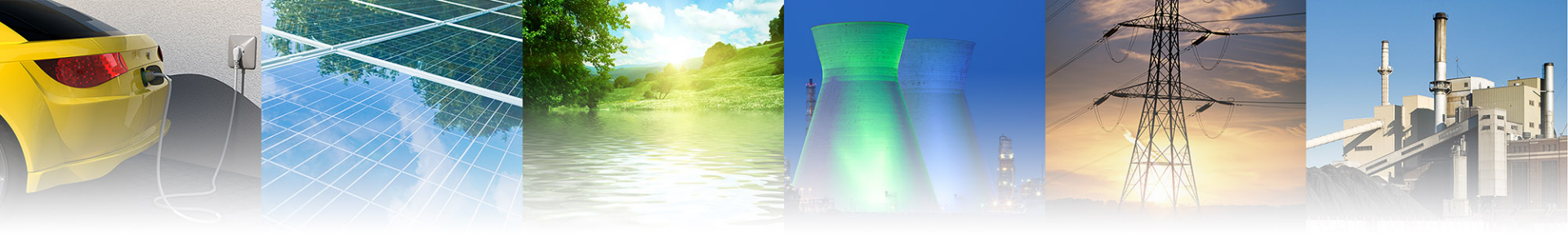

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Comments on the Draft Benzo(a)Pyrene IRIS Assessment

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IRIS Bimonthly Meeting
Arlington, VA
December 13, 2013

Major Points Made in Submitted Written Comments

1. The IRIS document mischaracterizes the weight of evidence that benzo(a)pyrene causes skin cancer in humans.
2. The IRIS document mischaracterizes the weight of evidence that BaP causes lung cancer in humans.
3. Forestomach tumor data should not be used to derive the Oral Slope Factor.
4. With regard to the derivation of the Inhalation Unit Risk, the only available inhalation study (Thyssen et al., 1981) is not suitable for dose-response modeling.
5. Notwithstanding the inadequate weight of evidence that BaP causes skin cancer in humans, a Dermal Slope Factor should not be derived.
6. Mouse skin overestimates carcinogenic risks in human skin.
7. The cancer risks presented in the IRIS document suffer from a lack of real-world validation.

Weight of Evidence for BaP and Skin Cancer

- Studies cited in the document are dated, reference certain occupational exposures more than 100 years ago
- Many of the studies cited are case reports, not epidemiologic studies
- Exposures cited in documents are complex and consist of more than just BaP; workers were exposed to other PAHs and many other chemical and non-chemical agents
- No contemporary epidemiology studies that demonstrate that BaP is a cause of human skin cancer in the modern world
  - In fact, just the opposite: modern epidemiology studies in chimney sweeps (Pukkala et al., 1995) and coal tar pharmaceutical users (e.g., Roelofzen et al. (2010) and others) show no increase in skin cancer

Weight of Evidence for BaP and Lung Cancer

Only three Tier I studies are cited in the document: many limitations

- **Armstrong and Gibbs (2009):** study in aluminum smelter workers exposed to PAH-containing mixtures, petroleum coke and coal tar pitch. Significant increase in SMR but lung cancers cannot be attributed to BaP exposure; smoking may play key role.
- **Spinelli et al. (2006)**: study in aluminum plant workers, did not have vapor-phase BaP measurements so true dose is underestimated. Neither cancer incidence nor mortality was significantly increased for lung cancer. Significant trend of increasing lung cancer incidence with increasing particulate BaP.
- **Xu et al. (1996):** Nested case-control study of lung cancer in iron and steel workers. Exposure assessment not clearly described (dust/BaP). Calculation of ORs not clearly described. ORs for lung cancer elevated in several groups (some with BaP exposure, some without). Cancer risk associated with total dust (strongest), silica dust and BaP. Recommend excluding this study.

Use of Forestomach Tumor Data

- With regard to the derivation of the Oral Slope Factor (OSF), forestomach tumors are not relevant to the assessment of human health and should therefore not be used for dose-response modeling.
- Humans do not have a forestomach or other organ that holds food prior to entry to the stomach, so BaP in food ingested by humans travels through the esophagus quickly before entering the stomach.
- The contact time of BaP in food with esophageal tissues is fast in both rodents and humans, so tumor incidence data from rodent esophageal tissue is a much more appropriate dataset for estimating human risk.
- More appropriate usage of esophageal tumors from Beland and Culp (1998) for benchmark dose modeling leads to an oral slope factor of 0.2 $(mg/kg\text{-}day)^{-1}$.

Suitability of Thyssen et al. (1981) for Derivation of an IUR

The only available inhalation study (Thyssen et al., 1981) is not suitable for dose-response modeling

- Confusion regarding exposure concentrations for both exposed and control animals
- Extremely high doses (47 mg/m^3 at highest dose, for short periods of time) leads to particle overload and exceedence of MTD
- Highest dose greater response than middle dose, no response at lowest dose (= threshold)
- Lack of clarity regarding number of animals, number of tumors observed, and dosages used in the study
- Data from Pauluhn et al. (1985) should be procured and examined

Derivation of Dermal Slope Factor

A DSF should not be calculated for multiple reasons:

- Dermal dosimetry is not amenable to dose-response assessment
  - Dermally administered BaP not cleared quickly as are oral doses; builds up in “depot” or “reservoir”
  - Repeated doses increase the depot dose: true daily skin dose >> daily administered dose
  - Average daily dose is irrelevant/inappropriate for dose-response assessment
- Inadequate and poorly defined dosimetry
  - Surface area of application unknown
  - Verification of BaP concentrations not described
- Exceedence of Maximally Tolerated Dose (MTD)
- Dismissal of 13 key studies that yield lower DSFs

Overestimation of Carcinogenic Risks to Humans Using Mouse Skin

- Humans exposed to high levels of BaP and other potentially carcinogenic PAHs do not develop skin cancer
  - Coal tar pharmaceutical product users: 20 key studies not cited by EPA, all negative for skin cancer
- Mouse skin more permeable to chemicals, including BaP, than is human skin or other animal skin
- Mouse skin known to be more sensitive to PAH-induced skin tumorigenesis than is human skin
  - Human skin xenograft model literature
- PAH-induced mouse skin tumors have a different genetic signature than human skin tumors

Real-World Validation

- Humans exposed to high levels of BaP and other potentially carcinogenic PAHs do not develop skin cancer
  - Assuming the proposed DSF is correct, the estimated lifetime excess risk of cancer is 1.65E-1 (using EPA's 1993 RPFs)
  - In the coal tar pharmaceutical user literature, a risk of 2 in 10 would have easily been detected, but no increases in skin cancer have been seen
- Proposed DSF would predict noticeable population-wide increases in skin cancer
  - Translates into potentially carcinogenic PAHs causing 10% of all skin cancers in the United States

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