MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

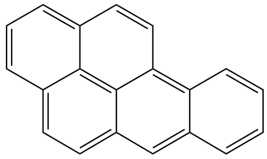
February 7, 2017

To: File for Benzo(a)pyrene and Other Carcinogenic PAHs (CAS No. 50-32-8, and others listed in Table 1)

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Levels for Polycyclic Aromatic Hydrocarbons

The initial risk screening level and secondary risk screening level (SRSL) for benzo(a)pyrene (B(a)P) are 1E-3 µg/m³ (0.001 µg/m³) and 1E-2 µg/m³ (0.01 µg/m³), respectively. The Initial Threshold Screening Level (ITSL) for B(a)P is 0.002 µg/m³ with 24-hr averaging time.



Cancer Risk Assessment

The U.S. Environmental Protection Agency (EPA, 2017) derived an Inhalation Unit Risk (IUR) for B(a)P of 6E-4 per µg/m³ for adult risk of cancer at 1 per million. EPA (2017, 2005) recommends that when the carcinogenic mode of action is mutagenic, the IUR is adjusted to account for the increased susceptibility of early life stages of development (i.e., infants and children). Rule 109(c) of the Air Pollution Control Rules, specifically defines the Initial Risk Screening Level as the "lifetime" risk at 1 per million risk. Since B(a)P causes cancer by a mutagenic mode of action (EPA, 2017), the IUR was adjusted to lifetime risk using EPA's default age-dependent-adjustment-factor (ADAF). EPA's guidance recommends the use of the following default adjustment factors for early-life exposures: increase the carcinogenic potency by 10-fold for children up to 2 years old, and 3-fold for children from 2 to 15 years old. These adjustments have the aggregate effect of increasing by about 60 percent (i.e., a factor of 1.6), the estimated risk for a 70-year (lifetime) constant inhalation exposure. The State of Michigan's Toxics Steering Group (TSG, 2012) reviewed the application of ADAFs in order to address the increased risk of carcinogens with mutagenic mode of action, and decided to adopt this policy. Applying the composite ADAF of 1.6 to the adult-only IUR for B(a)P is done as follows:

$IUR_{lifetime} = IUR_{adult} \times 1.6$
$IUR_{lifetime} = 6E\text{-}4 \text{ per } \mu g/m^3 \times 1.6$
$IUR_{lifetime} = 9.6E\text{-}4 \text{ per } \mu g/m^3$

The IRSL and SRSL, protective of lifetime exposure to B(a)P, are derived as follows:

IRSL = 1E-6/IUR
IRSL = 1E-6/(9.6E-4 per µg/m³)
IRSL = 1E-3 µg/m³ (0.001 µg/m³)

SRSL = 1E-5/IUR
SRSL = 1E-5/(9.6E-4 per µg/m³)
SRSL = 1E-2 µg/m³ (0.01 µg/m³)

Quantitative Estimate of Carcinogenic Risk From Inhalation Exposure to B(a)P

> Inhalation exposure to benzo[a]pyrene has been associated with squamous cell neoplasia in the larynx, pharynx, trachea, nasal cavity, esophagus, and forestomach of male Syrian golden hamsters exposed for up to 130 weeks to benzo[a]pyrene condensed onto sodium chloride particles (Thyssen et al., 1981). Supportive evidence for the carcinogenicity of inhaled benzo[a]pyrene comes from additional studies with hamsters exposed to benzo[a]pyrene via intratracheal instillation. The Thyssen et al. (1981) bioassay represents the only study of lifetime exposure to inhaled benzo[a]pyrene.
>
> A time-to-tumor dose-response model was fit to the time weighted average continuous exposure concentrations and the individual animal incidence data for the overall incidence of tumors in the upper respiratory tract or pharynx. The IUR of 6E-4 per µg/m^3 was calculated by linear extrapolation (slope factor = 0.1/BMCL10[1]) from a BMCL10 of 0.16 mg/m^3 for the occurrence of upper respiratory and upper digestive tract (forestomach) tumors in male hamsters chronically exposed by inhalation to benzo[a]pyrene (Thyssen et al., 1981).
> (EPA, 2017)

