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April 8, 2015

VIA EMAIL

Dr. Diana Wong, Designated Federal Officer ("DFO")
Science Advisory Board SAB Staff Office
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Re: Comments to the SAB Chemical Assessment Advisory Committee ("CAAC") Augmented for the Review of the Draft Benzo[a]pyrene IRIS Assessment (CAACBenzo[a]pyrene Panel)

Dear Dr. Wong:

The Utility Solid Waste Activities Group ("USWAG") submits these comments to the Environmental Protection Agency ("EPA" or the "Agency") Science Advisory Board ("SAB") Chemical Assessment Advisory Committee ("CAAC") Augmented for the Review of the Draft Benzo[a]pyrene ("BaP") Integrated Risk Information System ("IRIS") Assessment ("CAAC Panel").[1] USWAG appreciates the opportunity to provide comment to the CAAC Panel as it reviews EPA's September 2014 draft toxicological review of BaP ("2014 Draft BaP Assessment"). These comments are supported by and incorporate by reference the technical report prepared by Geosyntec Consultants entitled "Comments on EPA's Draft IRIS Toxicological Review of Benzo[a]pyrene (External Review Draft – September 2014)," prepared for USWAG and attached hereto as "Attachment A" (hereinafter referred to as the "Geosyntec Report").

USWAG, formed in 1978, is a consortium of approximately 130 electric utilities, power producers, utility operating companies, and utility service companies located throughout the country, including the Edison Electric Institute ("EEI"), the American Gas Association ("AGA"), the American Public Power Association ("APPA"), and the National Rural Electric Cooperative Association ("NRECA").[2] Together, USWAG members represent more than 73% of the total

[1] *See* 80 Fed. Reg. 2415 (Jan. 16, 2015).

[2] EEI is the principal national association of investor-owned electric power and light companies. AGA is the principal national association of investor-owned natural gas utilities. APPA is the national association of publicly-owned electric utilities. NRECA is the national association of rural electric cooperatives. Throughout these comments, we refer to our industry as the "utility" or "electric utility" industry. This term is intended to include those portions of the industry and those

electric generating capacity of the United States, and service more than 95% of the nation's consumers of electricity and 92% of the nation's consumers of natural gas.

The chemical risk assessments performed by EPA for inclusion in IRIS drive cleanup levels throughout the country and are therefore of great interest to USWAG members, collectively the owners and operators of thousands of facilities throughout the country, some of which are the subject of remedial action. These sites include those with historic contamination from manufactured gas plants ("MGPs"), often characterized by contamination from BaP and other polycyclic aromatic hydrocarbons ("PAHs"). USWAG appreciates the effort EPA has made to improve the IRIS process in recent years, including several changes geared towards making the process more transparent and systematic.[3] USWAG agrees that it is imperative that IRIS risk values be based on high-quality, current science, and that these values be presented in a clear and concise manner to ensure that they are properly applied towards the establishment of remediation goals.

The BaP assessment is of particular importance to the utility industry, not only because of the prevalence of BaP at MGP and other utility sites. The implications of the final assessment extend far beyond BaP-driven cleanups. In 2010, EPA proposed an approach for estimating cancer risks from exposures to all PAH mixtures based on the relative potency of BaP, the "index" or "reference" chemical.[4] In other words, the risk values established in the final BaP assessment will drive risk assessment for a broad range of chemicals going forward. Given the large number of sites at which BaP or other PAHs are risk drivers, it is critical that the risk values in the final BaP assessment be derived in a scientifically-sound manner.

In comments submitted to EPA on November 21, 2013 (attached hereto as "Attachment B"), USWAG raised concerns with several aspects of the August 21, 2013 draft BaP risk assessment,[5] including EPA's exclusion of relevant and available data, as well as the Agency's failure to explain how the novel dermal slope factor ("DSF") – the use of which is unprecedented in the IRIS risk assessment context – should be used in site assessment and in the derivation of risk-based cleanup values. These concerns were echoed by several commenters representing a vast range of the regulated community.[6]

USWAG members that generate electricity but do not directly provide electricity to the public and are technically not "utilities."

[3] *See* EPA News Release, "EPA Strengthens Chemical Assessment Process to Protect Public Health" (July 31, 2013), available online at http://www2.epa.gov/newsroom.

[4] *See* 75 Fed. Reg. 8937 (Feb. 26, 2010).

[5] *See* 78 Fed. Reg. 51719 (Aug. 21, 2013).

[6] *See* Docket No. EPA-HQ-ORD-2011-0391, available online at www.regulations.gov.

EPA purports to respond to these and other public comments in Appendix G of the current 2014 Draft BaP Risk Assessment. However, in many instances, including with respect to comments regarding the DSF and the literature survey/selection for BaP, EPA's dismissive explanation reflects an absence of careful consideration regarding the substance of the comments. Many of the problematic aspects of the August 2013 draft assessment have been carried over in, and represent critical flaws of, the current Draft BaP Assessment.

USWAG urges the CAAC Panel to consider EPA's failure to adequately consider and respond to the public comments made by USWAG and others, as well as the Agency's failure to address the underlying issues raised in those comments, as the CAAC Panel continues its review of the Draft BaP Assessment. The most serious scientific and technical shortcomings of the Draft BaP Assessment are discussed in detail in the Geosyntec Report, and include:

- The DSF Does Not Hold Up in a "Real World" Context: As has been explained to EPA by multiple commenters in the context of the August 2013 draft BaP assessment, application of the DSF proposed in the Draft BaP Assessment to real world conditions reveals the DSF to be unreliable. If the proposed DSF were accurate, exposure to BaP and PAH mixtures would be the primary driver of non-melanoma skin cancer ("NMSC"). However, a wealth of epidemiological studies overwhelmingly show that ultraviolet light, not BaP/PAH exposure, is the leading cause of NMSC. Further, long-term studies of dermal exposure to BaP through coal tar preparations used for medical purposes have shown no increased incidence of NMSC as a result of such exposure.

- Use of DSF Results in Unrealistic Risk Levels and Will Drive Unattainable Remediation Targets: The DSF included in the Draft BaP Assessment would drive regional screening levels ("RSLs") and remediation standards throughout the country that would suggest remediation is required for practically all urban soils in the United States. Moreover, the DSF drives an RSL for residential land use scenarios that is lower than or near the detection limit for BaP/ PAHs. This will frustrate and delay cleanups, creating significant hurdles for regulators and regulated entities alike – without any scientifically sound justification.

- Failure to Incorporate Critical National Research Council ("NRC") Recommendations Regarding Risk-of-Bias: In the broader IRIS context, EPA has undertaken significant effort to incorporate recommendations of the NRC regarding the IRIS process, including those set forth in NRC's

2011 report on EPA's Formaldehyde risk assessment,[7] as well as NRC's 2014 review of the IRIS process.[8] One such recommendation is that EPA incorporate risk-of-bias analysis into risk assessments in order to strengthen the systematic review and evidence integration processes. Indeed, in a June 2014 Public Science Workshop, EPA presented a working draft of the Agency's risk-of-bias evaluation framework for application in the risk assessment context. However, in the current Draft BaP Assessment, EPA has wholly ignored this recommendation.

- Failure to Account for Differences in Mouse and Human Epidermis and Dermal Metabolism: The Draft BaP Assessment is based largely on mouse (murine) data. However, a fundamental uncertainty exists in the cross-species extrapolation of mouse-to-human dermal exposure regarding the structural difference in skin between the two species. Simply put, human skin is significantly thicker and less permeable than mouse skin. Though the DSF is derived from mouse data, EPA fails to acknowledge or account for these differences in the Draft BaP Assessment. As was the case with the August 2013 draft BaP assessment, the current Draft BaP Assessment's reliance on mouse data to develop the DSF inappropriately overestimates the risk of human skin cancer resulting from BaP exposure.

These and other concerns are detailed in the Geosyntec Report.

* * * * *

USWAG appreciates the opportunity to comment on the development of this important risk assessment. Please contact USWAG counsel Allison Foley at Venable LLP (202-344-4416) with questions regarding these comments.

Respectfully submitted,

[redacted]

James R. Roewer
Executive Director

[7] NRC, "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde" (2011).
[8] *See* EPA, "National Research Council Review of the IRIS Assessment Development Process" http://www.epa.gov/iris/iris-nrc.htm (May 2014; current as of April 8, 2015).

Attachment A

Geosyntec Report

Geosyntec consultants

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Comments on EPA's *Draft IRIS Toxicological Review of Benzo[a]pyrene*

[External Review Draft – September 2014]

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April 8, 2015

EXECUTIVE SUMMARY

Geosyntec Consultants, Inc. (Geosyntec) has prepared these technical comments for consideration by the Science Advisory Board (SAB) Chemical Assessment Advisory Committee (CAAC) augmented for the Review of EPA's Draft Benzo[a]pyrene (BaP) IRIS Assessment (hereafter "*2014 Draft BaP Assessment*"). Our comments focus primarily on the dermal cancer slope factor (DSF) for BaP, which represents an entirely new endeavor for the IRIS Program. We believe that there are substantial uncertainties related to the development of the DSF and the ultimate utility of this value. We therefore urge the SAB CAAC to carefully scrutinize the basis and methods associated with its derivation, as well as consider the implications of its use in public health and regulatory decision making.

Geosyntec's comments are briefly summarized below. Each of these is discussed in greater detail in the document.

1) **Regional Screening Levels (RSLs) calculated with the proposed Dermal Slope Factor (DSF) are 15-times lower than current RSLs and will generate nearly unattainable remediation targets.** RSLs are used for risk-based decision making, as enforceable remediation standards, and for the evaluation of sampling data associated with due diligence activities. If adopted, the DSF would suggest remedial activities are required for practically all urban soils in the U.S. Additionally, the "new" dermal RSL value for residential land use scenarios is lower than or near the BaP/PAH detection limit in environmental media.

2) **Using the proposed DSF, exposure to urban soils will result in cancer risk above Superfund risk levels.** In their 2014 report, the NRC indicates that values defined in IRIS assessments are usually adopted with no further consideration, even if "safe" levels are found to be below background levels. As U.S. urban soils contain levels of PAHs above residential RSLs, the proposed DSF elicits that exposure to soil would result in skin cancer risk estimates that exceed the Superfund risk range by more than an order of magnitude. Thus, if the DSF were accurate, exposure to BaP and other PAH mixtures would be evidenced as a main driver of non-melanoma skin cancer (NMSC) incidence. In direct contradiction to this is the fact, supported by a wealth of epidemiological studies, that ultraviolet light is the overwhelming cause of NMSC. Further, absolutely no increased incidence of NMSC has been observed in studies of long-term dermal exposure to BaP through coal tar preparations used for medicinal purposes.

3) **The *2014 Draft BaP Assessment* does not incorporate critical NRC recommendations including risk-of-bias analysis.** The NRC recommends incorporation of risk of bias

analysis into IRIS assessments to strengthen the systematic review and evidence integration process. As it stands, no risk of bias analysis is included in the *2014 Draft BaP Assessment*. While appendix F of the report describes a "phased approach" that is being used to implement the NRC recommendations, both of these critical NRC recommendations are missing from the current draft. Further, no charge question regarding whether EPA has thus far successfully implemented the NRC recommendations was proposed for public comment.

4) **Important differences in mouse and human epidermis and dermal metabolism are not addressed or accounted for in the derivation of the DSF.** A fundamental uncertainty in the cross-species extrapolation of mouse-to-human dermal exposure studies is the structural difference in skin between the two species. In human skin, chemicals must permeate the 50 to 600 micrometer (um) thick epidermis in order to exert sustainable mutagenic effects that can lead to skin cancer. In stark contrast, only a 25 um thick, three-cell layer epidermis separates cellular targets from BaP-induced mutation in mice. Additionally, because of a much higher hair follicle density, mouse skin is more permeable to applied chemicals. Further, levels of the enzyme required to metabolize BaP, aryl hydrocarbon hydroxylase (AHH), are higher in mouse skin, thus, mouse skin produces more carcinogenic, reactive metabolites of BaP than does human skin.

