

January 21, 2016

Mr. Thomas Carpenter, Designated Federal Officer (DFO)
EPA Science Advisory Board Staff Office (1400R)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460

Via email: t.carpenter.thomas@epa.gov.

Subject: Comments of the Pavement Coatings Technology Council on *Science Advisory Board (SAB) Draft Report (12/21/2015) for Quality Review*

Dear Mr. Carpenter,

On behalf of the members of the Pavement Coatings Technology Council (PCTC) I again commend the SAB Benzo(a)Pyrene review panel for producing such a thorough and well thought through review of the EPA's Integrated Risk Information System (IRIS) Draft Toxicological Review of Benzo[a]pyrene (B(a)P). It can be argued that there is no substance in the IRIS system that is more complex. There are perhaps more toxicology studies of B(a)P available than any other substance. The bulk of these studies are of B(a)P as an individual compound – a substance to which no living being, animal or vegetable, is exposed outside the laboratory except as a constituent of materials containing PAH mixtures. One of the challenges faced in developing an IRIS assessment and reviewing that IRIS assessment is translating the voluminous literature available from the laboratory into an assessment of the relevance of that data to human health risks. In an IRIS assessment, the bridge between the lab and the real world is the Hazard Characterization.

One aspect of the Hazard Characterization is determining whether B(a)P meets EPA's criteria to be classified as a "known human carcinogen." Section 3.2.4 (lines 9-18) of the Draft Report reads as follows:

The SAB finds that the EPA has demonstrated that BaP is a human carcinogen in accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA 2005a). This conclusion was based primarily on animal studies and mechanistic data, with strong support from an excess of lung cancer in humans who are exposed to PAHs, but not to

BaP alone. This conclusion is consistent with the evaluations by other agencies, including the World Health Organization's International Agency for Research on Cancer (IARC 2010) and Health Canada (2015). Detailed consideration of the EPA criteria for whether or not a compound is considered a human carcinogen, as applied to BaP, follows.

EPA Criterion 1 - The compound in question is "Carcinogenic to Humans" when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.

I write today to ask the SAB to reconsider its draft conclusion in light of the findings of recent systematic reviews and other occupational exposure studies. The draft conclusion is based in part on a large number of old studies, most of which would not pass muster if subjected to a systematic review. As it happens, several systematic reviews of occupational exposure studies conducted in facilities where PAH-containing materials are used are available. These studies have not yet been incorporated into Hazard Characterizations by review bodies such as IARC. Attached to this letter for your consideration are summary tables, abstracts or descriptions of several recent systematic reviews of occupational exposures in industries that use PAH-containing materials. Several additional studies not reflected in the attachments are included in the reference list at the end of this letter.

The criterion requires "convincing epidemiological evidence of a causal association between exposure and cancer." The relative risk values reported in recent systematic reviews and recent occupational studies are below 3, which is the value generally recognized as indicating a "strong association."

PCTC asks the SAB to consider whether a Hazard Characterization conducted using the recently implemented systematic review and "fit for purpose" methodologies of the IRIS program would support a finding contrary to the moderate to weak association between exposures to PAH-containing materials and cancer reported in the recent literature. PCTC believes that EPA's findings would be consistent with other recent findings, and so urges the SAB to suggest that EPA follow its recently implemented methodology for reviewing IRIS substances in its revision of the B(a)P Hazard Characterization. Pending a finding by EPA that is contrary to other recent reviews, B(a)P does not meet the criteria for "convincing epidemiological evidence of a causal association between exposure and cancer."

Thank you for your attention. Please contact me if there are questions or you need additional information.

