

Aug 21, 2015

Public statement from Anne LeHuray PhD
on behalf of the Pavement Coatings Technology Council
to the

Scientific Advisory Board (SAB) Chemical Assessment Advisory Committee (CAAC) for the
review of the Draft Benzo[a]pyrene (BaP) IRIS Assessment.

Comments submitted to the SAB CAAC via email to Diana Wong

Good Afternoon,

I am speaking today on behalf of the Pavement Coatings Technology Council (PCTC). It is clear from the draft report that all of the members of the Benzo(a)Pyrene (BaP) panel have put much time and effort into the review of the draft IRIS document. Thank you for taking on this task, and for your thorough approach.

My comments are again focused on the hazard assessment in the draft IRIS assessment. Particularly on available information about human exposures to PAH-containing materials.

1. **The literature search should include keywords focused on epidemiology or other human exposure studies.** The draft report recommends that the keywords used in the literature search should be comprehensive and specifically mentions including additional target organs and effects. This recommendation is based on an absence of information about certain organs and effects in both the search strategy and the document as a whole. The search strategy also did not include keywords pertaining to human exposure studies and other aspects of hazard assessments. It seems probable that the reason the entire coal tar pharmaceutical literature was initially overlooked (see Figure LS-1) was from the absence of terms associated with hazard assessment in the search strategy. We ask the panel to point out that the search strategy should also include keywords relevant to hazard assessment.
 2. **The draft hazard assessment should be revised using systematic review techniques.** The SAB's draft report recommends that EPA consider additional studies of occupational exposure to BaP-containing substances and focuses particular attention on reviewing evidence of skin cancer in occupational exposure studies. We agree that the draft IRIS assessment would greatly benefit from additional attention to the quality and risk of bias of occupational and therapeutic exposure studies. As part of our review of the original literature used by EPA (via the IARC hazard identification reported in Baan et al., 2009) as evidence of skin cancer in cohorts exposed to PAH-containing materials, we found many studies that seemed not of sufficient quality for dermal cancer hazard identification. In his systematic review of evidence of skin cancer among populations exposed to coal tar, Spinelli et al. (2012) found only three studies of patients treated with coal tar-based pharmaceuticals met the quality and risk of bias criteria of his systematic review strategy. Further, the systematic reviews of occupational studies focused on respiratory and urinary
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tract cancers by Bosetti et al. (2007) and Rota et al. (2014) found modest risks that could be due to bias or confounding factors.

- 3. We agree that studies of therapeutic use of coal tar medications are not useful for slope factor derivation, but disagree that they do not inform hazard identification.** Attached to the written version of these comments is a photograph of the application of coal tar to a patient undergoing Goeckerman treatment in a clinical setting. FDA limits over-the-counter coal tar preparations to a maximum 5%. No such maximum concentration is applied in clinical settings as there is little evidence of adverse outcomes at any dose. With little evidence of unintended response, quantification of dose-response (and therefore a slope factor) is problematic, and these studies are not useful for this purpose. However, in the draft BaP IRIS assessment, the body of coal tar pharmaceutical literature is dismissed as being uninformative with little explanation. The draft SAB report expresses agreement with EPA's approach, stating:

The issue of the lack of an excess of skin tumors observed in most studies of therapeutic use of coal tar was discussed (Jones et al. 1985; Muller and Kierland 1964). The SAB agrees with the EPA that many of these studies suffer from small sample size, inadequate followup and a large potential for exposure misclassification. In addition, the skin of psoriasis patients who receive these treatments is not normal skin, which may have affected the outcome of the studies. The limitations of these studies make them largely uninformative with regard to the question of whether BaP induces skin cancer in humans. The historic studies of an excess of scrotal cancers in chimney sweeps, and more recent studies demonstrating an excess risk in asphalt workers, are consistent with exposure to BaP being a risk factor for skin cancer. (p. 19, lines 32-40)

Whereas some older studies of therapeutic uses of coal tar may be characterized by small sample size or inadequate follow up, a recent studies by Roelofzen et al. (2010) should be considered to have sufficient power to confirm observations made in previous studies. In their 2010 study, the cohort included 13,200 psoriasis or eczema patients with a median follow-up duration of 21 years. Exposure misclassification must always be taken into account in retrospective studies. The Roelofzen study confirms nearly a century's worth of studies of patients using coal tar therapies on their skin. Regarding differences between normal an psoriatic skin in humans, an elucidation of the literature seems called for.