In 1995, the Air Quality Division (AQD) started to regulate B(a)P and carcinogenic PAHs based on the recommendation of the Scientific Advisory Panel (SAP, 1995a; SAP, 1995b). The SAP recommended that the relative potency factors (RPFs) used by EPA (1993) be applied to 6 carcinogenic PAHs that cause cancer in the same way that B(a)P does. The new IUR used above to derive the IRSL and SRSL updates the November 4, 2015 AQD methodology by applying this EPA (2017) IUR. There is no change to the November 4, 2015 expanded number of 15 specific PAHs (Table 1), which superseded the approach described by EPA (1993) and confirmed by the SAP.

The expanded list of PAHs (Table 1) is based on California's Office of Environmental Health Hazard Assessment (OEHHA, 2011, 2015) potency equivalency factors (PEFs), which are analogous to the RPFs used by EPA. The general method of assessing the risk of a mixture of PAHs recommended by Michigan's SAP (1995a; SAP, 1995b) based on their relative potency to that of B(a)P is retained. The addressing of asphalt fume PAHs was originally recommended by the SAP (1995b) and was adopted by the AQD; this approach is also being updated by the current B(a)P IUR and PEFs.

It should be noted that three PAHs listed in Table 1 are not specifically given a PEF by OEHHA (2015): Dibenz(a,h)anthracene (CAS No. 53-70-3), 3-Methylcholanthrene (CAS No. 56-49-5), and 7,12-Dimethylbenz(a)anthracene (CAS No. 57-97-6). For these PAHs, a surrogate PEF was calculated based on their potency relative to B(a)P. OEHHA (2015) derived chemical-specific IURs for these PAHs.

[1] Benchmark Concentration at the 10% response level

Table 1. PAH Potency Equivalency Factors (PEFs)

CHEMICAL NAME	CAS NO.	PEF
Dibenz(a,h)anthracene	53-70-3	1.1①
3-Methylcholanthrene	56-49-5	5.7①
7,12-Dimethylbenz(a)anthracene	57-97-6	65①
Chrysene	218-01-9	0.01
Indeno(1,2,3-cd)pyrene	193-39-5	0.1
Benzo(a)anthracene	56-55-3	0. 1
Benzo(b)fluoranthene	205-99-2	0.1
Benzo(k)fluoranthene	207-08-9	0.1
Benzo(j)fluoranthene	205-82-3	0.1
5-Methylchrysene	3697-24-3	1
Benzo(a)pyrene	50-32-8	1
Dibenzo(a,e)pyrene	192-65-4	1
Dibenzo(a,h)pyrene	189-64-0	10
Dibenzo(a,i)pyrene	189-55-9	10
Dibenzo(a,l)pyrene	191-30-0	10
Asphalt fumes	8052-42-4	②

Footnotes for Table 1

① Surrogate PEFs, based on ratios of OEHHA (2015) IURs for Dibenz(a,h)anthracene, 3-Methylcholanthrene and 7,12-Dimethylbenz(a)anthracene to that of benzo(a)pyrene were used.

② Apply PEFs to predicted ambient impacts of individual PAHs within asphalt fumes mixture, then sum (see example as described in Table 3).

EPA (2010) drafted RPFs for these three PAHs based on their similarity to B(a)P. Since EPA (2010) considers these compounds as having potency relative to B(a)P, the Air Quality Division is following this approach. Because EPA's (2010) RPFs for these three compounds are draft, AQD is adopting the potency of these PAHs based on OEHHA (2015). However, in order to incorporate these potencies in to the PEF approach their IURs were used to derive a surrogate PEF. These three PAHs and their PEFs are treated the same as the other PAHs in the procedure described below.

Example of Assessing PAH Emissions and Ambient Impacts Pursuant to Rule 225

The method to assess B(a)P and the additional carcinogenic PAHs is shown below in Table 3. The combined maximum ambient impacts of all carcinogenic PAHs (as B(a)P equivalents) must be below the IRSL. The SRSL can be used in lieu of the IRSL, if appropriate, pursuant to Rule 225(2).

