MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Benzo(e)pyrene (CAS # 192-97-2)

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SUBJECT: Screening Level for Benzo(e)pyrene (CAS # 192-97-2)

Summary

The initial threshold screening level (ITSL) is 0.002 µg/m^3 (annual averaging time) for benzo(e)pyrene.

Uses and Physical Chemical Properties

Benzo(e)pyrene is an ortho- and peri-fused polycyclic arene consisting of five fused benzene rings. It is a constituent in coal tar and is found in trace amounts in tattoo ink. "Benzo(e)pyrene is also formed as a product of incomplete combustion of organic matter; it has been found in smoke from tobacco and marijuana cigarettes and in emissions from burning coal, wood, oil, and garbage. Benzo(e)pyrene has also been detected in both fresh and used motor oils, gasolines, and smoked and cooked food. Benzo(e)pyrene is purified for use in research laboratories…" (EPA, 2021).

Table 1. Physical/Chemical Properties of benzo(e)pyrene

Structure	
CAS Number	192-97-2
Synonyms	4,5-Benzopyrene; 1,2-Benzpyrene; B(e)P
Appearance/Odor	Colorless crystals or white crystalline solid
Molecular Weight	252.316 g/mol
Melting Point	177.5 °C
Boiling Point	492 °C at 76 mm Hg
Solubility: Water	Insoluble in water (0.0063 mg/L @ 25°C)
Vapor Pressure	5.70e-09 mmHg

Atmosphere half-life (d)	21.10 (measured in simulated sunlight)
Log K_{ow}	6.44
Henry's Law Constant	3.0X10-7 atm-m^3 /mole @ 25° C

Literature Search

The literature was searched to find relevant data to assess the toxicity of benzo(e)pyrene. The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder (searched 7/15/2022), U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR), European Chemical Agency (ECHA), and the U.S. National Toxicology Program (NTP).

Supporting Information and Key Study

Benzo(e)pyrene is listed on the EPA's Hazardous Air Pollutants list under polycyclic organic matter, which includes organic compounds with more than one benzene ring, and which have a boiling point greater than or equal to 100°C. The EPA does not have a reference concentration (RfC) or a reference dose (RfD) for chronic oral exposure (oral RfD), but EPA does have provisional peer reviewed toxicity values (PPRTV) for superfund with a chronic provisional RfC of 2E-6 mg/m^3 based on alternative analog information from benzo(a)pyrene (CAS # 50-32-8), which is structurally similar to benzo(e)pyrene and is considered a closer match for risk assessment than any of the polycyclic aromatic hydrocarbons.

There is very little animal or human toxicity information for benzo(e)pyrene. The available toxicity data is mostly from dermal, or intraperitoneal studies. *In vitro* study data indicates that benzo(e)pyrene has mutagenic activity only after metabolic activation. "In general, benzo(e)pyrene did not cause chromosomal damage *in vitro*; however, findings from *in vivo* studies are mixed and suggest that, under certain conditions, benzo(e)pyrene can cause chromosomal damage. Benzo(e)pyrene (or a metabolite) forms DNA adducts; however, most available *in vitro* and *in vivo* studies do not indicate that benzo(e)pyrene alters DNA damage/synthesis/repair" (EPA, 2021). A "rat study reported inhibited ^{3}H-thymidine uptake in thymus, spleen, bone marrow, and regenerating liver 24-48 hours after i.p. exposure to benzo(e)pyrene, suggesting decreased rates of DNA synthesis (Prodi et al., 1975). However, the study authors noted that findings may reflect general cytotoxicity of benzo(e)pyrene, rather than decreased DNA synthesis" (EPA, 2021). "Kitchin et al. (1993) and Kitchin et al. (1992) evaluated hepatic biochemical endpoints in female rats following acute oral exposure to benzo(e)pyrene. The rats were exposed twice to benzo(e)pyrene at 0 or 18 mg/kg via gavage in corn oil; the first dose was administered 21 hours prior to sacrifice and the second one 4 hours prior to sacrifice. No exposure-related changes in serum alanine aminotransferase (ALT) activity, hepatic ornithine decarboxylase activity, or hepatic cytochrome P450 (CYP450) content were observed" (EPA, 2021).

"Due to the lack of evidence…it is inappropriate to derive provisional toxicity values for benzo(e)pyrene because the limited database on the toxicity of benzo(e)pyrene is insufficient to support direct derivation. However, some information is available for this chemical, which although insufficient to deriving a provisional toxicity value under current guidelines, may be of use to risk assessors" (EPA, 2021). EPA (2021) applied the use of an alternative analogue approach, which "allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable" (EPA, 2021). "Three types of potential analogues (structural, metabolic, and toxicity-like) are identified to facilitate the final analogue chemical selection…All information was considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable analogue both toxicologically and chemically" (EPA, 2021).

"Based on the overall analog approach…benzo(a)pyrene is selected as the analog for benzo(e)pyrene for deriving the screening subchronic and chronic p-RfCs. The study used for the values for benzo(e)pyrene is a prenatal inhalation study of benzo(a)pyrene in rats (Archibong et al., 2002)" (EPA, 2021).