5) **Murine cells require fewer mutational events than human cells for malignant transformation.** Murine cells require two mutational events while human cells require at least five mutational events for malignant transformation that can result in skin cancers. The lower mutational threshold and resultant enhanced cancer susceptibility is due in part to longer telomeres which allow pre-cancerous cells to proliferate extensively. In humans, the gene encoding telomerase, which maintains telomere length, is repressed in nearly all cells; in mice, telomerase is constitutively expressed. The ease of rodent cell transformation in comparison to human cell transformation has been unequivocally established in the scientific community for decades, yet is not addressed in the 2014 *Draft BaP Assessment*.

6) **Evidence of differential carcinogenic requirements of murine and human skin can be visualized in human-to-mouse xenograft models.** Xenograft models illustrate the differential cancer threshold in mouse in human skin because grafted human skin does not develop tumors in response to BaP exposure while surrounding murine tissues do. Further, the grafted human skin conserves epidermal barrier function (a major factor in percutaneous absorptivity). While most xenograft models utilized immunocompromised

mice as graft hosts, much of the immune system is present and functional, including Natural Killer (NK) cells, which are integral components of the early antitumor response. The *2014 Draft BaP Assessment* inappropriately marginalizes the data gleaned from studies utilizing these powerful FDA-approved tools.

Geosyntec consultants

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INTRODUCTION

The comments presented herein focus on the proposed DSF for BaP because of what we perceive as an obvious disconnect between the DSF value, when considered in terms of its anticipated use in regulatory decision making, and the more robust information and data on the etiology and incidence of skin cancers in humans. This issue will have significant implications for public health and regulatory decisions in wide variety of settings and contexts.

The IRIS Program's responses to concerns of this nature have generally asserted that such issues belong under the umbrella of "risk management" rather than "risk assessment" under the familiar Red Book paradigm (NAS 1983) [1], and are thus beyond the scope of the IRIS Program. However, the 2009 National Research Council (NRC) report "Science and Decisions: Advancing Risk Assessment" recommends a paradigm shift that acknowledges the inexorable linkages between these two concepts (NRC 2009) and recommends that the risk assessment should proceed "*only after the risk-management questions that risk assessment should address have been clearly posed, through careful evaluation of the options available to manage the environmental problems at hand*"[2].

Rather than serving this purpose, the proposed DSF will actually create new concerns for risk managers that eclipse any risk associated with dermal exposures that they currently encounter in decision making associated with exposures to BaP and other polycyclic aromatic hydrocarbons (PAHs) in the environment.

SPECIFIC COMMENTS

1. <u>Impractical Consequences of the Dermal Slope Factor</u>

The Draft BaP Assessment proposes a novel DSF that is intended to provide estimates of skin cancer risk per microgram (ug) of BaP applied to the skin surface per day (i.e., units of ug/day). As detailed below, the proposed DSF will result in impractically low and potentially unattainable risk-based screening levels and remediation standards that will inevitably increase the costs of conducting environmental assessments, developing remediation strategies, and managing environmental exposures.

Appendix G of the *2014 Draft BaP Assessment* presents example "dermal dose and risk calculations" using the proposed DSF. These calculations were provided in response to comments suggesting that EPA perform calculations to evaluate whether the DSF is scientifically supportable. Rather than reflecting how IRIS toxicity values are used in the "real world," the EPA's example calculations utilized a number of central tendency exposure parameters instead of the more conservative reasonable maximum exposure

(RME) parameters required by EPA and other regulatory agencies in risk assessment reports and other regulatory submittals.

1.1 "Real World" Illustration Using EPA's Regional Screening Levels

To better illustrate the real world implications of the proposed DSF, Table 1 (below) shows a comparison between the current (January 2015) EPA Regional Screening Levels (RSLs) for BaP in soil for residential and industrial land use scenarios, and the prospective residential and industrial soil RSLs derived using the toxicity values proposed in the *2014 Draft BaP Assessment*.

- RSLs are developed and regularly updated by the EPA Superfund Program to provide default chemical-specific and media-specific risk-based "screening" values for residential and industrial exposure scenarios. The RSLs are derived using standard equations and default exposure factors intended to reflect RME conditions.

- RSLs are widely used throughout the U.S. and their use extends well beyond the Superfund risk assessment framework. For example, RSLs have been adopted by reference by many states for use in various regulatory programs that incorporate risk-based decision making. In cases where states have limited flexibility in risk-based remedial approaches, the RSLs can become *de facto* remedial standards.

- RSLs are also frequently used for the evaluation of sampling data associated environmental due diligence activities. In this setting, one party to a real estate transaction may use the RSLs as leverage to extract concessions from the opposing party. RSLs therefore have the potential to significantly complicate and delay real property transactions.

Table 1. RSL Comparison

	Current IRIS Values	2014 Proposed IRIS Values
Residential RSL (mg/kg)		
Ingestion	0.021	0.15
Inhalation	1,254	2,298
Traditional Dermal (systemic endpoint)	0.057	0.41
New Dermal (skin endpoint)	NA	0.001
RSL (excluding dermal endpoint)	0.015	0.112
RSL (including dermal endpoint)	NA	0.003
Industrial RSL (mg/kg)		
Ingestion	0.45	3.3
Inhalation	15,163	27,798
Traditional Dermal (systemic endpoint)	0.83	6.0
New Dermal (skin endpoint)	NA	0.013
RSL (excluding dermal endpoint)	0.29	2.12
RSL (including. dermal endpoint)	NA	0.013

Only RSL values for cancer endpoints are shown.
NA = not applicable, endpoint not considered in current RSLs.

The route-specific RSL values for the oral and inhalation exposure pathways increase in proportion to the proposed changes in the oral cancer slope factor (CSFo) and inhalation unit risk factor (URF). Likewise, the RSLs for the "traditional" dermal exposure route, which is calculated using the CSFo adjusted for absorption of BaP into the bloodstream also increases. However, the "new" dermal RSL values for the skin cancer endpoint calculated with the proposed DSF and the information provided in the Appendix G example risk calculations are approximately 15 times lower than the current RSL values that incorporate all three exposure routes. More importantly, the "new" dermal RSL value for residential land use scenarios is lower than the method detection limit for BaP in the most sensitive analytical method (SW-846 Method 8270D-SIM) widely available for the analysis of BaP and other PAHs in environmental media [3].

1.2 Background Levels Yield Implausible Risk Estimates Using the DSF

The Appendix G example calculations actually reinforce reviewer comments about the lack of credibility associated with the proposed DSF because they suggest that residential exposure to 100 ug/kg of BaP in soil, which is described by EPA as "a central estimate of several published measurements of uncontaminated sites," could result in an excess lifetime cancer risk (ELCR) of 7E-05 (or 7 in 100,000) for the dermal pathway alone. This implausible risk estimate is near the upper-end of EPA's acceptable risk range (i.e. 1E-04) under the Superfund program. As discussed in more detail below, consideration of BaP

concentrations in isolation is also suspect because EPA's relative potency factors (RPFs) are almost always used to express concentrations of multiple PAHs in terms of BaP toxic equivalents.

Multiple peer-reviewed studies in the scientific literature document the fact that the levels of PAHs in soils in cities across the U.S. are often considerably higher than the 100 ug/kg value cited for BaP in the Appendix G of the *2014 Draft BaP Assessment* [4-12]. BaP and other PAHs are formed during the incomplete combustion of organic material (e.g. coal, oil, wood, garbage, gasoline, charbroiled meat and tobacco). Although the highest concentrations of these chemicals are usually found in urban areas, these studies reflect the widespread distribution of BaP and other PAHs in soil as a result of both natural and anthropogenic sources. Figure 1 (below) shows the average background concentrations of PAHs expressed as BaP toxic equivalents in U.S. cities and/or regions.

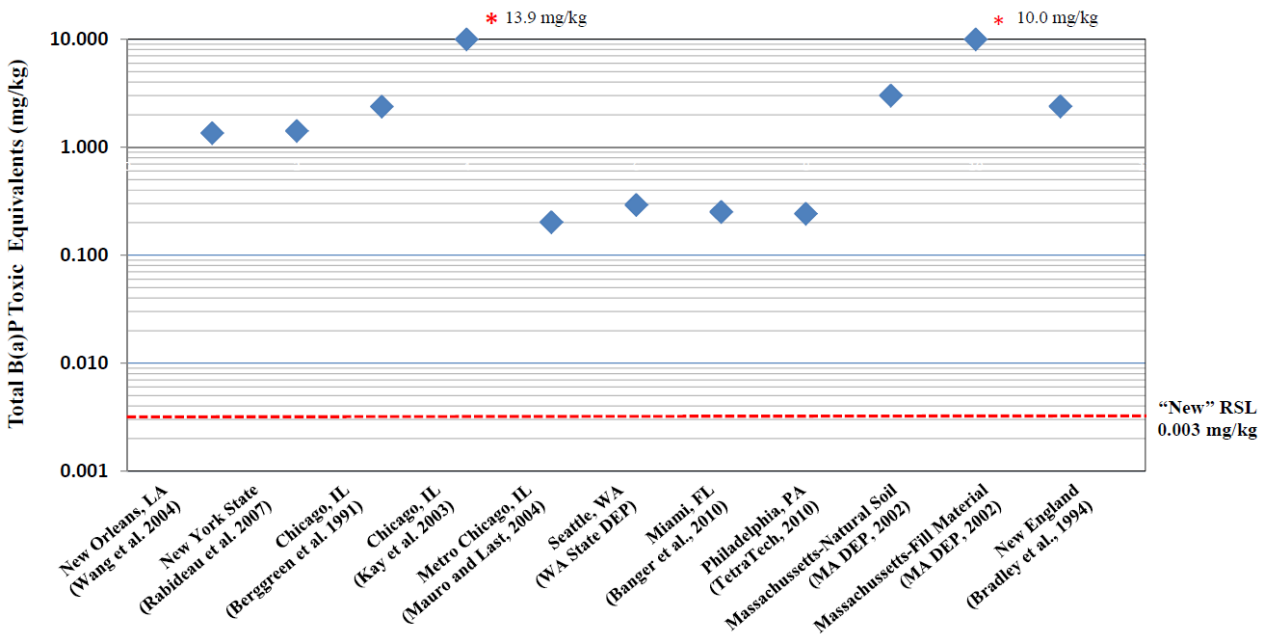

Figure 1. Average BaP Soil Concentrations in U.S. Cities.
This chart shows the average background concentrations of six carcinogenic PAHs expressed as BaP toxic equivalents calculated by Geosyntec using the current EPA RPFs and data from the 10 different background studies identified on the x-axis of the chart. For reference, the EPA RSL for residential scenarios based on the proposed IRIS toxicity values (0.003 mg/kg) is illustrated with the red dashed line.

Considering the fact that the EPA's 100 ug/kg "uncontaminated site" BaP level results in a skin cancer ELCR of 7E-05, the data shown in Figure 1 suggest that exposures to typical background levels of BaP and other PAHs would result in skin cancer risk estimates that

exceed the Superfund risk range by more than an order of magnitude (i.e. ELCR estimates for skin cancer in the range of 1E-03 to 1E-02).

The report for a July 14, 2011 congressional hearing on the IRIS Program that followed the NRC's review of the *Draft IRIS Assessment of Formaldehyde* (discussed in Comment 2) includes the following passage, which is particularly apropos considering the problems associated with the use of the BaP DSF discussed above.

