cancer inhalation unit risk for biphenyl, but stated that "the biphenyl case could be considered a borderline case between two cancer descriptors – 'suggestive evidence of carcinogenic potential' and 'likely to be carcinogenic to humans'. The descriptor of 'suggestive evidence of carcinogenic potential' is appropriate when a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion, given 'an extensive database that includes negative studies in other species,' and that 'additional studies may or may not provide further insights" (EPA, 2013). "Mechanistic data for urinary bladder tumors and limitations in liver tumor data better support the descriptor of 'suggestive evidence of carcinogenic potential' for biphenyl" (EPA, 2013). The EPA derived a carcinogenic risk oral slope factor of 8.2 x 10^{-3} $(mg/kg/day)^{-1}$ for biphenyl based on the 2-year cancer bioassay by Umeda et al. (2002) which found urinary bladder tumors in male F344 rats. Urinary bladder tumors are a rare tumor type. Although no other long term studies were found to directly corroborate these findings a shorter-term, 75-week dietary study in Wistar rats (Shiraiwa et al., 1989) found male rats with urinary bladder calculi and simple or diffuse hyperplasia and papillomatosis of the urinary bladder mucosa in the absence of neoplastic lesions. This suggests that urinary bladder tumors are a late developing tumor that may not be detected in shorter bioassays. Umeda et al. (2005) also found liver tumors in female BDF_1 mice during a 2-year dietary study with biphenyl.

Conversion of oral slope factor to inhalation:

The equation from Rule 231(3)(f) can be used to derive an IRSL from an oral slope factor derived from a 2-year dietary study using the following equation:

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

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

Since it is unknown what the absorption efficiency of the inhalation route or the oral route is, the value of 1 is substituted for both a and b. The value for q_1^* is the EPA carcinogenic oral slope factor of 8.2 x 10^{-3} mg/kg/day. Inserting the value for q_1^* above:

$$q_1^*(^{\mu g}/_{m^3})^{-1} = 0.0082(^{mg}/_{\frac{kg}{day}}) \times \frac{20m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{1}{1} = 0.000002343(^{\mu g}/_{m^3})^{-1}$$

Under Rule 231(1) the IRSL is determined as follows:

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

Where:
Unit risk = Additional lifetime cancer risk occurring in a population in which all individuals are exposed continuously for life to a concentration of 1 microgram per cubic meter of the chemical in the air they breathe.

Unit risk = q_1^*
Where:
q_1^* = This parameter is expressed in units of (microgram per cubic meter)$^{-1}$. Using the q_1^* value determined above in the IRSL equation:

$$IRSL = \frac{0.000001}{0.000002343(^{\mu g}/_{m^3})^{-1}} = 0.4268\ ^{\mu g}/_{m^3}$$

After rounding to 2 significant figures, the IRSL is 0.43 µg/m^3. According to Rule 231(4) the averaging time for an IRSL or SRSL is annual. Therefore, the IRSL for biphenyl is 0.43 µg/m^3 with an annual averaging time and the SRSL is 4.3 µg/m^3 with an annual averaging time. The initial threshold screening level (ITSL) for biphenyl (CAS # 92-52-4) will remain 13 µg/m^3 based on an 8-hour averaging time.

References:

ACGIH. 2001. Biphenyl. Documentation of the TLVs and BEIs. ACGIH Worldwide Signature Publications.

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

Deichmann WB; Kitzmiller KV; Dierker M; and Witherup S. 1947. Observations on the Effects of Diphenyl, o- and p-Aminodiphenyl, o- and p-Nitrodiphenyl, and Dehydroxyoctachlorodiphenyl Upon Experimental Animals. J. Ind. Hyg. Toxicol. 29:1-3.

EPA. 2013. Integrated Risk Information System. Biphenyl (CASRN 92-52-4; 8/27/2013). Retrieved data on 9/3/2013. Available online at http://www.epa.gov/iris/subst/0013.htm

Shiraiwa K; Takita M; Tsutsumi M; Kinugasa T; Denda A; Takahashi S; Konishi Y. 1989. Diphenyl induces urolithiasis does not possess the ability to promote carcinogenesis by N-ethyl-N-hydroxyethylnitrosamine in kidneys of rats. J Toxicol Pathol 2:41-48.

Umeda Y; Arito H; Kano H; Ohnishi M; Matsumoto M; Nagano K; Yamamoto S; Matusushima T. 2002. Two-year study of carcinogenicity and chronic toxicity of biphenyl in rats. J Occup Health 44: 176-183.

Umeda Y; Aiso S; Yamazaki K; Ohnishi M; Airto H; Nagano K; Yamamoto S; Matusushima T. 2005. Carcinogenicity of biphenyl in mice by two years feeding. J Vet Med Sci 67: 417-424.

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