Very truly yours



Anne P. LeHuray, Ph.D.
Executive Director

Attachment

References

- Armstrong, B. G., & Gibbs, G. (2009). Exposure–response relationship between lung cancer and polycyclic aromatic hydrocarbons (PAHs). *Occupational and Environmental Medicine*, 66(11), 740-746. doi:10.1136/oem.2008.043711
- Boffetta, P. (2010). Causation in the Presence of Weak Associations. *Critical Reviews in Food Science and Nutrition*, 50(s1), 13-16. doi:10.1080/10408398.2010.526842
- Bosetti, C., Boffetta, P., & La Vecchia, C. (2007). Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. *Annals of Oncology*, 18(3), 431-446. doi:10.1093/annonc/mdl172
- Gibbs, G. W., & Labreche, F. (2014). Cancer risks in aluminum reduction plant workers: a review. *J Occup Environ Med*, 56(5 Suppl), S40-59. doi:10.1097/jom.0000000000000003
- Langevin, S. M., Eliot, M., McClean, M. D., & Kelsey, K. T. (2014). Abstract 279: Head and neck squamous cell carcinoma risk among asphalt workers from the greater Boston area. *Cancer Research*, 74(19 Supplement), 279. doi:10.1158/1538-7445.am2014-279
- Rota, M., Bosetti, C., Boccia, S., Boffetta, P., & La Vecchia, C. (2014). Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014. *Archives of Toxicology*, 88(8), 1479-1490. doi:10.1007/s00204-014-1296-5
- Spinelli, J. J., Lai, A. S., Ng, C. H., Ward, H. D., Dhalla, A., Caspersen, J., & Wang, H. D. (2012). *Systematic Review for primary cancer of skin where there is prolonged contact with coal tar products, arsenic or cutting oils or prolonged exposure to solar ultraviolet light*. Report prepared for WorkSafeBC, Victoria, British Columbia. Retrieved from http://www.worksafebc.com/regulation_and_policy/policy_consultation/assets/pdf/PrimarySkinCancerCertainOccupationalExposuresComplete.pdf?_ga=1.260629197.1503806911.1431809356
- Taiwo, O. A., Slade, M. D., Cantley, L. F., Tessier-Sherman, B., Galusha, D., Kirsche, S. R., Cullen, M. R. (2015). Bladder Cancer Screening in Aluminum Smelter Workers. *Journal*

of Occupational and Environmental Medicine, 57(4), 421–427.

doi:10.1097/JOM.0000000000000377

Wagner, M., Bolm-Audorff, U., Hegewald, J., Fishta, A., Schlattmann, P., Schmitt, J., & Seidler, A. (2014). Occupational polycyclic aromatic hydrocarbon exposure and risk of larynx cancer: a systematic review and meta-analysis. *Occupational and Environmental Medicine*. doi:10.1136/oemed-2014-102317

What do recent studies say about carcinogenicity of CT?

- Recent trend – make sure you are relying on good data by performing a systematic review

Although any measure of risk would follow a continuous distribution and there are no predefined values that separate “strong” from “moderate” or “weak” associations, relative risks below 3 are considered moderate or weak. (Boffetta 2010)

Bosetti et al. 2007

Lung/Respiratory Cancers pooled relative risk (RR):

coal gasification	2.58 (95% CI 2.28–2.92)
coke production	1.58 (95% CI 1.47–1.69)
iron and steel foundries	1.40 (95% CI 1.31–1.49)
roofers	1.51 (95% CI 1.28–1.78)
carbon black production	1.30 (95% CI 1.06–1.59)

Bladder/urinary system cancers pooled relative risk (RR):

aluminum production	1.29, 95% CI 1.12–1.49
coal gasification	2.39, 95% CI 1.36–4.21
iron and steel foundries	1.29, 95% CI 1.06–1.57

Increased risks from lung and bladder cancers were found in PAH-related occupations. These were modest in most industries, apart from those for coal gasification, and whether they are due at least partially to some bias or confounding remains open to discussion. (Bosetti et al. 2007)

Rota et al., 2014: “It cannot be ruled out whether such excesses are due, at least in part, to possible bias or residual confounding.”

Table 2 Overall standardized mortality ratios (SMRs) and pooled relative risks (RRs) with 95 % confidence intervals (CIs) for selected cancer sites for workers exposed to polycyclic aromatic hydrocarbons in various industries and occupations

Industry, cancer site	No. of cohorts	Obs/Exp	SMR	Pooled RR ^a (95 % CI)	<i>p</i> value for heterogeneity
<i>Aluminum production</i>					
Larynx	7	71/63.4	1.12	1.15 (0.91–1.45)	0.700
Lung	10	1,314/1,154.7	1.14	1.07 (0.93–1.23)	<0.0001
Respiratory tract ^b	11	1,349/1,183.9	1.14	1.08 (0.95–1.23)	<0.0001
Bladder	10	279/202.2	1.38	1.28 (0.98–1.68)	0.002
Kidney	8	131/126.4	1.04	1.06 (0.89–1.25)	0.728
<i>Iron and steel foundry</i>					
Larynx	5	59/41.2	1.43	1.48 (1.14–1.91)	0.537
Lung	13	2,903/2,762.4	1.05	1.31 (1.07–1.61)	<0.0001
Respiratory tract ^b	14	2,932/2,784.7	1.05	1.31 (1.08–1.59)	<0.0001
Bladder	9	151/127.7	1.18	1.38 (1.00–1.91)	0.001
Kidney	6	68/69.4	0.98	1.03 (0.78–1.35)	0.304
<i>Asphalt workers</i>					
Larynx	2	45/42.7	1.05	1.89 (0.45–7.95)	0.013
Lung	3	827/735.7	1.12	1.59 (0.68–3.76)	<0.0001
Bladder	2	109/107.1	1.02	1.03 (0.82–1.30)	0.305
<i>Carbon black production</i>					
Lung	3	249/201.1	1.24	1.52 (0.91–2.52)	<0.0001
Respiratory tract ^b	4	283/243.6	1.16	1.30 (0.84–2.01)	<0.0001
Bladder	3	15/14.8	1.02	1.10 (0.61–2.00)	0.288