> "*When assessments make determinations that safe levels are below background levels, the IRIS program can reasonably claim that such factors can be weighed later in the risk management process. In reality, IRIS assessments are usually adopted with no further consideration. Some customers use IRIS because it is a useful source of information; while for other customers IRIS is mandatory, and those customers include state agencies. Customers who use IRIS for general information often rely upon other databases to complement an IRIS assessment. Other databases exist, which can provide some help, but for domestic regulatory purposes there is no satisfactory alternative to IRIS. And using an IRIS file as the scientific basis for a regulatory decision is expected and seldom challenged*."

These problems will be compounded if EPA implements the relative potency factors (RPFs) for PAHs as outlined in EPA (2010). In this report, EPA expands the number of individual PAHs with non-zero RPFs from 6 to 24. Under the current RPF framework, BaP has the largest RPF value (1.0), but the 2010 report identifies 6 PAHs with larger RPFs than BaP, ranging from 5 to 60.

This situation will impose significant costs on the regulated community as well as creating problems for EPA risk managers who will undoubtedly struggle with devoting already limited resources to chase background levels of BaP and other PAHs when there is no compelling evidence that these efforts will provide any public health benefit.

2. Incomplete Implementation of NRC Recommendations for the IRIS Program

The NRC recommendations for improving the IRIS Program outlined in Chapter 7 of its review of the *Draft IRIS Assessment of Formaldehyde* (NRC 2011) [13] resulted in a congressionally-mandated process and timeline for EPA to implement the NRC recommendations, including the formation of a standing NRC committee to provide oversight for the changes to the IRIS program. In its initial report entitled *Review of EPA's IRIS Process* (NRC 2014) [14], the NRC acknowledged some of the progress made by the IRIS Program and cited specific examples from the *2013 Draft BaP Assessment* in its initial report. However, that report also identified critical elements that had not been incorporated in the assessment. Appendix F of the 2*014 Draft BaP Assessment* provides a discussion of

the "phased approach" that is being used by the IRIS program to implement the NRC recommendations. However, this Appendix does not address why a number of the critical elements identified in the NRC report (2014) are still missing from the current draft. As discussed below, we believe the failure to address risk-of-bias is a significant deficiency, particularly with respect to the DSF.

2.1 Failure to Address Risk-of-Bias

A key recommendation from the NRC Committee pertains to the development of robust procedures for "Systematic Review and Evidence Integration." An outgrowth of this recommendation is the recognition of "risk-of-bias" assessment frameworks as tools to strengthen the systematic review and evidence integration process for IRIS assessments. (NRC 2014) [14].

NRC (2014) noted that the *2013 Draft BaP Assessment* did not include any discussion of risk-of-bias. In fact, in its discussion of the information presented in the evidence tables, the NRC states, "*there is no assessment of the risk of bias in the studies evaluated, so it is unclear how EPA will meet its goal of assessing the direction and magnitude of bias in epidemiologic or animal studies.*" The *2014 Draft BaP Assessment* is still conspicuously missing any discussion related to the assessment of risk-of-bias for the studies considered in the assessment. This is in spite of the fact that the EPA provided a working draft of a risk-of-bias evaluation framework at a Public Science Workshop in June 2014.

We urge the EPA to revise the Draft BaP Assessment to include a risk-of-bias assessment for the critical studies that it has used as primary data sources for the hazard identification and dose-response assessments. At a minimum, risk-of-bias should be assessed for the following studies: Culp et al. 1998; Thyssen et al. 1991; Arthur D. Little 1989; Sivak et al. 1998; Chen et al. 2012; and Archibong et al. 2002 [15-18].

We also urge EPA to fully consider NRC guidance regarding the conduct of risk-of-bias assessments, which stresses that assessing the "quality" of a study is not equivalent to assessing the risk-of-bias in a study. The NRC states that risk-of-bias relates to "*the internal validity of a study and reflects study-design characteristics that can introduce a systematic error (or deviation from the true effect) that might affect the magnitude and even the direction of the apparent effect*" [14].

This is an important distinction with respect to the critical studies used for the development of the DSF [15, 19], which were conducted according to Good Laboratory Practice (GLP) protocols that should support the generation of quality data. Nonetheless, a number of the issues identified in the public comments on the current and previous Draft BaP Assessments could reasonably be deemed to impart biases that increase the magnitude of the tumorigenic

response in mouse skin ultimately leading to inflated estimates of human risk. For example, one of the solvent vehicles (cyclohexane) used in the study has been shown to have tumor-promoting effects in a mouse skin initiation-promotion model [20]. In addition, the group treated with the highest concentrations of BaP experienced significant irritation and scabbing which has long been recognized to promote tumor growth and malignant transformation [21]. The extent of scabbing observed in the high BaP treatment group in this experiment provides sufficient evidence to conclude that the maximum tolerated dose (MTD) was exceeded, limiting the utility of the tumor data from this experiment for dose-response modeling [22].

2.2 No Charge Questions to the SAB CAAC on Implementation of NRC Recommendations

The charge questions provided by EPA to external reviewers of the *2013 Draft BaP Assessment* included a question related to the assessment of "EPA's success thus far" in implementing the NRC recommendations. Given that most, if not all, of the SAB CAAC members are familiar with the NRC recommendations and the resulting changes in the IRIS Program, it would have been appropriate to include a charge question to the committee members on this topic. Despite the absence of such charge questions, we encourage the committee members to provide input on this issue.

3. Use of Mouse Skin Painting Data Impart a High Bias to the DSF

The studies included in the dose-response assessment for the proposed DSF consist exclusively of mouse skin-painting experiments. While laboratory studies of murine models are useful, the limitations of these systems have not been recognized in the Draft BaP Assessment. Specifically, the fundamental differences in the mouse integumentary system have not been appropriately described or accounted for in the development of the DSF. Since the development of the DSF represents a new endeavor in the context of IRIS assessments, the methods should be carefully scrutinized and any limitations associated with the use of mouse data should be clearly explained. These factors are not adequately accounted for in the proposed BW^3/4 scaling factor.

3.1 Epidermal Structure and Sensitivity to Carcinogens

The dermal route of exposure differs from oral and inhalation exposures because the skin contains a physical barrier consisting of a stratified epidermis that is composed of keratin-rich cells (keratinocytes) in different stages of cellular differentiation. The outermost epidermal layer, the stratum corneum is composed of a contiguous sheet of terminally differentiated keratinocytes embedded in a flexible, lipid-rich matrix. The remaining layers of the epidermis consist of keratin-rich squamous epithelial cells. The layer of the epidermis adjacent to the dermis, the basal stratum, contains proliferative epidermal stem cells [23].

The human epidermal layers are depicted in Figure 2 (below), with the stratum corneum being the outermost and the stratum basale being the innermost layer adjacent to the dermis.

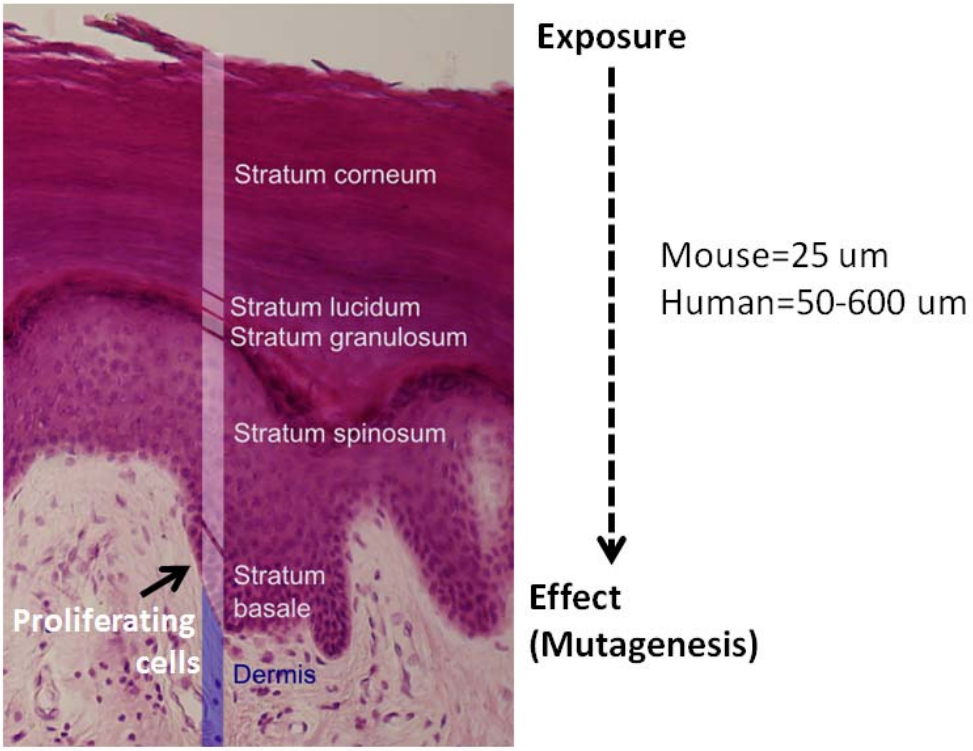

Figure 2. Differences in Epidermal Thickness in Mice and Humans
"Epidermal layers" by Mikael Häggström, based on work by Wbensmith
File:WVSOM Meissner's corpuslce.JPG by Wbensmith. Layers were drawn according to image at Home Page of Deborah S. Dempsey, Department of Biological Sciences, Northern Kentucky University.
Licensed under CC BY-SA 3.0 via Wikimedia Commons:
http://commons.wikimedia.org/wiki/File:Epidermal_layers.png#/media/File:Epidermal_layers.png

Because epidermal cells provide "first-line" protection from environmental assaults, including chemical carcinogens and UVR, epidermal cells are at risk for acquiring an oncogenic mutation. Yet few overt skin cancers originating from differentiated epithelial cells develop because they almost never acquire more than one mutation, and multiple mutations are typically required for a cell to undergo malignant transformation [24-26]. Thus, genetic lesions induced by carcinogens in the outer epithelium are lost through the normal processes of terminal differentiation and epithelial shedding.

Evidence that the consequences of an oncogenic assault depend on the cell's proliferative capacity has come from experiments in which the same oncogene is differentially expressed in separate layers of the epidermis of transgenic mice [27]. When *ras* is driven by a

promoter expressed only during terminal differentiation, no carcinomas form, however regressive, benign papillomas are sometimes observed. Conversely, if *ras* is driven by promoter that is expressed exclusively in proliferating epidermal cells, the mice develop malignant carcinomas.

Further, malignant tumor formation does not occur when oncogenes are ectopically expressed in stem cell progeny that have limited proliferative capacity ("transit-amplifying cells") or in terminally differentiated keratinocytes [26]. While there is limited evidence that mutant terminally differentiated cells in the upper layers of the epidermis can promote stem cell tumorigenesis through an altered growth factor microenvironment [26], the overwhelming scientific evidence indicates that stem cells are the targets of malignant transformation because of their proliferative capacity and potential to undergo further mutagenic assault and develop genomic instability. Thus, the basal keratinocytes comprising the stratum basal in the innermost layer of the epidermis are susceptible to mutagenic transformation that characterizes the BaP mode of action of dermal cancer [26, 28].

These observations suggest that in human skin, chemicals must permeate the barrier layers in order to exert sustainable mutagenic effects that can ultimately lead to skin cancer. Therefore the human epidermis plays a critical role in providing physical protection from chemical exposure.