In order to determine compliance with the IRSL it is recommended that the modeled ambient air impact of the particular PAH be multiplied by the PEF (sometimes called a relative potency factor or RPF), resulting in relative B(a)P predicted ambient impacts (PAIs; Table 3). These are then summed with all the other carcinogenic PAHs in the mixture. It is noted that an alternative acceptable method would involve converting PAH emissions to B(a)P equivalent emissions prior to dispersion modeling, and comparison of the combined ambient air impact to the B(a)P IRSL and SRSL.

Table 3. Example PAH Emissions and Application of Rule 225

Pollutant	Initial Risk Screening Level (µg/m³)	Avg. Time	Example PAI* (µg/m³)	PEF**	B(a)P-equivalent PAI (µg/m³)
Benzo(a)pyrene	0.001	annual	2.1E-5	1	2.1E-5
Benz(a)anthracene		annual	4.0E-5	0.1	4.0E-6
Benzo(b)fluoranthene		annual	5.5E-6	0.1	5.5E-7
Benzo(k)flouranthene		annual	5.5E-6	0.1	5.5E-7
Dibenzo(a,e)pyrene		annual	5.6E-6	1	5.6E-6
3-Methylcholanthrene		annual	6.2E-7	5.7	3.5E-6
Chrysene		annual	5.2E-5	0.01	5.2E-7
Dibenz(a,h)anthracene		annual	5.5E-6	1.1	6.1E-6
Indeno(1,2,3-cd)pyrene		annual	5.5E-6	0.1	5.5E-7
				Sum =	4.2E-5

* Predicted Ambient Impact, as determined by air dispersion modeling or other appropriate method.
** Potency Equivalency Factor (OEHHA, 2015) is the carcinogenic potency relative to benzo(a)pyrene.

In the example above (Table 3), the sum of B(a)P-equivalent ambient air impacts is 4.2E-5 µg/m³. Since the combined impact is less than the IRSL of 1E-3 µg/m³, the emissions comply with Rule 225(1).

Future Evaluation of PAHs

EPA's Science Advisory Board (SAB, 2011) has published a review of EPA's draft, "Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures" (EPA, 2010). The SAB review panel made several recommendations that EPA will likely address before EPA's (2010) draft RPF approach is finalized. The next steps in EPA Integrated Risk Information System's (IRIS's) review process for B(a)P is an updated toxicological report on PAH RPFs, followed by an external peer review and public comment. AQD will wait for EPA IRIS's updated draft RPFs and will review the findings at that time.

Non-Cancer Risk Assessment of Benzo(a)Pyrene

The derivation of the ITSL for B(a)P was based on the reference concentration (RfC) of 0.002 µg/m³ derived by EPA (2017). EPA (2017) based their RfC on a developmental inhalation study in rats by Archibong et al. (2002) and the observed decreased embryo/fetal survival (i.e., increased resorptions) following exposure to B(a)P on gestation days (GDs) 11−20. The lowest-observed-adverse-effect level (LOAEL) of 25 µg/m^3 based on decreased embryo/fetal survival was selected as the point of departure (POD). The LOAEL was adjusted to account for the discontinuous daily exposure to derive the POD_{ADJ} and the human equivalent concentration (HEC) was calculated from the POD_{ADJ} by multiplying by the regional deposited dose ratio ($RDDR_{ER}$) for extrarespiratory (ER) (i.e., systemic) effects, as described in Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA, 1994). These adjustments resulted in a POD_{HEC} of 4.6 µg/m^3, which was used as the POD for RfC derivation. The RfC was calculated by dividing the POD by a composite

uncertainty factor (UF) of 3,000 to account for toxicodynamic differences between animals and humans (UF of 3), inter-individual differences in human susceptibility (UF of 10), LOAEL-to-no-observed-adverse-effect level (NOAEL) extrapolation (UF of 10), and deficiencies in the toxicity database (UF of 10).

