



*We must develop new perspectives and new methods for estimating the risk of environmental PAHs on the basis of new information.*

### To BaP or Not to BaP? That Is the Question

Benzo[*a*]pyrene (BaP), a polycyclic aromatic hydrocarbon (PAH) and animal carcinogen, is used by regulators as the basis for quantitative risk estimation of PAH-containing combustion by-products (1). Is BaP an appropriate predictor of cancer risk for products of incomplete combustion?

A multidose, 2-year (chronic) feeding protocol developed by the National Institute of Environmental Health Sciences is a study design for identifying and characterizing chemicals that pose a cancer risk. The National Center for Toxicological Research (NCTR) of the U.S. Food and Drug Administration and EPRI used this protocol to study tumor outcomes in mice fed BaP and coal tar (2). Coal tar is a BaP-containing material found in Superfund sites and in sites once used in the production of manufactured gas.

Tumor incidence was very different for coal tar and BaP. Coal tar caused tumors in lung, skin, forestomach, small intestine, and liver and also caused hemangiosarcomas and histiosarcomas in various organs. BaP caused tumors in forestomach, tongue, esophagus, and larynx.

In mice fed coal tar, the lung was the most sensitive organ site for tumor formation. In mice fed BaP, the forestomach was the most sensitive site for tumor formation. Significantly, BaP did not induce lung tumors, even though there was evidence that BaP or an active metabolite of BaP had reached lung tissue (3). Ingested coal tar is a systemic tumorigen; ingested BaP is a contact tumorigen.

When an agent causes tumors in more than one site, as is the case for ingested coal tar and BaP, tumor incidence in the most sensitive tissue site is used for risk assessment. In the NCTR/EPRI study, health risks of coal tar would be based on lung tumor incidence and health risks of BaP would be based on forestomach tumor incidence. Gaylor et al. (4) concluded that "... carcinogenicity of coal tars cannot be fully accounted for by BaP content [of coal tar] since BaP alone did not induce tumors of the lung."

The findings of the 2-year feeding study are consistent with other data on the contribution of BaP to lung tumor induction by environmental PAHs. In 1972 the Committee on Biological Effects of Atmospheric Pollutants of the National Academy of Sciences evaluated the relationship of BaP dose and lung cancer mortality. Based on epidemiologic evidence from urban dwellers, British gas workers, and topside coke-oven workers, the committee concluded that a BaP lung cancer mortality ratio relationship "lacks plausibility" because an increased dose increment of 100-fold between the urban resident and the British gas worker hardly increased the cancer mortality ratio. On the basis of implantation studies in the rat, Grimmer et al. (5) estimate that BaP contributes between 0.17 and 4% of the lung carcinogenic potency of condensates from diesel and gas engine exhaust, flue gas from residential furnaces, and sidestream cigarette smoke.



The lack of lung tumorigenicity of ingested BaP contrasts with the extensive body of information that demon-

strates the efficacy of BaP for inducing skin tumors in mice when applied directly to skin. The ability to form skin tumors after dermal application contributes considerably to the weight of evidence approach used to establish whether a PAH is a suspected human carcinogen. However PAH metabolism is different in different organs. Mouse skin has some metabolizing enzymes in common with mouse liver, but lacks others (6). For BaP, tumorigenicity in skin following topical administration does not predict tumorigenicity in lung following ingestion.

Clearly the route of administration plays a role in tumorigenesis because BaP induces lung tumors when administered by intraperitoneal injection or oral intubation, at least in a susceptible strain of mice (7,8). For regulatory purposes, laboratory studies using a route of administration consistent with environmental exposure are preferred. Thus ingestion, inhalation, or topical administration are preferred over oral intubation, intratracheal instillation, surgical implantation, or intraperitoneal injection.

Determining the cancer risk of any chemical requires knowledge of its potency. BaP potency is currently calculated from data in two studies. Neither study was designed or conducted for the purpose of developing a BaP cancer potency factor, and neither is adequate for this application. In the first study (9), forestomach tumor incidences were determined when BaP was fed to mice of different ages for varying durations, with varying follow-up times and uncertain pathological evaluations. The preferred protocol is a lifetime exposure in mature rodents using rigorous laboratory procedures including the highest quality pathologic evaluation. In the second study (10), single tumor incidences that individually were not significant from three different sites (esophagus, larynx, and forestomach) were combined and evaluated as if they were a single tumor type. The preferred protocol bases the cancer potency factor on tumor incidence in the most sensitive individual site.