In contrast to human skin, the murine epidermis generally comprises only two-three keratinocyte layers and is approximately 25 um thick [29, 30]. Typically the thickness of the human epidermis varies between 60 and 100 um in most areas yet can be up to 600 um in the plantar (sole of foot) and palmar (palm of hand) regions [23]. Thus the barrier epidermis of human palms, which are most likely to contact BaP-contaminated soil, is 24 times thicker than the murine epidermis.

Figure 3 (below) shows hematoxylin and eosin stained sections of human skin and mouse skin. The striking difference in epidermal thickness is easily visualized by the purple hematoxylin stain. (Figure modified with labels from Khavari, 2006)

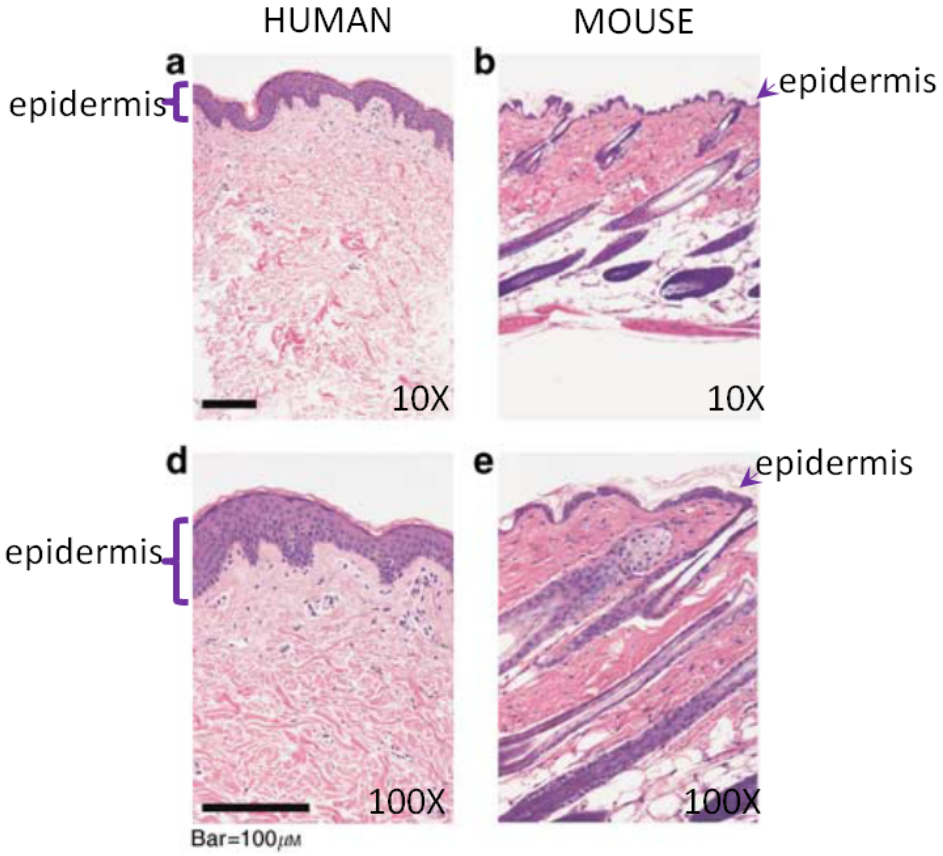

Figure 3. Histological comparison of normal human (a, d), mouse skin (b, e).
The figure serves to illustrate some of the differences in the anatomy of human versus mouse skin described in the text. Mouse epidermis generally comprises only three cell layers and is ~25 um thick, whereas human epidermis commonly constitutes 6–10 cell layers and ranges from 50-600 um thick (2-24x thicker than mouse epidermis).

Other structural differences in mouse and human skin include a substantially thicker dermis, a significantly lower density of hair follicles, differential protein expression in non-cutaneous tissue compartments, a loosely (rather than tightly) connected epidermal-to-subcutaneous connection, the presence of a cutaneous muscle layer (the panniculus carnosus) that is not present in humans, and differential resident immune subsets [23].

While the results of skin-painting studies support a carcinogenic role for PAHs, the reliance on the results of skin painting studies in laboratory mice for purposes of human health risk assessment should be accompanied by explicit recognition of, and accounting for, the important biological differences between the skin of the mice and the skin of humans as described above.

These differences were recognized years ago and have been acknowledged by the scientific community in numerous toxicological and mechanistic studies. For example increased permeability was noted in early studies and attributed to hair follicle density as densely-haired animal skin was found to be highly permeable to chemicals [31-33]. Kao (1985) [33] showed in a species comparison of permeability that murine skin was three times more permeable than human skin.

3.2 Differential Mutational Requirements for Tumorigenesis

Hahn and Weinberg (2002) conducted experiments to elucidate the specific processes associated with carcinogenic transformation in human cells. They proposed a process involving a minimum of five separate events. First, cells must be immortalized through the sequestration/inactivation of the tumor suppressor proteins Rb, p53, and the phosphatase PP2A must be inactivated to result in constitutive activation of survival pathways. Second, rare telomerase-expressing clonal outgrowths undergo further cell divisions. As cells proliferate, increasing genomic instability allows for mutations of common oncogenes such as *ras* which promote a mitogenic signaling program [34, 35].

Mice are more susceptible to cancer formation because transformation of murine cells requires only two mutational events [26, 34, 36]. Enhanced murine cancer susceptibility is due in part longer telomeres facilitated by the ectopic expression of telomerase which maintains telomere length and contributes to oncogenesis by allowing pre-cancerous cells to proliferate beyond the number of replicative doublings allotted to their normal precursors. Thus, in the presence of carcinogens such as BaP, murine cells are more likely to undergo clonal replication and develop tumors. In contrast, the gene that encodes telomerase protein is strongly repressed in most normal human cells.

3.3 Metabolic Differences in Murine and Human Skin

A comparative analysis of mouse and human cells in response to BaP (in coal tar shampoo) further illustrates the inherent sensitivity of the mouse to tumor formation. Crump et al (2000) evaluated metabolic and DNA repair activities in mice and human systems. Mouse skin cells underwent neoplastic transformation when cultured in the presence of BaP while human cells did not, even under higher concentrations and for longer exposure durations. These results were partially attributed to the findings that steady-state and coal tar-inducible levels of aryl hydrocarbon hydroxylase (AHH) were 10-fold higher in mouse skin. Thus, mouse skin produces more reactive metabolites of BaP than does human skin.

4. <u>Skin Graft Studies Support Key Species Differences</u>

Humanized mouse skin models created by surgically grafting human skin onto immunocompromised mice are widely recognized as valuable tools for toxicological studies,

including biochemical and percutaneous absorption studies. Several studies using these models generally indicate that human skin is less sensitive to PAH/BaP-induced tumorogenesis. Several reviewers have noted some of these studies in comments on the *2013 Draft BaP Assessment*. The EPA responses to these comments have focused on the uncertainties related to the physiological and morphological properties of the human skin in these xenograft models. The basis of the skepticism appears to stem from a study by Kappes et al. (2004) [37], discussed these types of uncertainties.

Nevertheless, we believe that the experiments with xenograft models provide important insights into the apparent differences between mouse and human skin sensitivity to PAH/BaP-induced tumorogenesis as demonstrated by successful tumor initiation by UV light exposure. Further, these models are FDA approved for the study of cancer research. The characteristics of skin grafts are discussed below:

4.1 Conserved Epidermal Barrier Function

Higounenc et al. (1994) studied the barrier properties of human epidermis grafted for 1 to 3 months onto nude mice as compared with normal human skin. The permeability of human skin for tritiated water and the transepidermal water loss exhibited no significant changes after grafting onto nude mice. Additionally, grafting did not qualitatively affect the lipid or ceramide composition of human epidermis. The results of this study suggest that grafted epidermis has the same morphological pattern as normal human epidermis [38]. Similarly, a histological analysis of 124 normal and psoriatic human skin grafts on congenitally athymic nude mice revealed that the grafts exhibited normal human epidermal keratinization patterns throughout the post-grafting period [39].

4.2 Conserved Immune Components

Early studies of normal and psoriatic human skin grafts on athymic nude mice showed after grafting, the immunological identities of the intercellular compartments and basement membrane were preserved [39]. A study by Richmond et al. (2008) provides a more recent assessment of the integrity of the immune system in a xenograft model. Although some components of the immune system are missing in nude or SCID mouse models (namely, T cells of the adaptive immune system), in athymic nude mice, the B cells, dendritic cells and granulocytes are all relatively intact, and there is a compensatory increase in both natural killer (NK)-cell activity and tumoricidal macrophages in these mice [40].

4.3 Lower Epidermal /tumor Formation in Response to Chemical Carcinogens

In a study by Graem et al. (1986) human skin grafts on nude mice were exposed to two topical applications of DMBA (1 mg/50 uL of acetone) and/or two applications of TPA in

(10 ug /50 uL of acetone). Murine epidermal tumors were observed in approximately 35% of the hosts at the border of the grafts with no tumor formation in any of the grafts [41].

Urano et al. (1995) investigated chemical carcinogenesis of weekly topically applied DMBA (20 uL of 200 nmol) and BaP (300 nmol in acetone) for a 25 to 27 week duration. Both DMBA and BaP plus UV irradiation and alternate applications of the carcinogens in combination with UV radiation failed to produce tumors, yet all treatments induced skin papillomas in the host mouse skin adjoining the grafted human skin. The authors concluded that the results indicated that susceptibility of human skin to these carcinogenic stimuli is lower than that of mouse skin [42].

Sobelle et al. (1996) studied the effects of DMBA, UVB, or DMBA + UVB in human skin grafted onto CB17 SCID mice. DMBA treatment or UVB treatment alone caused murine carcinomas in 6% and 45%, respectively, of murine skin while no tumors were observed in the human grafts. Combination DMBA + UVB treatments caused 23% of murine carcinomas and 3.6% in human skin. The authors noted that the grafted skin survived indefinitely with characteristic human architecture and immunological phenotype that are stable for the life span of the host and concluded that their studies demonstrate that "commonly used rodent models may significantly overestimate the human carcinogenic potential of tested agents" [43].

In a similar study of human skin xenografts in CD-17 SCID mice, Kurtz et al. (2004) found that weekly applications of DMBA (200 ug/200 uL acetone) for six weeks or a single dose of DMBA (200 ug) followed by twice weekly applications of TPA (10 ug/200 uL acetone) for six weeks caused papillomas in 100% of host adjacent skin. No papillomas were seen in the identically treated human skin on the xenografted SCID mice. These authors concluded, "*In general, our present findings suggest that commonly used rodent models could overestimate the carcinogenic potential of agents for humans*" [44].

4.4 Skin Graft Conclusions

While these studies were previously identified in comments on the *2013 Draft BaP Assessment*, the EPA was not convinced that human skin xenograft models were an appropriate for the study of human percutaneous absorption and chemical carcinogenesis. The EPA cited Kappes et al. (2004) [37] stating, "*However, it is unclear that this human skin xenograft model preserves the physiological and morphological properties of human skin in vivo*."

As detailed above there is sufficient data to support the conclusion that human xenograft models can maintain the epidermal barrier function and parallel immune function of normal human skin. The results of these studies should be evaluated in the Systematic Review and

Evidence Integration process. In concert with other factors addressed in our comments, the xenograft studies provide valuable insights to differences in mouse and human skin.

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Attachment B

USWAG Comments
November 21, 2013

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November 21, 2013

VIA ELECTRONIC DELIVERY AT WWW.REGULATIONS.GOV

Office of Environmental Information (OEI) Docket
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue N.W.
Washington, DC 20460
Attn: Docket ID No. EPA-HQ-ORD-2011-0391

Re: Comments on Draft Toxicological Review of Benzo[a]pyrene
Docket ID No. EPA-HQ-ORD-2011-0391

To whom it may concern:

The Utility Solid Waste Activities Group ("USWAG") submits these comments on EPA's draft toxicological review of benzo[a]pyrene ("BaP"), released for public review on August 21, 2013 ("Review Draft").[1] USWAG appreciates the opportunity to comment on this draft risk assessment prepared for inclusion in the Integrated Risk Information System ("IRIS").

