BENZO(A)PYRENE CANCER TOXICITY CRITERIA UPDATES: IMPLICATIONS FOR HUMAN HEALTH RISK

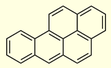
Behrsing, T., Gettmann, K., Sciullo, E., Wade, M.
Department of Toxic Substances Control (DTSC), CalEPA, Sacramento, CA, USA

ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) from natural and anthropogenic sources are common contaminants at CA sites. To assess risk from carcinogenic PAHs (cPAHs) other than naphthalene, cPAHs can be converted to benzo(a)pyrene-equivalents (BaP-EQ) using Potency Equivalency Factors (PEFs). The total BaP-EQ concentration is used to calculate risk and can be compared to ambient PAH levels. In recent years newer BaP cancer toxicity criteria have been developed or proposed, and early life exposure adjustments have been incorporated. In 2010, CalEPA derived an oral cancer slope factor (CSFo) of 1.7 (mg/kg-day)$^{-1}$ [2.9 with Age-Sensitivity Factors], which is less than the 1993 CSFo of 12 (mg/kg-day)$^{-1}$. In 2013, USEPA released a Public Comment Draft CSFo of 1 (mg/kg-day)$^{-1}$, inhalation unit risk (IUR) of 5E-4 (µg/m3)$^{-1}$, and dermal slope factor (SF) of 0.005 (µg/day)$^{-1}$. The draft CSFo is 7-fold lower than USEPA's current criterion, and derivation of a dermal SF is unique. Use of updated criteria and early life adjustments has implications for risk as shown for Site A with 1.8 mg/kg BaP in soil. Using CalEPA's 1993 CSFo and no early life adjustments, residential risk was 4.7E-5. Using the 2010 CSFo and 2013 draft CSFo and IUR with age dependent adjustment factors (ADAFs), risks are reduced to 2.9E-5 and 1.7E-5. Industrial risk using the 1993 CSFo was 1.4E-5. Risks using the 2010 CSFo and 2013 draft CSFo and IUR are 2E-6 and 1.2E-6. Impacts of the newer criteria are greater for industrial risk because ADAFs are not used. Industrial soil risk-based levels using the 2010 CSFo and 2013 draft CSFo and IUR with standard assumptions are 0.9 and 1.5 mg/kg. These values approach or exceed upper bound ambient PAH levels often considered in remedial decisions. However, direct dermal contact risk using the draft dermal SF may impact risks conversely and methods to evaluate this exposure route are needed. Potential impacts of revised BaP criteria on PEFs must also be considered. Given the prevalence of cPAHs at CA sites, issues related to BaP toxicity criteria updates require consideration and evaluation.

INTRODUCTION

- PAHs are common contaminants at CA hazardous waste sites.
- Sources of PAH contamination in environment
  - Natural sources (e.g., wildfires)
  - Anthropogenic sources (e.g., combustion of fossil fuels, incinerators, vehicle exhaust)
- PAHs occur as complex mixtures in the environment. ATSDR reports there are >100 PAHs (ATSDR 1996).
- Given the ubiquitous nature and large number of sources (particularly in urban areas), the issue of ambient versus site-related PAH contamination is an important consideration in human health risk assessments (HHRAs), and ultimately risk management decisions.
- Cancer versus noncancer endpoints
  - Many PAHs lack noncancer criteria.
  - Surrogates may be used, but cancer risk historically has been the primary driver at PAH sites.
  - As such, this presentation focuses on cancer risk.
- In recent years newer BaP cancer toxicity criteria have been developed or proposed, and early life exposure adjustments have been incorporated. Updated criteria and early life adjustments have important implications for assessing risk.



