## Background

Benzo[a]pyrene causes skin cancer in mice following dermal exposure; in fact, dermal exposure studies of other chemicals often use benzo[a]pyrene as a positive control for carcinogenicity. Humans are dermally exposed to benzo[a]pyrene through contaminated soil and sediment, and the EPA's program and regional offices have expressed a need for toxicity values for dermally active chemicals, such as benzo[a]pyrene. To meet this EPA need, in September 2014 the EPA released a draft IRIS assessment of benzo[a]pyrene that included an approach for estimating the risk of skin cancer following dermal exposure. This was the first time a health agency has developed and proposed a solution to this problem.

In July 2015, the EPA's Science Advisory Board Chemical Assessment Advisory Committee released a first draft of their peer-review advice on the 2014 draft IRIS benzo[a]pyrene assessment. Their draft report made several recommendations, including that the extrapolation from mice to humans be supported by a more coherent, logical structure. They also recommended that skin cancer risk be modeled as a function of absorbed dose rather than applied dose of benzo[a]pyrene.

The IRIS program is initiating a public science discussion on this topic in order to obtain a broad range of scientific perspectives on how to approach this problem.

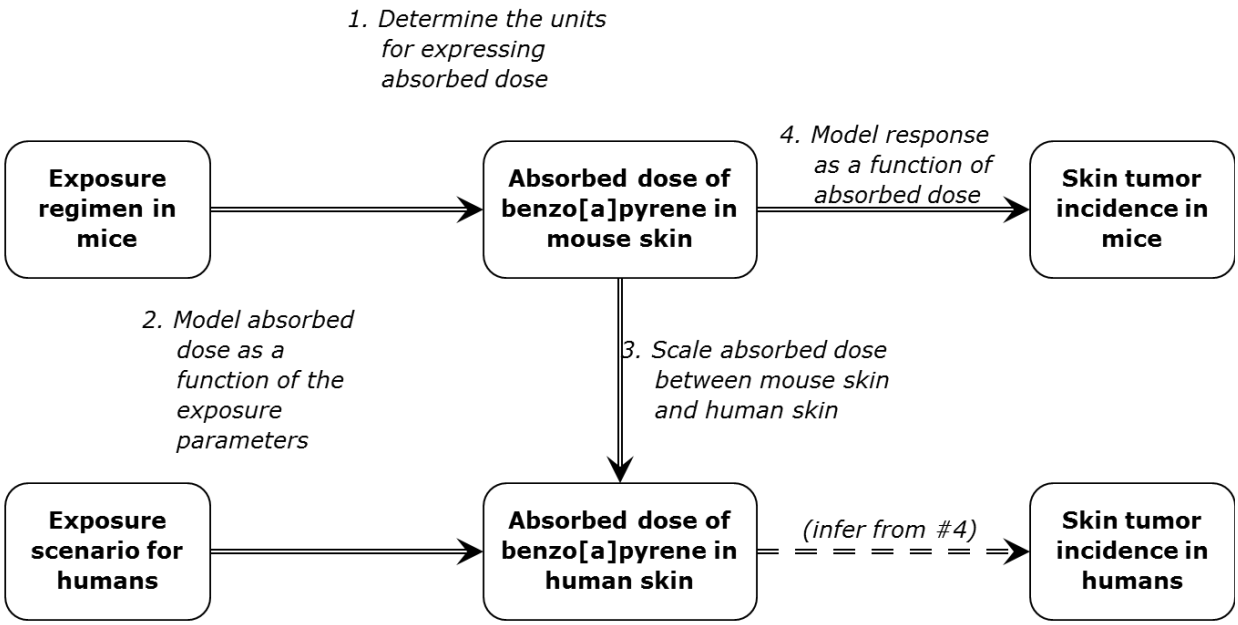
## Data for estimating lifetime risks from skin cancer in mice following dermal exposure

The EPA's 2014 draft IRIS benzo[a]pyrene assessment reviewed the known carcinogenicity studies of benzo[a]pyrene administered to mice via dermal exposure. After excluding less than lifetime studies, studies that did not test multiple doses of benzo[a]pyrene, and studies only with dose levels inducing 90–100% incidence of tumors, 10 studies remained (see Table 1-16 of the 2014 draft IRIS benzo[a]pyrene assessment for information on the design and results of these studies).

## Proposed conceptual framework

The challenge of estimating the potential risk of human skin cancer from dermal exposure to benzo[a]pyrene can be broken down into several steps:

1. Determine the appropriate units for expressing absorbed dose.
2. Develop a model of absorbed dose as a function of the experimental exposure regimen in mice.
3. Scale absorbed dose between mouse skin and human skin.
4. Model the incidence of skin tumors in mice as a function of absorbed dose, scaled to humans.




**Proposed conceptual framework for deriving a dermal slope factor for benzo[a]pyrene from skin tumors in mice**

## Questions for public science discussion

### 1. Determining the units for expressing absorbed dose.

The CAAC noted that both total mass of benzo[a]pyrene and mass per unit of skin area have been used as dose metrics in previous publications (Knafla et al., 2011; 2006; Hussain et al., 1998; LaGoy and Quirk 1994; Sullivan et al., 1991), and that "there does not appear to be any empirical data available to inform a choice between these two dose metrics or to select another." Whichever dose metric is selected, it will need to be paired with an appropriate exposure equation for estimating an average daily dose of benzo[a]pyrene absorbed into human skin (an example equation can be found on p. G-14 of the supplemental information for the 2014 draft IRIS benzo[a]pyrene assessment). *The IRIS program is seeking public input on points that are important to consider and would be informative in selecting a dose metric.*

### 2. Modeling absorbed dose as a function of exposure parameters.

The CAAC noted that for the mouse study used to derive the dermal slope factor, applied dose closely approximates absorbed dose. The CAAC described conditions where this would be the case: the mass of the chemical is too small to cover completely the application area, the time between dose applications is long, and metabolism in the viable epidermis (the target tissue) is not saturated. In experimental studies where applied dose does not closely approximate absorbed dose, it would be important to estimate the absorbed dose from the exposure parameters in the study.

The CAAC also recommended that for subsequent use of the dermal slope factor to estimate the human cancer risk from an environmental exposure, the cancer risk should be estimated from the absorbed dose, and that the absorbed dose should be estimated from the exposure scenario.

Thus, there are recommendations to estimate absorbed dose both for an experimental exposure regimen in mice and for an environmental exposure scenario for humans. *The IRIS program is seeking public input on factors to consider in developing a model of absorbed dose of benzo[a]pyrene as a function of the parameters of applied dose.*

### 3. Scaling absorbed dose between mouse skin and human skin.

After consideration of limitations in the available toxicokinetic data, EPA selected allometric scaling (i.e., body-weight$^{3/4}$) and presented alternative approaches in the supplemental information for the 2014 draft IRIS benzo[a]pyrene assessment (see Appendix E). The CAAC noted that the science is uncertain for choosing the best approach for scaling absorbed dose from mouse skin to human skin. It is unknown whether whole-body toxicokinetics using allometric scaling is the most appropriate model within the skin compartment. The CAAC recommended consideration of thickness of the viable epidermis and metabolic rates in this tissue. *The IRIS program is seeking public input on factors, with particular attention to quantitative factors, to better inform a scaling approach from mouse skin to human skin.*

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