Using the data from the NCTR/EPRI study, which incorporated the preferred rigorous laboratory procedures, Gaylor et al. (11) calculated a potency factor for BaP of 1.2/mg/kg/day. This is only one-sixth the value reported in the Integrated Risk Information System (IRIS) of the U.S. Environmental Protection Agency (U.S. EPA) and derived from the less-than-adequate studies. Because the potency factors for other PAHs in IRIS rely on the potency factor for BaP, any change in the BaP potency factor would change the potency factors for all other PAHs.

Environmental PAHs are always found as complex mixtures, but most laboratory studies are conducted using a single chemical. Results from studies with a single agent may not predict results when

that agent is part of a mixture of other chemicals. BaP in the presence of other PAHs in a mixture formulated to approximate their relative abundance in an environmental coal tar (12) did not induce tumors, whereas BaP by itself did (13). One interpretation is that the other PAHs reduced the tumorigenic effectiveness of BaP. If this is generally true, the actual potency of BaP in environmental PAHs may be much less than the potency determined in studies of BaP alone. Regulatory determinations based currently on the IRIS BaP potency may be too conservative.

Taken together, these data strongly suggest that a regulatory scheme based on BaP to estimate the risk posed by coal tars and other environmental PAHs is inconsistent with the role of BaP in human lung cancers, the health outcome upon which regulation should be based. Yet there is a need to address and correct the potential human health risk posed by PAH-contaminated sites. Are there alternatives to BaP for estimating risks of PAHs?

One approach considers an environmental PAH such as coal tar as if it were a single chemical. This method is supported by the analysis of Gaylor et al. (11), who found that estimates of potency for lifetime tumor risk at different tissue sites for two different coal tars in the NCTR/EPRI study varied by a factor of < 2. More data are needed to ensure that this is true for other coal tars and perhaps for other environmental PAHs. A shortcoming is that weathered PAHs in soil tend to differ from native tars in their PAH composition. Risk could be overestimated or underestimated depending on whether the carcinogenic factor is enriched or depleted.

Another approach is to identify a lung tumor-inducing PAH better suited for risk assessments than BaP. A recent discovery may point the way. 7H-benzo(*c*)fluorene is a little-studied PAH that had not been implicated in cancer outcomes because it did not induce mouse skin tumors on dermal exposure (14,15). It is generally accepted that tumor formation by PAHs is associated with the formation of genetic damage, termed DNA adducts. Now, researchers have found that 7H-benzo(*c*)fluorene is likely to be responsible for significant levels of DNA adducts in the lungs of mice fed coal tar (16). 7H-benzo(*c*)fluorene administered by intraperitoneal injection induces lung tumors in susceptible mice (17), suggesting a role for 7H-benzo(*c*)fluorene in coal tar-induced lung tumors. Studies are currently under way to determine if ingested 7H-benzo(*c*)fluorene alone, or in the presence of other PAHs, induces lung tumors.

Experimental data indicate that the extensive knowledge scientists and regulators have on carcinogenesis by BaP is of limited value when estimating the human health risk of environmental PAHs. The science currently supporting the U.S. EPA's use of BaP for risk assessment of PAHs was not designed for that purpose. Because there are so many sources of environmental PAHs, it is especially important that PAH risk be evaluated appropriately and accurately. We must develop new perspectives and new methods for estimating the risk of environmental PAHs on the basis of new information. We must be especially aware of tumor induction following ingestion and inhalation because these constitute major routes of exposure in

humans. We must appreciate the contributions to human lung tumor incidence of PAHs that have been neglected because they do not induce tumors when they are painted on mouse skin.