Benzo(a)pyrene

OVERVIEW – EVALUATING CANCER RISK FROM cPAHS

- Eight cPAHs (Table 1) are commonly evaluated in HHRAs. cPAHs can be evaluated as individual compounds or using the benzo(a)pyrene-equivalent (BaP-EQ) approach.
- BaP-EQ Approach
  - Concentrations of cPAHs (other than naphthalene) can be converted to BaP-EQ concentrations using Potency Equivalency Factors (PEFs) with BaP as the index compound.
  - The total BaP-EQ concentration is calculated as the sum of the BaP-EQs for each of the cPAHs.
  - US EPA and CalEPA OEHHA have developed PEFs (Table 1).
    - The USEPA PEF for dibenz(a,h)anthracene is 1.
    - Using CalEPA PEFs, dibenz(a,h)anthracene has typically been included in the BaP-EQ calculation using a PEF which is a ratio of the oral cancer slope factors (CSFo) for BaP and this PAH.
- Naphthalene is evaluated separately, using the CalEPA OEHHA Inhalation Unit Risk (IUR) for naphthalene (3.4E-5 [µg/m^3]$^{-1}$). Naphthalene must also be considered for vapor intrusion to indoor air exposures.

Table 1. Summary of cPAH PEFs

	CalEPA OEHHA (CalEPA 2009a)	US EPA (USEPA 2013a)
Chemical	**PEF**	**PEF**
Benzo(a)anthracene	0.1	0.1
Benzo(a)pyrene	1	1
Benzo(b)fluoranthene	0.1	0.1
Benzo(k)fluoranthene	0.1	0.01
Chrysene	0.01	0.001
Dibenz(a,h)anthracene	**0.34[a]**	**1**
Indeno(1,2,3-cd)pyrene	0.1	0.1
Naphthalene	NA	NA

[a] Not listed in OEHHA 2009a; PEF shown was calculated as a ratio of the dibenz(a,h)anthracene CSFo (4.1 [mg/kg-d] $^{-1}$) and historical CalEPA BaP CSFo (12 [mg/kg-d] $^{-1}$): 4.1 ÷ 12 = 0.34

BaP CANCER TOXICITY CRITERIA UPDATES

Oral Cancer Slope Factor Comparison (Table 2)

- 1992 USEPA and 1993 CalEPA CSFo's are both based on the 1967 Neal and Rigdon study
- 2010 CalEPA and 2013 Draft Public Comment USEPA CSFo's are based on the 1998 Culp et al
  - Culp et al. considered to be of much higher quality than Neal and Ridgon study (CalEPA 2010)
  - Deficiencies of Neal and Rigdon study (CalEPA 2010, USEPA 2013b):
    - Combined males and females
    - Variable number of animals in each group
    - BaP administration began at different ages (3 weeks to 6 months old)
    - Treatment over different time intervals
    - Less than lifetime exposure
    - No vehicle control group

Table 2. BaP CSFo Summary

	(mg/kg-d)$^{-1}$	Tumor Type	Study
USEPA IRIS (1992)	7.3	Forestomach, squamous cell papillomas and carcinomas; Forestomach, larynx and esophagus, papillomas and carcinomas (combined)	Oral feeding study in CFW mice (Neal and Rigdon 1967); Oral feeding study in Sprague-Dawley rats (Brune et al 1981)
CalEPA (1993)	12	Gastric tumors (papillomas and squamous cell carcinomas)	Oral feeding study in CFW mice (Neal and Rigdon 1967)
CalEPA (2010)	1.7[a]	Forestomach/oral cavity tumors	Oral feeding study in B6C3F1 mice (Culp et al 1998)
USEPA Draft Public Comment (2013b)	1	Forestomach, esophagus, tongue, larynx (alimentary tract) squamous cell tumors	Oral feeding study in B6C3F1 mice (Culp et al 1998)

[a] CalEPA's Public Health Goal (PHG) was calculated using a CSFo of 2.9. This value was calculated using the 1.7 (mg/kg-d)$^{-1}$ and Age Sensitivity Factors (ASFs).