USWAG, formed in 1978, is an association of over one hundred energy utilities, utility operating companies, energy companies, and associations including the Edison Electric Institute ("EEI"), the American Gas Association ("AGA"), the American Public Power Association ("APPA"), and the National Rural Electric Cooperative Association ("NRECA").[2] Together, USWAG members represent more than 73% of the total electric generating capacity of the United States, and service more than 95% of the nation's consumers of electricity and 92% of the nation's consumers of natural gas.

The chemical risk assessments performed by EPA for inclusion in IRIS drive cleanup levels throughout the country and are therefore of great interest to

[1] *See* 78 Fed. Reg. 51719 (Aug. 21, 2013).
[2] EEI is the principal national association of investor-owned electric power and light companies. AGA is the principal national association of investor-owned natural gas utilities. APPA is the national association of publicly-owned electric utilities. NRECA is the national association of rural electric cooperatives. Throughout these comments, we refer to our industry as the "utility" or "electric utility" industry. This term is intended to include those portions of the industry and those USWAG members that generate electricity but do not directly provide electricity to the public and are technically not "utilities."

USWAG members, collectively the owners and operators of thousands of facilities throughout the country, some of which are the subject of remedial action. These sites include those with historic contamination from manufactured gas plants ("MGPs"), often characterized by contamination from BaP and other polycyclic aromatic hydrocarbons ("PAHs"). USWAG appreciates the effort EPA has made to improve the IRIS process in recent years, including several changes geared towards making the process more transparent and systematic.[3] USWAG agrees that it is imperative that IRIS risk values be based on high-quality, current science, and that these values be presented in a clear and concise manner to ensure that they are properly applied towards the establishment of remediation goals.

The BaP assessment is of particular importance to the utility industry, not only because of the prevalence of BaP at MGP and other utility sites. The implications of the final assessment extend far beyond BaP-driven cleanups. In 2010, EPA proposed an approach for estimating cancer risks from exposures to all PAH mixtures based on the relative potency of BaP, the "index" or "reference" chemical.[4] In other words, the risk values established in the final BaP assessment will drive risk assessment for a broad range of chemicals going forward. Given the large number of sites at which BaP or other PAHs are risk drivers, it is critical that the risk values in the final BaP assessment be derived in a scientifically-sound manner.

The Review Draft for BaP, which includes a dermal slope factor ("DSF") for the first time in the IRIS context, raises certain concerns which warrant reconsideration by the Agency. In sum:

- <u>Inclusion of the Dermal Slope Factor</u>: For the first time in an IRIS risk assessment, EPA has included a DSF, but the Review Draft fails to explain how this toxicity criterion should be used in site assessment, and in the derivation of risk-based cleanup values. Moreover, the Review Draft ignores the well-established soil-chemical interactions that will result in the binding of BaP to soil in a manner that significantly diminishes exposure to skin surface.

- <u>Failure to Consider Exposed Skin Surface in Development of Dose Metric</u>: EPA has in the Draft Review expressed the DSF using a dose metric that is constant regardless of the surface area over which skin exposure occurs. In other words, the approach set forth in the Review Draft would lead to the same theoretical cancer risk regardless of whether the entire body was exposed to BaP or only a fraction of a square-centimeter of skin.

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[3] *See* EPA News Release, "EPA Strengthens Chemical Assessment Process to Protect Public Health" (July 31, 2013), available online at http://www2.epa.gov/newsroom.
[4] *See* 75 Fed. Reg. 8937 (Feb. 26, 2010).

- Exclusion of Relevant Studies: The Review Draft is flawed by its failure to consider studies that indicate nonlinearities in the dose-response pattern, particularly at low doses. As a result, the Draft Review improperly assesses the cancer risk from exposure to BaP at low doses.

- Absence of Human Data: The Review Draft does not provide any human studies linking human exposure to BaP with human skin cancer. The Review Draft's reliance on animal (mouse) data to develop the DSF inappropriately overestimates the risk of human skin cancer resulting from BaP exposure.

- Exclusion of Data on Smoking-Related Exposure to BaP: In developing the Review Draft, EPA failed to consider the existing large database on human cancer among individuals exposed regularly to BaP from cigarette smoke. These data, which show only a modest elevation in certain forms of cancer as a result of smoking-related BaP exposure, simply do not bear out the cancer risks that would be estimated by the proposed DSF.

- Absence of Human Data on Developmental Effects; High Uncertainty Factor: The organ/system-specific reference value ("RfD") included in the Review Draft is highly uncertain. In considering the developmental effects of BaP on humans, EPA itself acknowledges that there is no direct evidence that BaP will cause such developmental effects in humans. In deriving this RfD, EPA has therefore used an incredibly large uncertainty factor (300) to account for (1) extrapolation from animals to humans (x10), inter-individual differences in human susceptibility (x10), and deficiencies in the toxicity database (x3). A risk assessment based on such uncertain values drives results that are misleading and unreliable from a decision-making perspective; the RfD value is therefore inappropriate in the context of a risk assessment that will have such a significant impact in the remediation context.

- Detection Levels for BaP: Based on conversations USWAG member companies have had with commercial labs conducting PAH analysis, there is a current method which would allow detection to the levels put forth by EPA in the Review Draft for soil cleanup levels. However, the concentration would be identified as an estimated concentration, meaning that the confidence level for this result would be low. It is not appropriate to mandate screening levels for dermal contact based on estimated concentrations, which may overestimate the levels for BaP and other PAHs, driving unnecessary cleanups and associated costs.

These and other concerns are detailed in the November 21, 2013 technical report prepared by Exponent entitled "Focused Comments to EPA Regarding the Toxicological Review of Benzo[a]pyrene: Public Comment Draft," attached hereto as Attachment A and incorporated by reference herein.

* * * * *

USWAG appreciates the opportunity to comment on the development of this important risk assessment. Please contact USWAG counsel Allison Foley at Venable LLP (202-344-4416) with questions regarding these comments.

Respectfully submitted,

James R. Roewer
Executive Director

Office of Environmental Information Docket
Docket ID No. EPA-HQ-ORD-2011-0391
November 21, 2013

Attachment A

Focused Comments to EPA Regarding the Toxicological Review of Benzo[a]pyrene: Public Comment Draft

Prepared for the Utility Solid Waste Activities Group

This document was developed to provide feedback to the United States Environmental Protection Agency (EPA) regarding the technical derivation of regulatory toxicity criteria proposed in the *Toxicological Review of Benzo[a]pyrene Public Comment Draft* ("Review Draft") that was issued on August 21, 2013. The comments contained herein are focused largely on discussion of the dermal slope factor (DSF) for cancer. This focus was selected based on the precedent-setting nature of the proposed criterion, and the relative importance of this value in risk-based assessments of contaminated sites. It should not be interpreted to imply concurrence with any or all other aspects of the document.

Key Conclusions

Our review of the Review Draft identified several technical areas that merit reconsideration from EPA. The key conclusions of our review are:

- Expressing the DSF using the dose metric of $(\mu g/day)^{-1}$ implies that the risk of skin tumors is independent of chemical loading rate on the skin surface. The failure to base the potency estimate on the dose of BaP per unit skin area is not scientifically defensible for this direct-acting carcinogen.
- While acknowledging that assessment of potential risks from human exposure to BaP in soils is likely to be the use of the DSF that receives the most comments, the Draft Review fails to provide context for using this new toxicity criterion in site assessment. It also fails to acknowledge the well-established soil/chemical interactions that will result in binding of BaP to soil in a manner that will diminish exposure at the skin surface. Additionally, the confusion regarding the use of the DSF for assessing risk from soil is apparent in the Review Draft, wherein EPA attempts, incorrectly, to develop a soil screening value for BaP based on the proposed DSF.
- The quantitative evaluation of the DSF is flawed by the failure to adequately consider non-linear dose-response models when extrapolating from high-dose studies to predict cancer risks at low doses. As conducted, the quantitative evaluation results in a DSF that is an overestimate, due to the exclusion of studies that indicate nonlinearities in the dose-response pattern, particularly at low doses.

- EPA overlooked the opportunity to "ground truth" the proposed DSF by comparing estimates of skin tumors derived using the DSF against empirical data on actual cancer risks provided by the available human epidemiology for disease among BaP-exposed smokers, or against cancer risk from exposure to BaP in soil at background concentrations.
- The non-cancer endpoint based on developmental effects is highly uncertain, because it does not include any technically sound data that relate to humans and requires the application of a relatively high uncertainty factor. The motivation for having such a value appears to be related to using the value for cumulative risk assessment. Given the uncertainties in such cumulative assessments, the inclusion of toxicity values that are highly uncertain is likely to give unreliable information for judging the relative contributions of the broad range of stressors included in a cumulative assessment.

Each of these items is discussed further, below.

Implications of Toxicity Values for Soil Cleanup Levels

For more than a decade, BaP (as an individual chemical) and PAHs (as a chemical class) have consistently ranked among the top 10 priority substances at hazardous waste sites in the U.S. (ATSDR 2013). Included among these hazardous waste sites are over 1500 MGP (manufactured gas plant) sites, at which PAHs are the primary chemicals of concern. Many of these sites still require remediation, and estimated cleanup costs typically range into the tens of millions of dollars per site (EPRI 2013 Research Portfolio: Program 50). Because of the prevalence of these chemicals at many contaminated sites, it is very important to identify toxicity values for application to these sites.

A demonstration of how the proposed toxicity values that are discussed in the Review Draft would affect screening of contaminated sites is depicted in Table 1, which lists the health-based screening levels for BaP in residential soil that would be derived based on the toxicity values proposed in the Review Draft.

Table 1. Impact of proposed toxicity values for benzo[a]pyrene on residential soil screening levels

		Value	Units	Soil Screening Concentration (mg/kg)		
Carcinogenic Endpoints (values include ADAF)						
Proposed	Oral Cancer Slope Factor	1	$(mg/kg\text{-}day)^{-1}$		0.11	
Proposed	Inhalation Unit Risk (cancer)	0.0005	$(\mu g/m^3)^{-1}$		2,613	
Proposed	**Dermal Cancer Slope Factor**	**0.005**	**$(\mu g/day)^{-1}$**	**--**	**0.00041**	**a**
Noncarcinogenic Endpoints						
Proposed	Reference dose (oral)	0.0003	mg/kg-day	--	17	
Proposed	Reference concentration (inhalation)	2E-06	mg/m^3	--	2,837	

Notes: ADAF - Age-dependent adjustment factor, used to account for mutagenic mode of action

[a] Does not incorporate adjustment for fraction of contaminant absorbed dermally from soil (ABS). For BaP, the EPA-recommended value is (
0.13 (or 13%).

Using EPA default inputs for the calculation of preliminary remediation goals (PRGs) for a residential setting, together with the toxicity criteria proposed in the Review Draft, the soil screening values would be:

- 0.11 mg/kg, based on the proposed oral cancer slope factor. Note that this soil screening concentration includes exposures from direct ingestion, as well as for systemic BaP exposures following dermal absorption of BaP from soil, incorporating EPA's recommendation of 13% absorption of a dose applied in soil.
- 2,613 mg/kg, based on cancer risk from inhalation of BaP-contaminated soil, using the proposed inhalation unit risk factor.
- 0.00041 mg/kg, based on the dermal slope factor for cancer. Note that no standard equations exist for the derivation of risk using a DSF. The value here was derived using EPA default values, including those for target cancer risk (1×10^{-6}), the adherence factor for soil on skin, exposed skin surface area, exposure duration, exposure frequency, and lifetime. Values were adjusted for child and adult exposure periods, and incorporated the ADAF for childhood exposures.
- 17 mg/kg, based on the RfD. Note that this calculation includes direct-ingestion exposures, as well as systemic BaP exposures following dermal absorption of BaP from soil, incorporating the EPA-recommended value of 13% of BaP as the fraction in soil that adheres to skin and would be absorbed from the soil.
- 2,837 mg/kg, based on the reference concentration (RfC) for inhalation exposure.