**Lawrence S. Goldstein**  
EPRI  
Palo Alto, California  
E-mail: lgoldste@epri.com

## REFERENCES AND NOTES

1. U.S. EPA. Health Effects Assessment of Polycyclic Aromatic Hydrocarbons (PAHs). EPA 540/1-86-013. Cincinnati OH:Environmental Criteria and Assessment Office, 1984.
2. Culp SJ, Gaylor DW, Sheldon WG, Goldstein LS, Beland FA. A comparison of the tumors induced by coal tar and benzo(a)pyrene in a two year bioassay. *Carcinogenesis* 19:117-124 (1998).
3. Culp SJ, Warbritton AR, Smith BA, Li EE, Beland FA. DNA adduct measurements, cell proliferation, and tumor mutation induction in relation to tumor formation in B6C3F1 mice fed coal tar or benzo(a)pyrene. *Carcinogenesis* 21:1433-1440 (2000).
4. Gaylor DW, Goldstein LS, Krewski D, Moolgavkar S. Recent bioassay results on coal tars and benzo(a)pyrene: implications for risk assessment. *Regul Toxicol Pharmacol* 28:178-179 (1998).
5. Grimmer G, Brune H, Dettbarn G, Jacob J, Misfeld J, Mohr U, Naujack K-W, Timm J, Wenzel-Hartung R. Contribution of polycyclic aromatic hydrocarbons and other polyaromatic compounds to the carcinogenicity of combustion source and air pollution. In: *Genetic Toxicology of Complex Mixtures* (Waters MD, Waters FB, Lewtas J, Moore MM, Nesnow S, eds). New York:Plenum Press, 1990:127-140.
6. Einhoff HJ, Story WT, Marcus CB, Larsen MC, Jefcoate CR, Greenlee WF, Yagi H, Jerina DM, Amin S, Park SS, et al. Role of cytochrome P450 enzyme induction in the metabolic activation of benzo[*c*]phenanthrene in human cell lines and mouse epidermis. *Chem Res Toxicol* 10:609-617 (1997).
7. Stoner GD, Krol RA, Norlund DJ, Greisiger E, Morgan M. Test for carcinogenicity of benzo(a)pyrene, pyrene, 2-acetylaminofluorene and 4-acetylaminofluorene in the strain A mouse lung tumour bioassay. In: *Evaluation of Short-term Tests for Carcinogens*, Volume 2 (Ashby J, deSerres FJ, Shelby MD, Margolin BH, Ishidate M Jr, Becking GC, eds). Cambridge, UK:Cambridge Press, 1988:2.30-2.34.
8. Stoner GD, Greisiger EA, Schut HA, Pereira MA, Loeb TR, Klauing JE, Bransletter DG. A comparison of the lung adenoma response in strain A/J mice after intraperitoneal and oral administration of carcinogens. *Toxicol Appl Pharmacol* 72:313-323 (1984).
9. Neal J, Rigdon RH. Gastric tumors in mice fed benzo(a)pyrene: a quantitative study. *Texas Rep Biol Med* 23:553-557 (1967).
10. Brune H, Deutsch-Wenzel RP, Habs M, Ivankovic S, Schmah D. Investigation of the tumorigenic response to benzo(a)pyrene in aqueous caffeine solution applied orally to Sprague-Dawley rats. *J Cancer Res Clin Oncol* 102:153-157 (1981).
11. Gaylor DW, Culp SJ, Goldstein LS, Beland FA. Cancer risk estimation for mixtures of coal tars and benzo(a)pyrene. *Risk Anal* 20:81-85 (2000).
12. Chaloupka K, Steinberg M, Santostefano M, Rodriguez LV, Goldstein L, Safe S. Induction of Cyp1a-1 and Cyp1a-2 gene expression by a reconstituted mixture of polynuclear aromatic hydrocarbons in B6C3F1 mice. *Chem Biol Interact* 96:207-221 (1995).
13. Goldstein LS, Weyand EH, Safe S, Steinberg M, Culp SJ, Gaylor DW, Beland FA, Rodriguez LV. Tumors and DNA adducts in mice exposed to benzo[*a*]pyrene and coal tars: implications for risk assessment. *Environ Health Perspect* 106(suppl 6):1325-1330 (1998).
14. Bachmann WE, Cook JW, Dansi A, de Worms CGM, Haslewood GAD, Hewett CL, Robinson AM. The production of cancer by pure hydrocarbons - IV. *Proc R Soc London Ser B* 123:343-368 (1937).
15. LaVoie EJ, Tulley-Freilior L, Bedenko V, Girach Z, Hoffmann D. Comparative studies on the tumor initiating activity and metabolism of methylfluorenes and methylbenzofluorenes. In: *Chemical Analysis and Biological Fate: Polynuclear Aromatic Hydrocarbons*, 5th International Symposium (Cooke M, Dennis AJ, eds). Columbus OH, Battelle Press, 1981:417-427.
16. Koganti A, Singh R, Rozett K, Modi N, Goldstein LS, Roy TA, Zhang F-J, Harvey RG, Weyand EH. 7H-Benzo(*c*)fluorene: a major DNA adduct-forming component of coal tar. *Carcinogenesis* 21:1601-1609 (2000).
17. Weyand E. Personal communication.