Inhalation Unit Risk Factor Comparison (Table 3)

- No IUR is currently available on USEPA IRIS
- No updated CalEPA IUR (CalEPA 2010 pertains to drinking water)
- CalEPA 1993 and USEPA 2013 are both based on Thyssen et al study

Table 3. BaP IUR Summary[a]

	(µg/m^3)$^{-1}$	Tumor Type	Study
USEPA IRIS (1992)	Not available	-	-
CalEPA (1993)	1.10E-03	Respiratory tract tumors	Inhalation study in hamsters (Thyssen et al 1991)
USEPA Draft Public Comment (2013b)	5.00E-04	Upper respiratory and digestive tract tumors	Inhalation study in hamsters (Thyssen et al 1991)

[a] CalEPA's 2010 PHG document for drinking water does not derive an IUR.

Dermal Cancer Slope Factor (Table 4)

- No CalEPA or USEPA dermal slope factor (SF) for BaP currently available
- 2013 Draft Public Comment SF would be USEPA IRIS's first dermal SF
  - The draft value is for a local effect
  - Not intended to estimate systemic risk following dermal absorption of BaP into the systemic circulation

Table 4. Draft Public Comment Dermal Slope Factor[a]

	(µg/day)$^{-1}$	Tumor Type	Study
USEPA Draft Public Comment (2013b)	5.00E-03	Skin tumors	Dermal exposure in C3H/HeJ mice (Sivak et al 1997); Dermal exposure in C57L mice (Poel 1959)

[a] **No dermal SF is currently available on US EPA IRIS. No CalEPA dermal SF has been developed.**

EARLY LIFE EXPOSURE ADJUSTMENT

- When developing quantitative estimates of cancer risk, USEPA recommends integrating age-specific values for both exposure and toxicity/potency for chemicals exhibiting a mutagenic mode of action. The 10-fold (0-2 years) and 3-fold (2-16 years) age-dependent adjustments in slope factor are combined with age-specific exposure estimates when estimating cancer risks from early life exposure to carcinogens that act through a mutagenic mode of action. USEPA uses the term "Age-Dependent Adjustment Factor" (ADAF) (USEPA 2005).
- CalEPA recommends a similar approach, but differs notably from USEPA by: 1) Including the third trimester of pregnancy for the 10-fold age adjustment, and 2) Including all carcinogens regardless of purported mechanism of action, unless chemical-specific data exist to the contrary. CalEPA uses the term "Age Sensitivity Factor" (ASF) (CalEPA 2009b).
- ASFs should only be used in risk assessments that evaluate child receptors such as residential scenarios.

IMPLICATIONS OF UPDATED CSFo AND IUR & EARLY LIFE ADJUSTMENTS FOR RISK

Sample Risk-based Screening Levels for BaP in Soil

- The USEPA RSL Calculator was used to evaluate the impact of the 2010 CalEPA CSFo, the 2013 USEPA Draft Public Comment CSFo and IUR on risk-based screening levels for BaP in soil.
- RSL calculator defaults for BaP were used, except to modify the toxicity criteria and turning off the ADAFs for the historical CalEPA assumption calculations. Although CalEPA OEHHA recommends evaluating early life exposures for the third trimester of pregnancy, the RSL calculator ADAFs were used in this preliminary screening evaluation for the residential scenario.
- As shown in Table 5:
  - Risk-based screening levels for BaP in soil are greater than values based on historical CalEPA assumptions.
  - Impacts of the newer criteria are greater for the industrial scenario because ADAFs are not used.
  - The estimated revised industrial soil risk-based levels approach or exceed upper bound ambient PAH levels often considered in remedial decisions.
- An important limitation of this evaluation is that the impact of the Draft Public Comment dermal SF was not considered. The USEPA RSL calculator uses the CSFo to evaluate systemic risk following dermal absorption. Evaluation of local risk from dermal absorption is not available in the calculator.