Obs/Exp observed/expected number of cancer cases/deaths

^a Calculated as a weighted average of the SMRs through random-effects models

^b Including lung and other respiratory cancers not specified

Taiwo et al. 2015

Objective: To present results of a bladder cancer screening program conducted in **18 aluminum smelters in the United States** from January 2000 to December 2010.

Methods: Data were collected on a cohort of workers with a history of working in **coal tar pitch volatile exposed areas** including urine analysis for conventional cytology and ImmunoCyt/uCyt+ assay.

Results: ImmunoCyt/uCyt+ and cytology in combination showed a sensitivity of 62.30%, a specificity of 92.60%, a negative predictive value of 99.90%, and a positive predictive value of 2.96%. Fourteen cases of bladder cancer were detected, and the standardized incidence ratio of **bladder cancer** was **1.18 (95% confidence interval, 0.65 to 1.99)**. Individuals who tested positive on either test who were later determined to be cancer free had undergone expensive and invasive tests.

Conclusions: Evidence to support continued surveillance of this cohort has not been demonstrated.

Gibbs & LaBreche, 2014

OBJECTIVE AND METHODS: This review examines epidemiological evidence relating to cancers in the primary **aluminum industry** where most of what is known relates to Soderberg operations or to mixed Soderberg/prebake operations.

RESULTS AND CONCLUSIONS: Increased lung and bladder cancer risks have been reported in Soderberg workers from several countries, but not in all. After adjustment for smoking, these cancer risks still increase with **cumulative exposure to benzo(a)pyrene, used as an index of coal tar pitch volatiles exposure.**

Limited evidence has been gathered in several cohorts for an increased risk of tumors at other sites, including stomach, pancreas, rectum/rectosigmoid junction, larynx, buccal cavity/pharynx, kidney, brain/nervous system, prostate, and lymphatic/hematopoietic tissues (in particular non-Hodgkin lymphoma, Hodgkin disease, and leukemia). Nevertheless, **for most of these tumor sites, the relationship with specific exposures has not been demonstrated clearly and further follow-up of workers is warranted.**

Armstrong & Gibbs 2009

Objectives: To estimate the exposure–response function associating **polycyclic aromatic hydrocarbon (PAH) exposure and lung cancer, with consideration of smoking.**

Methods: Mortality, occupational exposure and smoking histories were ascertained **for a cohort of 16 431 persons (15 703 men and 728 women) who had worked in one of four aluminium smelters in Quebec** from 1950 to 1999. A variety of exposure–response functions were fitted to the cohort data using generalised relative risk models.

Results: In 677 lung cancer cases there was a clear trend of increasing risk with increasing cumulative exposure to PAH measured as benzo(a)pyrene (BaP). A linear model predicted a **relative risk of 1.35 (95% CI 1.22 to 1.51)** at 100 $\mu\text{g}/\text{m}^{-3}$ BaP years, but there was a significant departure from linearity in the direction of **decreasing slope with increasing exposures**. Among the models tried, the best fitting were a two-knot cubic spline and a power curve ($\text{RR} = (1 + bx)^p$), the latter predicting a relative risk of 2.68 at 100 $\mu\text{g}/\text{m}^{-3}$ BaP years. Additive models and multiplicative models for combining risks from occupational PAH and smoking fitted almost equally well, with a slight advantage to the additive.

Conclusion: Despite the large cohort with long follow-up, the shape of the exposure–response function and the mode of **combination of risks due to occupational PAH and smoking remains uncertain**. If a linear exposure–response function is assumed, the estimated slope is broadly in line with the estimate from a previous follow-up of the same cohort, and somewhat higher than the average found in a recent meta-analysis of lung cancer studies.

Spinelli et al. 2012

In summary, there is **no evidence** to suggest there is an increased risk of **skin cancer** from prolonged exposure to coal tar alone as determined through this systematic review. There is a scarcity of well conducted epidemiological studies that are specific to occupational exposure to coal tar to assess the relationship. Studies on the topical use of coal tar therapy are often contaminated by the combined effect of other known carcinogenic exposures such as ultraviolet light, a known human carcinogen, used in PUVA therapy. **There is a need for further well-conducted epidemiological studies of populations exposed to coal tar and its by-products** to ascertain whether coal tar is carcinogenic to skin after prolonged contact in an occupational setting.