In contrast, the historic (on might say anecdotal) study of London chimney sweeps is confirmed by NONE of the penecontemporaneous studies of chimney sweeps elsewhere in Europe and in the United States. Attribution of credibility to one low quality study that confirms a point of view while dismissing as "largely uninformative" multiple low to medium to high quality studies that point to a different conclusion could be said suggest a risk of bias.

We urge the SAB to recommend that EPA consider the coal tar pharmaceutical literature in conjunction with occupational exposure studies of PAH-exposed industries (including 18th and 19th century chimney sweeps who did not get scrotal cancer) as well as the evidence of differences between mouse and human skin in evaluating whether BaP is a human dermal carcinogen.

4. **The existing evidence does not support classification of BaP as a human carcinogen. There exists no “strong evidence” that key precursor events occur in humans. There is no “strong support” for this proposition as (1) there is only modest – and possibly biased and/or confounded - evidence of an excess of lung tumors among PAH-exposed humans and (2) equivocal to no evidence of an excess of other anticipated effects (bladder cancer, dermal cancer).** The inadequacies (noted previously) in the draft IRIS hazard assessment have resulted in a mischaracterization of the human cancer hazard of PAH-containing substances. Considering the SAB’s deliberations, it seems clear that the SAB believes that BaP as an individual compound may, based on MOA arguments, be anticipated to be a human carcinogen. However, we believe that well-conducted modern studies of populations exposed to PAH-containing compounds either occupationally or therapeutically do not provide the “strong evidence” required to meet criteria 3 or 4 of EPA’s Cancer Guidelines (EPA, 2005). We urge the SAB to withhold its endorsement of the “human carcinogen” classification of PAH-containing materials, without necessarily fully agreeing with FDA’s “generally recognized as safe and effective” classification. Alternatively, the SAB could make clear that the endorsement applies only to BaP individually based on MOA considerations. We ask the SAB to recommend that EPA revise the hazard assessment using systematic review techniques and taking the entire body of epidemiological literature as well as relevant literature on species differences into account before it endorses EPA’s proposed classification.

Thank you for your attention.

CITATIONS

- Baan, R., Grosse, Y., Straif, K., Secretan, B., El Ghissassi, F., Bouvard, V., Coglianò, V. (2009). A review of human carcinogens—Part F: Chemical agents and related occupations. *The Lancet Oncology*, 10(12), 1143-1144. doi:[10.1016/S1470-2045\(09\)70358-4](https://doi.org/10.1016/S1470-2045(09)70358-4)
- 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
- Cogliano, V. (2015). Memorandum to Dr. D. Wong titled *Post-peer-review comment by Dr. Anne LeHuray regarding report by Dr. John J. Spinelli*. 21 May. Available at <http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/32619301836A190D85257DB2005F2B69?OpenDocument>
- 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
- Roelofzen, J. H. J., Aben, K. K. H., Oldenhof, U. T. H., Coenraads, P.-J., Alkemade, H. A., van de Kerkhof, P. C. M., Kiemeneij, L. A. L. M. (2010). No Increased Risk of Cancer after Coal Tar Treatment in Patients with Psoriasis or Eczema. *J Invest Dermatol*, 130(4), 953-961.
- 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*. Retrieved from http://www.worksafebc.com/regulation_and_policy/policy_consultation/assets/pdf/PrimarySkinCancerCertainOccupationalExposuresComplete.pdf?_ga=1.260629197.1503806911.1431809356



Patient undergoing coal tar application
as part of Goeckerman treatment.

Photo courtesy of the University of Michigan Health System