Table 5. Sample Risk-Based Screening Level Calculations for BaP in Soil

	CSFo (mg/kg-d)$^{-1}$	IUR (µg/m^3)$^{-1}$	ADAFs Used for Residential Scenario?	BaP in Soil (mg/kg) Residential Soil Screening Level	BaP in Soil (mg/kg) Industrial Soil Screening Level
Historical CalEPA Assumptions	12	1.10E-03	No	0.038	0.128
2010 CalEPA CSFo and Early Life Exposure Adjustments (residential only)	1.7	1.10E-03	Yes	0.063	0.906
USEPA 2013 Draft Public Comment CSFo and IUR, and Early Life Exposure Adjustments (residential only)	1	5.00E-04	Yes	0.108	1.54

Site A

- An industrial site located in the San Francisco Bay Area with PAH contaminated soil.
- A ratio approach was used to estimate the risk from PAHs in soil using: 1) an exposure point concentration (EPC) of 1.8 mg/kg and 2) the screening levels shown in Table 5.
- Regardless of which BaP toxicity criteria are used or whether early life exposure adjustments are applied, the cancer risk for the resident is within the risk management range (10^{-6} to 10^{-4}).
- While the industrial cancer risk using historic CalEPA assumptions is within the risk management range, when using the 2010 CalEPA and Public Draft Comment 2013 USEPA criteria the cancer risk of 1.2E-06 approaches the point of departure for risk management decisions.
- For the industrial scenario, the 2010 CalEPA and proposed 2013 USEPA criteria could impact whether remediation is recommended.

Table 6. Risk at Site A with 1.8 mg/kg BaP in Soil

	Residential	Industrial
Historical CalEPA Assumptions	4.7E-05	1.4E-05
2010 CalEPA CSFo and Early Life Exposure Adjustments (residential only)	2.9E-05	2.0E-06
USEPA 2013 Draft Public Comment CSFo and IUR, and Early Life Exposure Adjustments (residential only)	1.7E-05	1.2E-06

DISCUSSION and SUMMARY

- While CalEPA's 2010 CSFo and USEPA's 2013 Public Draft Comment CSFo are lower than historical CSFos, the revised and proposed criteria are both based on Culp et al. (1998) and are less than 2-fold different. The newer CSFo's are based on higher quality data using current risk assessment methodology.
- CalEPA's 1992 IUR and USEPA's 2013 Public Draft Comment IUR are both based on Thyssen et al (1991) and are only 2-fold different.
- Compared to industrial scenarios, the impact of the new CalEPA CSFo and USEPA's 2013 Public Draft Comment CSFo and IUR is less significant for residential scenarios since early life adjustments are now used. Incorporation of early-life adjustments off-set the impact of the lower CSFo.
- Industrial soil risk-based levels using the new or proposed criteria approach or exceed upper bound ambient PAH levels often considered in remedial decisions. As such, this may impact cleanup decisions.
- The Public Draft Comment dermal SF would be the first dermal cancer criterion on USEPA's Integrated Risk Information System (IRIS).
  - The impact of the proposed dermal slope factor on risk was not considered in the sample calculations of BaP soil screening levels or Site A presented here. Direct dermal contact risk using the draft dermal SF may have significant impacts on risk.
  - Standard risk assessment methods to evaluate local risk from dermal absorption will be needed if a dermal SF is ultimately adopted. Currently, USEPA's RAGS Part E acknowledges that direct dermal contact can result in direct dermal toxicity, including skin cancer (USEPA 2004). RAGS Part E does not address dermal toxicity associated with direct contact, but indicates that the guidance may be revised to incorporate additional information on portal-of-entry effects as it becomes available.
- The potential impacts of revised BaP criteria on cPAH PEFs must also be considered. BaP is used as the index compound for calculating BaP-EQ concentrations. To date, the CalEPA PEFs for cPAHs other than BaP are all less than one. However, the new CalEPA CSFo for BaP is less than the CalEPA CSFo for dibenz(a,h)anthracene.
- The CalEPA revised CSFo was finalized as part of the BaP PHG in 2010. However, the USEPA Public Draft Comment BaP criteria are *draft* only at this time.
  - The USEPA Public Draft Comment BaP criteria were released for review and comments in August 2013. In December 2013, USEPA held a public meeting to engage stakeholders in early discussions on the draft assessment. In January 2014, USEPA announced a request for nominations for experts to augment the Science Advisory Board (SAB) Chemical Assessment Advisory Committee (CAAC) for the upcoming review of the draft BaP assessment.
  - Following public comment and external peer review, the assessment will be revised. The assessment will then undergo a final USEPA internal review and a review by other federal agencies and the Executive Office of the President. Once final, the assessment will be posted to the IRIS database.