Additional Considerations for the Initial Threshold Screening Level

For the endpoint of decreased embryo/fetal survival (increased resporptions) supporting the overall RfC, exposure during the first (and potentially second) trimester of pregnancy would be the likely window of susceptibility. However, it is not known if multiple exposures are necessary or if one 24-hour period would be sufficient to result in developmental toxicity. Since the exposure period in the Achibong et al. (2002) study occurred over a relatively short time period, it would not be appropriate to assign a chronic, long-term averaging time to the RfC.

Additional concern should be noted for two coincident factors related to the amount of health protectiveness of the RfC for B(a)P:

1. the existence of benzo[a]pyrene in the environment as one component of complex mixtures of polycyclic aromatic hydrocarbons (PAHs), each with potential developmental effects and their potential additive effects, and
2. exposure to benzo[a]pyrene occurs by multiple routes of exposure in addition to inhalation, including oral and dermal routes

Both of these factors add an unknown amount of uncertainty to the RfC. For this reason, as well as others (see Appendix) the AQD concurs with EPA (2017) in the application of a 10-fold UF for database deficiencies in this case.

Table 4. Summary of EPA (2017) Derivation of RfC for B(a)P

RfC	2×10^{-3} µg/m^3
System	Developmental
Basis	Decreased embryo/fetal survival
POD*	LOAEL**: 0.0046 mg/m^3
Composite UF***	3000

*Point of Departure
** Lowest-observed-adverse-effect-level
*** Uncertainty Factor

$ITSL = POD_{HEC}/(3 \times 10 \times 10 \times 10)$
$ITSL = (4.6\ \mu g/m^3)/(3000)$
$ITSL = 0.00153\ \mu g/m^3$
$ITSL = 0.002\ \mu g/m^3$ (rounded to 1 significant figure[2])

The ITSL was derived pursuant to Rule 233(1)(b), with an additional 10-fold uncertainty factor for database deficiencies (see Appendix). Pursuant to Rule 233(2), the averaging time is 24-hr.

The ITSL for B(a)P is 0.002 µg/m³ with 24-hour averaging time.

[2] "The precision and accuracy in the numerical risk estimates currently do not permit more than one significant figure to be presented." As stated on page 1-10 of EPA (1987)

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Appendix: EPA's Rationale for 10-fold Uncertainty Factor for Database Deficiency

Excerpt From: Toxicological Review of Benzo[a]pyrene
[CASRN 50-32-8] January 2017
Integrated Risk Information System
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC
EPA/635/R-17/003Fa
www.epa.gov/iris

2.2.8. Uncertainties in the Derivation of the RfD and RfC

The following discussion identifies uncertainties associated with the RfD and RfC for benzo[a]pyrene. To derive the RfD, the UF approach (U.S. EPA, 2000, 1994a) was applied to a POD based on neurobehavioral changes in rats treated developmentally. To derive the RfC, this same approach was applied to a POD from a developmental study for the effect of decreased embryo/fetal survival. UFs were applied to the POD to account for extrapolating from an animal bioassay to human exposure, the likely existence of a diverse population of varying susceptibilities, and database deficiencies. These extrapolations are carried out with default approaches given the lack of data to inform individual steps.

The database for benzo[a]pyrene contains limited human data. The observation of effects associated with benzo[a]pyrene exposure in humans is complicated by several factors including the existence of benzo[a]pyrene in the environment as one component of complex mixtures of PAHs, exposure to benzo[a]pyrene by multiple routes of exposure within individual studies, and the difficulty in obtaining accurate exposure information. Data on the effects of benzo[a]pyrene alone are derived from a large database of studies in animal models. The database for oral benzo[a]pyrene exposure includes two lifetime bioassays in rats and mice, two developmental studies in mice, and several subchronic studies in rats.

Although the database is adequate for RfD derivation, there is uncertainty associated with the database including that the principal study for the RfD exposed animals during a relatively short period of brain development, potentially underestimating the magnitude of resulting neurological effects. Also, the database lacks comprehensive multigeneration reproductive/developmental toxicity studies, and immune system endpoints were not evaluated in the available chronic-duration or developmental studies. Additionally, the only available chronic studies of oral or inhalational exposure to benzo[a]pyrene focused primarily on neoplastic effects, leaving non-neoplastic effects mostly uncharacterized.