This summary demonstrates that soil screening values based on the proposed DSF would be lower than the screening value derived based on any other proposed toxicity criterion, by a factor of over 200-fold.

As described above, these screening values will have a broad impact on the remediation of the many contaminated sites at which BaP specifically (or PAHs in general) are risk drivers. This severe impact is without justification. This is because, as discussed in detail below, the DSF provided is flawed in its derivation. Also significant is the fact that, in its current form, the DSF will result in significant confusion regarding its application to contaminated sites. This confusion will result because of the illogical units of expression (µg BaP per day) used in the Review Draft. These issues are described further, below.

Technical Issues with the Dermal Slope Factor

The Review Draft states that it "provides the first dermal slope factor for the IRIS database." Given the novelty of this toxicity endpoint as the basis for a toxicity criterion in IRIS, it is incumbent on EPA to exercise all due diligence in the technical derivation of this value, and to

fully consider the implications of the DSF's application in risk assessment. As it stands, however, the derivation of the DSF is fundamentally flawed. As stated previously, the DSF for BaP will likely have significant impacts on the assessment of other chemicals in the future. Additionally, this value has broad implications, because BaP serves as the benchmark chemical against which the toxicity of other PAHs is assessed.

The comments provided herein are developed from the perspective of the risk assessor using the toxicity values provided by EPA in site-specific evaluations of BaP- or PAH-contaminated sites. These comments seek to identify issues that will result in ambiguity when applying the DSF in risk-based screening generally, or in the context of site-specific assessment and related remedial action decision making at contaminated sites.

The significance of the DSF is paramount, because if implemented in its current form, skin cancer from dermal exposure to BaP in soil becomes the risk driver for exposure to BaP-contaminated environmental media.

For the reasons explained below, it is not appropriate to allow the derived DSF for BaP to set precedent or drive risk estimates, because its derivation is fundamentally flawed.

Dose Metric Used in DSF Not Appropriate for Expressing Skin Cancer Risk

The value of DSF currently presented in the Review Draft is expressed in units of risk per µg/d (i.e., expressed in units of $(\mu g/d)^{-1}$). This metric is not appropriate, because implicit in the use of these units is the assumption that the surface area over which exposure occurs is irrelevant—that is, that the risk is the same whether the subject chemical is administered over a fraction of a square centimeter of skin surface, or is evenly distributed over the broader surface area assumed for adult exposure to soil, or even if applied over the entire body surface. As proposed, one would determine the same theoretical cancer risk despite the fact that the skin loading rate of BaP could vary by many orders of magnitude, a finding that is not consistent with the technical basis from which the DSF was derived.

For example, using the proposed DSF of 0.005 $(\mu g/d)^{-1}$, a 10^{-4} risk would be associated with daily BaP exposure of 0.02 µg/day. If this dose is spread over 1 cm^2 (a surface area that is consistent with the critical toxicity study of Poel 1959, discussed further below), it results in a dermal loading rate of BaP of 2×10^{-2} $\mu g/cm^2$-d. If spread over the 5,700-cm^2 skin surface area assumed in the default PRG calculation for adult soil exposures, then the dermal loading rate of BaP is 3.5×10^{-6} $\mu g/cm^2$-d. If the full adult body surface area (average value across males and females) of 19,450 cm^2 is used, then the dermal loading rate would be 1.0×10^{-6} $\mu g/cm^2$-d. Therefore, across these exposure scenarios, any of which might be used in a site-specific risk assessment, the calculated risk would remain the same despite skin loading rates that varied by four orders of magnitude. This is counterintuitive and not consistent with what can be inferred from the dose-response and mode of action from the studies of skin tumor induction following dermal application of a direct-acting toxicant such as BaP, where the target tissue is the viable epidermis, and the toxicity is limited to local tumors after long-term application to skin (Grimmer et al. 1983).

In developing the DSF, EPA should have considered the application of the value in risk assessment, and the logical inconsistencies that would arise for the reasons outlined above. In looking at this same issue, other researchers and regulators have attempted to derive skin cancer slope factors that specifically endeavor to express the value in terms of dose per unit skin area (Knafla et al. 2011). EPA should have anticipated similar considerations based on this published literature, or simply on considerations of appropriate use of the toxicity criterion in risk assessment. To date, EPA guidance for assessing dermal toxicity (U.S. EPA 2004) specifically declines to address appropriate risk assessment methods for direct-acting toxicants applied to skin, stating that dermal toxicity factors are not available and that guidance will be "revised to incorporate additional information on portal of entry effects as it becomes available." Clearly, the authors of this guidance have considered the potential nuances of assessing risk for BaP, because they specifically identify the "lack of dermal slope factor for PAHs" as an area of particularly high uncertainty, and this is considered to be a significant data gap.

Expressing the risk of skin tumor induction from dermally applied BaP in terms of chemical loading to the skin is challenging, because the critical toxicity studies identified by EPA don't describe their dosing regimens in terms of skin loading. These studies express their exposures in units of mass applied and time. However, interpreting the risk in terms of dermal loading appears consistent with these studies, because they identify tumors only in the exposed areas, and because BaP (and other PAHs) has generally been demonstrated to produce tumors at the site of administration (e.g., Grimmer et al. 1983; ATSDR 1995). Two studies form the critical basis for the DSF derived in the Draft Review. Poel (1959) dosed male mice on a shaved interscapular area, and the experimental procedure specifically states to include histological preparations of the interscapular skin of all animals, indicating that the induction of skin tumors is a localized reaction, and does not result in skin tumors in unexposed areas. For example, the BaP skin-painting study by Davies et al. (1969) indicates that "the skin of the painted area was examined at weekly intervals throughout the experiment, immediately after shaving, for the presence of skin tumours." Therefore, the risk of skin tumors is not independent of the chemical loading to skin, as would be implied by expressing the DSF in units of $(\mu g/day)^{-1}$ in the manner used in the Review Draft.

Of the two studies that EPA identifies as critical in forming the technical basis of the DSF, it is possible to estimate the chemical loading to skin from one. Sivak et al. (1997) report on the results from dermal application to shaved dorsal skin, but don't provide adequate detail to assess the specific surface area of skin upon which doses were loaded. However, loading information can be inferred from the study by Poel (1959). In this study, each application consisted of a drop from a needle calibrated to deliver $0.0075 cm^3$ per drop, and "between successive drops the solvent was allowed to evaporate from the skin in order to limit the spread of the carcinogen." Data reported in EPA's *Exposure Factors Handbook* (2011) indicate that a water/ethanol mixture forms a film thickness on skin of 0.00325 to 0.00655 cm following application or immersion. Combining this information with the information from Poel (1959) that the dose was applied in a 0.0075-mL drops indicates that the surface area receiving a dose ranged from about 1.2 cm^2 to 2.3 cm^2.

The Review Draft recognized that "one study indicates that at high doses of benzo[a]pyrene carcinogenic potency is related to mass applied per unit skin and not to total mass" (Davies

1969), but points out that the response "may be due to promotional effects, such as inflammation" that are observed at high BaP doses. As discussed below (see Mode of Action for BaP-Induced Skin Tumors), nearly all the data on elevated rates of skin tumors, which contributed to EPA's DSF calculation presented, were associated with promotional effects specific to the site of application of BaP, as recognized by the authors of many of the studies reviewed by EPA for derivation of the DSF. Consequently, the skin tumor production is proportional to the average BaP concentration achieved in the target dermal tissue at the site of BaP dosing. Because BaP is absorbed at a relatively slow rate , its local concentration will be directly proportional to the BaP dose applied to the treated dermal surface area.

It is thus reasonable to assume that a BaP-induced increase in the risk of skin tumors is related to the dose and duration at the local site of dermal BaP application. A DSF for BaP should therefore be expressed in dosimetry units that are biologically relevant to tumor risk assessment for this endpoint, such as daily dose of BaP applied per unit dermal surface area treated.

As outlined above, the failure to base potency estimates on the dose per unit area of exposed skin is not scientifically defensible for this direct-acting carcinogen, and any other interpretation is not plausible. Expressing the DSF in units of $(\mu g/d)^{-1}$ specifically yields the counterintuitive conclusion that risk is not related to the loading rate of chemical onto the skin surface, is technically inaccurate, and will result in considerable confusion in the application to site assessments.

Uncertainty in Applying DSF to Exposure from Environmental Media

Despite acknowledging that the likely application of the DSF is in the assessment of risk from exposure to soil at contaminated sites, the Review Draft fails to acknowledge well-established research regarding the soil/chemical interactions that would bind BaP to soil and thereby diminish exposure at the skin surface or to provide a meaningful discussion of how the DSF would be used in the risk assessment process. In fact, the example provided serves to further confound potential users, and indicates that even within EPA, professional staff is uncertain about the use of this new toxicity criterion.

In the uncertainty section, the Review Draft discusses the contention that soil contact exposures are likely the dominant pathway for human exposure to BaP from environmental media. The Review mentions the limitation of using BaP applied to skin in a volatile solvent as providing a larger dose of BaP than would occur from soil and acknowledges that there may be an associated overestimation in risk. The discussion fails to mention, however, that it is well known that interactions between chemicals and soil constituents impede the dose of chemicals to skin when the chemical dose is applied in soil. This phenomenon has been established across a broad diversity of organic and inorganic chemicals (e.g., reviews provided by Spalt et al., 2008; U.S. EPA 2004; Health Canada 2012), and specifically for BaP in soil (Wester et al. 1990; U.S. EPA 2004). In fact, for systemic exposure to BaP, default methods provided by EPA include the assumption that only 13% of the dose applied in soil is available for absorption (U.S. EPA 2004; U.S. EPA 2013b), which is an overestimate of absorption from soil, given the specific design of the particular study that forms the basis. Given EPA's acknowledgment of

soil as the predominant exposure pathway for human exposure to BaP in environmental media, the Review Draft should provide direct guidance regarding how to incorporate adjustments to appropriately calculate BaP doses from soil, accounting for the binding of BaP to soil.

More broadly, given the lack of precedent in the development or application of a DSF, EPA has an important responsibility to communicate how this value is to be used in the context of site-specific risk assessment, site screening, and selection of remedy for contaminated sites. Had EPA been diligent in considering the ultimate application of a DSF (essentially following their own guidance on defining data quality objectives), some of the considerable limitations of the proposed value would have come to light. The DSF in its current form presents logical inconsistencies that result in significant confusion with regard to application in risk assessment. A perfect example is provided in the final section of the Draft Review. In this section, the document attempts to demonstrate the appropriate application of age-dependent adjustment factors for application in risk assessment, including for estimation of BaP cancer risk following lifetime dermal exposure (Table 2-15).