REFERENCES

- Agency for Toxic Substances and Disease Registry (ATSDR) 1996. ToxFAQs for Polycyclic Aromatic Hydrocarbons (PAHs) (http://www.atsdr.cdc.gov/tfacts69.pdf)
- Brune H, Deutsch-Wenzel RP, Habs M, Ivankovic S, Schmahl D 1981. Investigation of the tumorigenic response to benzo(a)pyrene in aqueous caffeine solution applied orally to Sprague-Dawley rats. J Cancer Res Clin Oncol 102:153-7.
- Culp SJ, Gaylor DW, Sheldon WG, Goldstein LS, Beland FA. 1998. A comparison of the tumors induced by coal tar and benzo(a)pyrene in a 2-year bioassay. Carcinogenesis 19:117-24.
- California Environmental Protection Agency (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA) 1993. Benzo[a]pyrene as a Toxic Air Contaminant. Part B. Health Effects of Benzo[a]pyrene. Air Toxicology and Epidemiology Section.
- CalEPA OEHHA 2009a (Updated May 2011). Air Toxics Hot Spots risk Assessment Guidelines Part II: Technical Support Document for Cancer Potency Factors, Appendix B (http://www.oehha.ca.gov/risk/ChemicalDB/index.asp)
- CalEPA OEHHA 2009b. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. (http://oehha.ca.gov/air/hot_spots/2009/TSDCancerPotency.pdf)
- CalEPA OEHHA 2010. Public Health Goal for Benzo(a)pyrene in Drinking Water. Pesticide and Environmental Toxicology Branch (http://www.oehha.ca.gov/water/phg/091610bghgs.html)
- Neal J, Rigdon RH 1967. Gastric tumors in mice fed benzo(a)pyrene: a quantitative study. Texas Rep Biol Med 25:553-7.
- Poel, WE 1960. Skin as a test site for the bioassay of carcinogens and carcinogen precursors [IARC Monograph]. In IARC Monographs on The Evaluation of Carcinogenic Risk of Chemicals To Man (pp. 611-631)
- Sivak, A,Niemeier, R, Lynch, D, Beltis, K, Simon, S, Salomon, R, Latta, R, Belinky, B, Menzies, K, Lunsford, A, Cooper, C, Ross, A, Bruner, R 1997. Skin carcinogenicity of condensed asphalt roofing fumes and their fractions following dermal application to mice. Cancer Lett 117: 113-123.
- Thyssen, J, Althoff, J, Kimmerle, G, Mohr, U 1981. Inhalation studies with benzo[a]pyrene in Syrian golden hamsters. J Natl Cancer Inst 66: 575-577.
- US Environmental Protection Agency (USEPA) Integrated Risk Information System 1992 (Last Revised 1994; Assessed 2013). Benzo[a]Pyrene (BaP) (http://www.epa.gov/iris/subst/0136.htm#quantest)
- USEPA 2004. Risk Assessment Guidance for Superfund, Volume 1: Human Health Evaluation Manual Part E, Supplemental Guidance for Dermal Risk Assessment, Interim (http://www.epa.gov/oswer/riskassessment/ragse/index.htm)
- USEPA 2005. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (http://www.epa.gov/raf/publications/pdfs/childrens_supplement_final.pdf)
- USEPA 2013a. Regional Screening Levels for Chemical Contaminants at Superfund Sites (http://www.epa.gov/reg3hwmd/risk/human/rb-concentration_table/index.htm)
- USEPA 2013b. Public Comment Draft Toxicological Review of Benzo[a]pyrene in Support of Summary Information on the Integrated Risk Information System (IRIS), Supplemental Information (http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=66193)

DISCLAIMER

Professional affiliations are listed for contact purposes only. Analysis and conclusions contained herein are solely those of the authors and do not represent guidance or official policy of the California Department of Toxic Substances Control or California Environmental Protection Agency.