> *"Archibong et al. (2002) evaluated the effect of exposure to inhaled benzo(e)pyrene on fetal survival and luteal maintenance in timed-pregnant F344 rats. Prior to exposure on GD 8, laparotomy was performed to determine the number of implantation sites, and confirmed pregnant rats were divided into three groups, consisting of rats that had four to six, seven to nine, or more than nine conceptuses in utero. Rats in these groups were then assigned randomly to the treatment groups or control groups to ensure a similar distribution of litter sizes. Animals (10/group) were exposed to benzo(a)pyrene: carbon black aerosols at concentrations of 25, 75, or 100 µg/m^3 via nose-only inhalation, 4 hours/day on GDs 11-20. Control animals were either sham-exposed to carbon black or remained entirely unexposed… Aerosols showed a trimodal distribution (average of cumulative mass, diameter) <95%, 15.85 µm; 89%, <10 µm; 55%, <2.5 µm; and 38%, <1 µm (Inyang et al., 2003). Ramesh et al (2001a) reported that the MMAD (± geometric SD) for the 55% mass fraction with diameters <2.5 µm was 1.7 ± 0.085. Progesterone, esgtradiol-17β, and prolactin concentrations were determined in plasma collected in GDs 15 and 17. Fetal survival was calculated as the total number of pups divided by the number of all implantation sites determined on GD 8. Individual pup weights and crown-rump length per litter per treatment were determined on PND 4 (PND 0 = day of parturition)"* (EPA, 2021).

> *"Archibong et al. (2002) reported that exposure of rats to benzo(a)pyrene caused biologically and statistically significant (p ≤ 0.05) reductions in fetal survival compared with the two control groups; fetal survival rates were 78.3, 38.0, and 33.8% per litter at 25. 75, and 100 µg/m^3, respectively, and 96.7% with carbon black or 98.8% per litter in untreated controls… Consequently, the number of pups per litter was also decreased in a concentration-dependent manner. The decrease was ~50% at 75 µg/m^3 and ~65% at 100 µg/m^3, compared with sham-exposed and unexposed control groups. No effects on hormone levels were observed on GDs 15 or 17 at the low dose. Biologically significant decreases in mean pup weights (expressed as g per litter) of >5% relative to the untreated control group were observed at doses ≥75 µg/m^3 (14 and 16% decreases at 75 and 100 µg/m^3,*

respectively, p<0.05). There were no statistically significant differences from the control groups in crown-rump length…" (EPA, 2021).

"Benzo(a)pyrene exposure at 75 µg/m^3 caused a statistically significant decrease in plasma progesterone, estradiol, and prolactin on GD 17; these levels were not determined in the rats exposed to 100 µg/m^3 (Archibong et al., 2002). Plasma prolactin is an indirect measure of the activity of decidual luteotropin, a prolactin-like hormone whose activity is necessary for luteal maintenance during pregnancy in rats. Control levels of prolactin increased from GD 15 to 17, but this increase did not occur in the rats exposed to 75 µg/m^3. Although the progesterone concentration at 75 µg/m^3 was significantly lower than in controls on GD 17, the authors thought that the circulating levels should have been sufficient to maintain pregnancy; thus, the increased loss of fetuses was thought to be caused by the lower prolactin levels rather than progesterone deficiency. The reduced circulating levels of progesterone and estradiol-17β among benzo(a)pyrene-treated rats were thought to be a result of limited decidual luteotropic support for the corpora lutea and thereby decreasing the plasma levels of progesterone and estradiol-17β. The low estradiol-17β may decrease uterine levels of progesterone receptors, thereby resulting in fetal mortality. Based on biologically and statistically significant decreases in pups/litter and percent fetal survival/per litter, the LOAEL was 25 µg/m^3; no NOAEL was identified" (EPA, 2021).

The EPA selected benzo(a)pyrene as the analog for benzo(e)pyrene and used the study above to derive a chronic provisional reference concentration (p-RfC). The LOAEL of 25 µg/m^3 was converted to a LOAEL(HEC) of 4.6 µg/m^3 (0.0046 mg/m^3), using a composite uncertainty factor (UF_c) of 3,000.

UF_A (extrapolating from animal to human) of 3
UF_D (database) of 10
UF_H (human-to-human variability) of 10
UF_L (LOAEL-to-NOAEL) of 10
UF_S (subchronic-to-chronic) of 1

The LOAEL(HEC) of 0.0046 mg/m^3 ÷ UF_c of 3,000 equals 2 x 10^{-6} mg/m^3, which is the p-RfC for benzo(e)pyrene.

ITSL Derivation

According to Rule 336.1232(1)(a) in part 2 of Act 451, an ITSL can be derived from an inhalation reference concentration (RfC). The ITSL for benzo(e)pyrene equals the inhalation RfC. The ITSL for benzo(e)pyrene will be adopted from the EPA PPRTV p-RfC of 2 x 10^{-6} mg/m^3 (0.002 µg/m^3). According to Rule 336.1232(2)(b), the averaging time is annual. Therefore, the ITSL for benzo(e)pyrene is 0.002 µg/m^3 based on an annual averaging time.

IRSL Derivation

Although there is information on the mutagenicity and genotoxicity of benzo(e)pyrene, there are no oral or inhalation studies available to determine an IRSL. "Available dermal, lung implantation, and i.p. carcinogenicity studies in animals suggest that benzo(e)pyrene has some carcinogenic potential, although findings are inconsistent across studies and the relevance of these findings to oral or inhalation exposure in unclear. Under the USEPA Cancer Guidelines (EPA, 2005), there is "*Inadequate Information to Assess Carcinogenic Potential"* of benzo(e)pyrene by oral or inhalation exposure" (EPA, 2021).

References

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