The confusion in the use of the DSF is particularly demonstrated in column 4 of Table 2-15, wherein "Sample Exposure Concentration" is presented. By parity to the prior table where the inhalation unit risk, expressed in units of $(\mu g/m^3)^{-1}$, is multiplied by a sample exposure concentration expressed in units of $\mu g/m^3$ to estimate theoretical risk from inhalation exposure, the authors attempt to use the Dermal Unit Risk, expressed in units of $(\mu g/d)^{-1}$, and multiply that value by a concentration in an effort to calculate theoretical dermal cancer risk. Unfortunately, in doing so, the table ends up in the impossible concentration units of "µg/d." Any practical risk assessor or environmental scientist will recognize that, while a value expressed in units of $\mu g/m^3$ is a defensible "concentration" term for chemicals in air, the units of µg/d do not represent a *concentration* applicable to any environmental medium. In light of the precedent-setting nature of including a DSF in this Review Draft, it is incumbent on EPA to provide meaningful instruction regarding the appropriate application of the prescribed value. In the absence of such instruction, it can be reasonably anticipated that the DSF will be applied inappropriately, and it is impossible to provide comprehensive comments regarding the technical limitation associated with the new toxicity criterion.

Quantitative Evaluation of the Dose-Response Relationship for Dermal Cancer

Technical review of the Draft Review for information on the assumed mode of action (MOA), and other aspects of the dose-response assessment for the DSF, reveals several shortcomings that should be remedied before implementing a DSF for BaP can even be considered. Among the major issues identified are:

- A failure to adequately note and account for observed cytotoxicity in the studies of dermal toxicity associated with topical administration of BaP
- Ignoring data from studies that EPA identified as "critical" to development of the DSF, and from other studies that indicate a non-linear dose-response relationship at low doses of dermally applied BaP

- Failure to provide a specific rationale for the basis of using an interspecies scaling factor in the derivation of the DSF
- A failure to consider available data on cancer incidence among a large human population with topical BaP exposures: data on cancer rates among smokers provide the opportunity to "ground truth" the DSF for use in estimating human cancer risk.

These issues are described below.

Mode of Action for BaP-Induced Skin Tumors

In the Review Draft, EPA failed to consider non-linear dose-response models to extrapolate from high-dose skin-painting studies to predict cancer risk from low-level exposures (such as would result from contaminated environmental media). A non-linear approach was not considered adequately in the modeling of risk. Ignoring other approaches is not consistent with the series of frameworks that EPA has developed or otherwise recognizes for addressing the issue of MOA (U.S. EPA 2005). The failure to adequately consider non-linear MOAs for dermal application of BaP ignores threshold-based key events in the dermal carcinogenesis of BaP, and results in an inflated estimate of DSF that is not supported by the available studies, nor by EPA's own guidance for extrapolation. The technical details supporting these findings are presented below.

The proposed analysis of carcinogenic potency for BaP-induced skin tumors assumes that increased risk at low BaP doses is a linear function of BaP dose applied to skin, implying a linear MOA for this tumor endpoint (U.S. EPA 2013a, p. 2-45). As noted above, the EPA review recognizes that the Davies (1969) study indicated that clearly tumorigenic doses of BaP also elicit promotional effects, such as inflammation. The discussion in the Review Draft concerning MOA for BaP carcinogenicity begins with the following conclusion (U.S. EPA 2013a, p. 1-68 – 1-69):

> The primary mode of action by which benzo[a]pyrene induces carcinogenicity is via a mutagenic mode of action. This mode of action is presumed to apply to all tumor types and is relevant for all routes of exposure. The general sequence of key events associated with a mutagenic mode of action for benzo[a]pyrene is: (1) bioactivation of benzo[a]pyrene to DNA-reactive metabolites via three possible metabolic activation pathways: a diol epoxide pathway, a radical cation pathway, and an *o*-quinone and ROS pathway; (2) direct DNA damage by reactive metabolites, including the formation of DNA adducts and ROS-mediated damage; (3) formation and fixation of DNA mutations, particularly in tumor suppressor genes or oncogenes associated with tumor initiation; and (4) clonal expansion of mutated cells during the promotion and progression phases of cancer development. …
>
> Benzo[a]pyrene is a complete carcinogen, in that it can act as both an initiator and a promoter of carcinogenesis. Initiation via direct DNA damage (key event 2) can

> occur via all three metabolites of benzo[a]pyrene. DNA damage that is not adequately repaired leads to mutation (key event 3), and these mutations can undergo clonal expansion (key event 4) enabled by multiple mechanisms also induced by benzo[a]pyrene, including AhR binding leading to an upregulation of genes related to biotransformation, growth, and differentiation, and regenerative cell proliferation resulting from cytotoxicity and a sustained inflammatory response. However, there is not sufficient evidence that these mechanisms, which contribute to the promotion and progression phases of cancer development, act independently of DNA damage and mutation to produce benzo[a]pyrene-induced tumors (please see Other possible modes of action, below. The available human, animal, and in vitro evidence supports a mutagenic mode of action as the primary mode by which benzo[a]pyrene induces carcinogenesis.

To support this interpretation, EPA cites various sources of experimental evidence, including a study by Albert et al. (1991) that examined the dose-response relationship and the time course of BaP-induced skin damage, DNA adduct formation, and tumor formation in female mice treated dermally with 0, 16, 32, or 64 µg of BaP once per week for 29 weeks and followed until sacrifice at week 35. The review states that time-course data from this study "indicate that benzo[a]pyrene-induced increases in BPDE-DNA adducts preceded the appearance of skin tumors, consistent with the formation of DNA adducts as a precursor event in benzo[a]pyrene-induced skin tumors" (U.S. EPA 2013a, p. 1-73). This conclusion misrepresents the observations and conclusions of the study authors, by omitting any discussion of data from this study that demonstrated definitively, and quantitatively, that pervasive dermal tissue injury was induced by all BaP dose levels investigated in this study, with induced cell replication and inflammation observed at the two highest dose levels. The focus of the study was to investigate the hypothesis that "a dose of carcinogen that causes tissue damage may initiate an inflammatory response, cellular and tissue disruption, and regenerative cell proliferation associated with cell killing, which may in turn promote tumorigenesis" (Albert et al. 1991). While DNA-adduct levels were observed to be roughly proportional to applied dose, tumor response was remarkably nonlinear, with pronounced tumor-formation at 35 weeks observed only in the highest dose group (Albert et al. 1991). The fact that adduct levels were observed to attain approximate dynamic-equilibrium levels in skin tissue after only two or three weekly exposures, while mouse skin tumors invariably take two dozen or more weeks to develop, implies that the EPA's conclusion that the study data were "consistent with the formation of DNA adducts as a precursor event in benzo[a]pyrene-induced skin tumors" is true almost by definition, and in no way invalidates other possible MOAs for BaP-induced skin tumors. The observed increase in cell proliferation was concluded to have "occurred in response to an increase in carcinogen-induced cell death" (Albert et al. 1991). Albert et al. (1991) concluded that "The substantial cell killing and regenerative proliferation, and the correspondence between the dose-response patterns for epidermal damage and tumors … provided evidence that the tissue damage associated with the high dose levels of B[a]P used in this study reflected tumor-promoting activity in this mouse epidermal tumorigenesis model."

Thus, the observations of Albert et al. (1991) are at odds with EPA's conclusion regarding the MOA for BaP-induced skin tumors, and are not consistent with the linear-extrapolation method applied by EPA (2013a,b) to model tumor dose-response to derive a DSF. The results of the study clearly raise the possibility that DNA adduct formation is not the sole driving key event

responsible for BaP-induced skin tumors, but rather that the likely independent key events of cytotoxic/cell proliferative and associated inflammatory responses also are critical mode of action mediators of tumorigenicity, and absent these key event responses, tumor outcomes are not expected. The possibility that the MOA for BaP-induced skin tumors is driven by local cytotoxicity is supported by follow-up experiments performed by Albert et al. (1996), which were not discussed or cited in the EPA (2013a,b) Review Draft. This follow-up study of epidermal cell kinetics and DNA adduct levels, measured morphological changes in skin following weekly dermal applications for 29 weeks of 16-, 32-, and 64-µg BaP doses to female ICR/Harlan mice. This study was conducted to investigate the relationships of these parameters to the timing, incidence, and morphology of the elicited tumors. A second experiment done by Albert et al. (1996) measured the same parameters after 1, 3, 5, and 8 months of lower weekly topical doses of BaP (4, 8 or 16 µg). The inflammatory response to topical BaP administration measured in this study was determined to be primarily monocytic in character, with a delayed and less-intensive manifestation at low doses, consistent with a Type IV contact-sensitization reaction that BaP has been observed to elicit in rodent skin (Albert et al. 1996). Although the low-dose dose-response pattern observed for BaP-induced cytotoxicity is consistent with a nonlinear threshold-like response based on data obtained after the 16-, 32-, and 64-µg BaP doses (Figure 1), total inflammation was observed to be significantly and approximately equally elevated after five months of weekly topical exposure to only 4 or 8 µg BaP, at levels approximately half those elicited by weekly 16-µg BaP doses (see Figure 5 of Albert et al. 1996.) Albert et al. (1996) concluded that "a definitive modeling of the relationship of inflammation to tumor formation would require a much broader range of dosage than used so far." However, inflammatory responses observed at doses <16 µg BaP in this study suggest that BaP is capable of killing cells and inducing associated inflammation at the lowest dose levels at which BaP has been observed to induce skin tumors in any study.

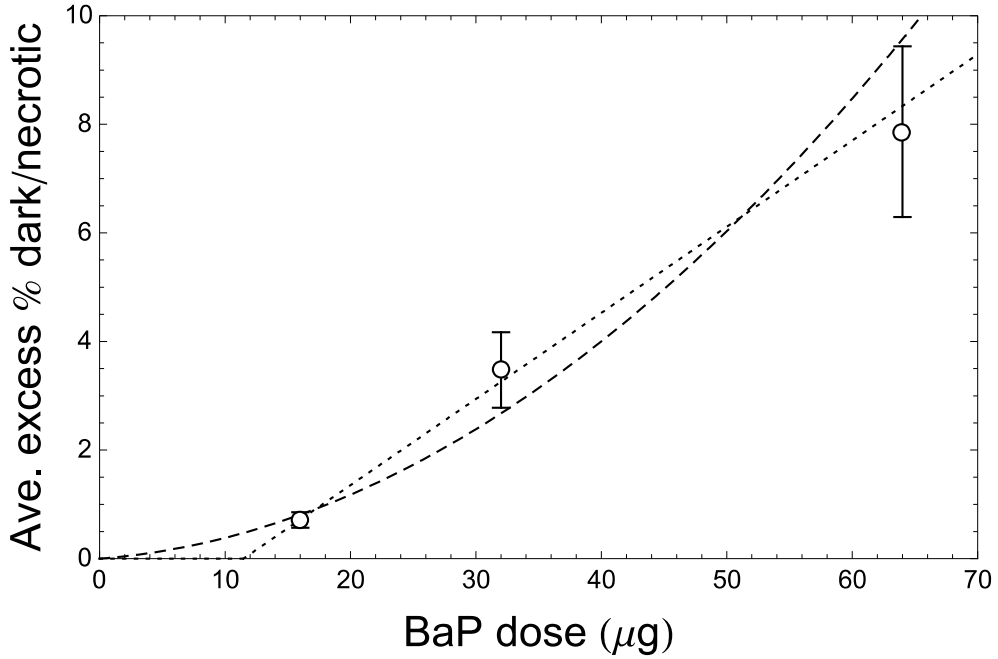

Figure 1. Average excess percentage of keratinocytes that were either dark or necrotic over a period of four days following the fourth of four weekly topical BaP doses (in 50 μL acetone) to female Harlan (ICR) mice, fit to a linear-quadratic response model (dashed curve) and a linear-threshold (LT) model (dotted curve), which both fit the data adequately by chi-square goodness of fit test ($p = 0.065$, and $p = 0.66$, respectively). The implied intercept of the LT model is significantly negative ($p = 0.00016$, by 2-tail t-test). Error bars denote ±1 SE. Estimated from Figure 3 of Albert et al. (1996).