Additional uncertainty remains that the POD for the overall impact of neurodevelopmental effects might be lower than the selected POD. Specifically, if individual animal data for the Track 4 rats were available, consideration of the changes in any of the three behavioral tests as indicating an abnormal response for each rat would better represent the total behavioral effect, and could result in a lower POD. In addition, as altered performance in these three behavioral tests was more severe when tested in adult, as compared to juvenile, animals, it is possible that testing animals at even older ages (i.e., after PND 75) would reveal even more sensitive effects of exposure. However, experiments addressing these possibilities were not available and these remain unaddressed uncertainties. Overall, this POD is the best supported value that can be derived using the currently available information, recognizing the multiple effects observed in the same study.

The only chronic inhalation study of benzo[a]pyrene was designed as a lifetime carcinogenicity study and did not examine noncancer endpoints (Thyssen et al., 1981). In addition, subchronic and short-term inhalation studies are available, which examine developmental and reproductive endpoints in rats. Developmental studies by the inhalation route identified biologically significant reductions in the number of pups/litter and percent embryo/fetal survival and possible neurodevelopmental effects following gestational exposures. A 14-day premating reproductive study in female rats observed decreased ovulation rate and ovary weight in treated animals. Additionally, a 60-day oral study in male rats reported male reproductive effects (e.g., decreased testes weight and sperm production and motility), but provides limited information to characterize dose-response relationships with chronic exposure scenarios. The study selected as the basis of the RfC provided limited information regarding the inhalation exposures of the animals. Specifically, it is not clear whether the reported concentrations were target values or analytical concentrations and the method used to quantify benzo[a]pyrene in the generated aerosols was not provided. Requests to obtain additional study details from the authors were unsuccessful; therefore, the assumption was made that the reported concentrations were analytical concentrations.

Results from several different studies indicate that the endpoint of decreased number of pups per litter may be impacted during different sensitive windows of exposure, likely by different modes of action. The critical study used for the derivation of the RfC treated dams following implantation and quantification of conceptuses, from GD 11 to 20 and observed a decrease in embryos/fetuses per litter (Archibong et al., 2002). Another study treated female rats for 2 weeks immediately prior to mating and observed a decrease in ovulation rate (e.g., number of oocytes released) and a decreased number of pups born per litter (Archibong et al., 2012). Yet another study treated animals by intraperitoneal (i.p.) injection with benzo[a]pyrene by on GDs 1−5, observed a decrease in the number of implantation sites, and hypothesized that benzo[a]pyrene exposure may effect endometrial receptivity (Zhao et al., 2014). These three studies observed similar effects during different exposure windows, indicating that an exposure that included treatment prior to mating and through gestation would likely result in an even greater reduction in the number of pups produced per litter. Therefore, it is possible that the critical study used for the RfC may have observed a greater reduction of pups born per litter if exposure covered a more comprehensive duration.

Another area of uncertainty in the database pertains to the lack of information regarding fertility in animals exposed gestationally to benzo[a]pyrene, especially in light of developmental studies by the oral route indicating reduced fertility in the F1 generation and decreased reproductive organ weights. The database also lacks a multigenerational reproductive study via the inhalation route. Areas of uncertainty include the lack of chronic inhalation studies focusing on noncancer effects, limited data on dose-response relationships for impaired male or female fertility with gestational exposure or across several generations, and limited data on immune system endpoints with chronic exposure or developmental exposure to benzo[a]pyrene.

The toxicokinetic and toxicodynamic differences for benzo[a]pyrene between the animal species in which the POD was derived and humans are unknown. PBPK models can be useful for the evaluation of interspecies toxicokinetics; however, the benzo[a]pyrene database lacks an adequate model that would inform potential differences. There is some evidence from the oral toxicity data that mice may be more susceptible than rats to some benzo[a]pyrene effects (such as ovotoxicity) (Borman et al., 2000), although the underlying mechanistic basis of this apparent difference is not understood. Most importantly, it is unknown which animal species may be more comparable to humans.