In addressing other possible MOAs for BaP-induced skin tumors besides its assumed MOA given above, EPA concedes that BaP "has both inflammatory and immunosuppressive effects that may function to promote tumorigenesis" and that "there are tumor promoting effects of PAH exposures that are not mutagenic," but that "it was determined that, in comparison to the large database on the mutagenicity of benzo[a]pyrene, there were insufficient data to develop a separate mode of action analysis for these promotional effects" (U.S. EPA 2013a, p. 1-76, 1-77). Notably, the EPA Review Draft and Supplemental Materials contain no summary of experimental data concerning BaP-induced dermal toxicity as an acute, subchronic, or chronic endpoint. This precludes discussion of how such a systemic listing of such study data may pertain to BaP induction of skin tumors, similar to summaries that it lists for other toxic endpoints—despite available relevant literature such as the Albert et al. (1996) study (not reviewed by in the Draft Review), and other studies such as Albert et al. (1991) that EPA reviewed in a perfunctory and misleading way.

The omission of an evaluation of the direct dermal (noncancer) toxicity leads EPA to support a purely genotoxic MOA without a critical evaluation of the existing relevant data. It is well recognized that regenerative cell replication, independent of any direct genotoxic effects, is expected to increase background rates of tumor incidence (NRC 1994, 2011; Bogen 2008). The

studies by Albert et al. (1991, 1996) demonstrate that BaP-induced inflammation, cell killing, and cell replication was highly likely to have occurred at tumorigenic BaP dose levels used in every bioassay that EPA relied on to calculate a DSF. Therefore, the approach used to calculate a DSF, which ignored the likelihood of cytotoxic effects as an independent key event in tumor outcomes (and hence their likely impact on estimated risk), is not scientifically credible. Alternative approaches to use in the case of a likely dual-MOA carcinogen, such as BaP, have been described (Bogen 2008; NRC 2011).

Biased and Non-Transparent Skin-Tumor Potency Analysis

The criteria used to select the specific studies from which to derive the DSF are biased toward studies with little power to identify upward-curving low-dose dose-response patterns, thereby biasing the DSF toward an overestimate of risk that is not consistent with what would be supported by the available body of literature. The application of EPA's Benchmark Dose software to estimate the DSF compounds this problem.

The Review Draft explains the basis of its selection of studies used for DSF calculation as follows:

> … among the three better designed and reported studies (Sivak et al., 1997; Roe et al., 1970; Poel, 1959), male mice were more sensitive than female mice. Consequently, without any information indicating which data set is more relevant for extrapolation to humans, the male mouse results from the higher quality studies (Sivak et al., 1997; Poel, 1959) were selected for the proposed dermal slope factor. The female mouse results (Roe et al., 1970) were not considered further. The average of the BMDL10s for the two male data sets was 0.068 μg/day.

However, the method used to select studies for DSF calculation appears to selectively eliminate two studies (Roe et al. 1970; Schmidt et al. 1973) of the three (also including Sivak et al. 1997) that exhibited enough low-dose dose-response resolution to identify likely convex-upward curvature in the dose-response function. The criteria used for this selection therefore appear to be unjustifiably biased toward selecting studies with lesser power to identify upward-curving low-dose dose-response patterns.

A similar problem is inherent in the BMDS software used by EPA to derive $BMDL_{10}$ values used in the calculation of the DSF. Many of the BaP studies used relatively wide dose ranges, and somewhat larger numbers of animals, compared to those used in tumor bioassays for many other chemicals. Consequently, the available data support the selection of a lower benchmark risk (BMR) such as 1% or 5%, rather than default selection of 10% as the benchmark. Failure to use these lower BMR values unnecessarily biases estimated slope factors upward when applied to studies that incorporate a substantial amount of data at relatively low doses at which tumor incidence rates are only marginally elevated. Specifically, use of the $BMDL_{10}$ forces evaluation of the estimated response function at the BMR (increased risk) value of 10%, despite the presence of substantial and significant sublinear curvature that may exist in a particular dose-response data set. The goal of slope estimation is to determine the lowest positive linear

slope consistent with a dose-response data set. Therefore, the most efficient procedure to estimate the relevant upper-bound slope is to use a sufficiently flexible model that incorporates a linear coefficient in dose that, by definition, will dominate at low doses. Monte Carlo methods to implement this type of approach, which are simpler and have been shown to be at least as reliable as the BMDS/BMDL approach, have been described (Bogen 2011). Such an alternative approach avoids unnecessary BMR-selection bias.

The Review Draft states:

> No established methodology exists to adjust for interspecies differences in dermal toxicity at the point of contact; however, allometric scaling using body weight to the ¾ power was selected based on known species differences in dermal metabolism and penetration of benzo[a]pyrene. In vitro skin permeation was highest in the mouse, compared to rat, rabbit, and human, and was enhanced by induction of CYP enzymes (Kao et al., 1985). Using this approach, rodents and humans exposed to the same daily dose of a carcinogen, adjusted for $BW^{3/4}$, would be expected to have equal lifetime risks of cancer.

The rationale presented by EPA requires clarification. If the target tissue for BaP-induced skin tumors consists of some component of the viable epidermis of skin, such as the basal layer, then virtually the entire amount of each dose applied to a specific area of skin will pass through the target tissue. On chronic administration, topically administered BaP will equilibrate in concentration with the BaP present in that target tissue. Because the DSF units are presented as mass of BaP per day, not the typical exposure unit of mass per unit body weight per day, it is not clear what justification underlies the proposed method of dose adjustment. Likewise, it is not clear how the information on inter-species differences in permeation *through* skin in vitro bears on estimating dose *to* the skin layer in vivo.. That is, in vivo permeation through skin clears that skin of administered BaP, thus reducing the effective BaP dose to the target tissue of concern. Therefore, the allometric scaling is not appropriate for evaluating skin cancer from direct-contact dermal exposures. A full discussion of the interspecies scaling, with complete derivation, should be provided.

Proposed DSF is Not Consistent with Human Epidemiology

The estimated DSF of 0.005 per µg/day merits a reality check against available human epidemiology data. Data on cancer rates in humans exposed regularly to BaP from cigarette smoke do not bear out the cancer risks that would be estimated by the proposed DSF. This large database on human cancer among smokers provides a useful "reality check," and should have been considered by EPA before proposing a DSF that is not consistent with what is known from human epidemiology. Similarly, the background concentrations of BaP in soil can provide a useful "reality check" that should have been considered.

Smoking has been associated with only a modest elevation in certain forms of skin cancer (Leonardi-Bee 2012). In contrast, the DSF implies that the surfaces of the mouth and nasopharangeal regions of cigarette smokers should be subject to pronounced elevations in corresponding epithelial tumors due to direct contact with BaP from inhaled cigarette smoke.

Mainstream cigarette smoke contains 20 to 30 ng BaP per cigarette, and sidestream smoke contains about three times more BaP (IARC 2012). A smoker typically inhales mostly mainstream smoke, so a smoker of one pack (20 cigarettes) per day would inhale an average of 500 ng BaP/day, of which approximately 30% (~0.15 μg) is expected to be deposited jointly, and approximately equally, on internal oral and nasopharangeal surfaces (Sahu et al. 2013). The corresponding theoretical cancer risk using the DSF is 0.15 μg/day x 0.005 per μg/day = 75 per 100,000. This value can be compared to the known incidence of oral cancer. The background incidence of oral cancer in the U.S. is approximately 10 per 100,000 (NIDCR 2013), and that of nasopharangeal cancer is approximately 1 per 100,000 (Hui and Chan 2013), yielding a combined incidence of approximately 11 per 100,000. Thus, the DSF implies a relative risk (RR) of ~7 for the combined incidence of oral and nasopharangeal cancer, and an RR of ~70 for just nasopharangeal cancers, among smokers compared to nonsmokers. No such elevated RR among smokers has been observed, indicating that the DSF appears to overestimate tumor risks to BaP-exposed human epithelial surfaces, even accounting for substantial ingestion and/or dilution of inhaled cigarette smoke deposited on oral and nasopharangeal mucosal surfaces.

Issues with Deriving an RfD Based on Uncertain Developmental Effects

The Review Draft for BaP includes for the first time an organ/system-specific reference value (RfD) based on developmental, reproductive, and immune-system toxicity data. The review indicates that the reference value may be useful for cumulative risk assessments that consider the combined effect of multiple agents acting on the same biological system. What is also clear is that the value is highly uncertain and reflects an effort on the part of EPA to generate values that can be used as part of other types of assessment (e.g., cumulative risks). However, given the large uncertainties in the value, using this value for cumulative risk assessment is likely to increase rather than resolve the uncertainties associated with such assessments.

Uncertainties in the RfD Value

To derive an RfD value, EPA has applied an uncertainty factor of 300 to available data. This large uncertainty factor reflects the general lack of precise information for understanding actual toxicity. This composite uncertainty factor (UF) of 300 is used by EPA to account for the extrapolation from animals to humans (10), for interindividual differences in human susceptibility (10), and for deficiencies in the toxicity database (3). As EPA acknowledges, there is no direct evidence that BaP will cause developmental effects in humans. Instead, the IRIS document relies solely on animal studies that indicate that BaP "may be associated" with developmental, reproductive, and immunological effects. Evidence for any of these potential effects on humans is limited to indicators of exposure such as the occurrence of adducts. Thus, for BaP, EPA is greatly limited in what it can say about the potential for these types of effects in humans, and supports its IRIS assessment with the logic that, generally, based on observations from other chemicals, effects in humans can be inferred from studies on animals, but that no evidence for these effects in humans has been associated specifically for exposure to BaP. In other words, if the chemical **may** cause effects on animals, it **may** also cause those effects in humans.

Based on the text of the Review Draft, it appears that EPA's motivation for developing an RfD value for BaP is that this would permit estimates of cumulative risks that would involve combining the exposures and risks associated with BaP with those associated with other chemicals. With respect to BaP, the interest in having a value for cumulative risk assessment purposes is likely related to assessing human exposures in urban environments where BaP and other PAHs are commonly elevated. Cumulative risk assessments are inherently uncertain, and the inclusion of stressors with known high uncertainties will tend to inflate rather than resolve the uncertainty in such assessments. As noted above, the uncertainty being introduced by the RfD for BaP is huge. Making use of highly uncertain values for risk assessment and especially for cumulative risk assessments introduces those large uncertainties into the assessments. A cumulative risk assessment that includes chemical stressors with a wide band of uncertainty is likely to lead to results that are misleading and unreliable for decision-making.

Perspective on RfD

The review document does not provide perspective regarding the occurrence of developmental effects that would allow users to understand risks associated with exposure to a specific chemical. If EPA concludes that it will continue with a highly uncertain RfD, we strongly recommend that the agency consider inclusion of a perspective regarding the nature and prevalence of developmental effects.

Among humans, birth defects remain an important adverse health consequence, despite many years of research investigating their causes and potential ameliorative strategies. While the financial and emotional impacts of birth defects on individual families are enormous, the scale of the problem is not appreciated by the general public. According the National Center for health Statistics (Hamilton et al. 2005), there were 4,115,590 births in the United States during 2004, which equates to the birth of a baby approximately every 7.4 seconds. According to the March of Dimes (2009), one of every eight babies (~514,450 babies) is delivered pre-term; a pre-term or low-birth-weight baby is born every two minutes; and a baby with a birth defect is born every 4½ minutes. Heron (2007) shows that approximately one in every five infant deaths is a consequence of birth defects, and that the leading causes of nearly one-half of all infant deaths are related to birth defects, low birth weight, or complications of pregnancy.

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