IRIS Public Science Meeting: B[a]P dermal slope factor

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Introduction

- The purpose of this IRIS Public Science Meeting is to discuss science issues pertinent to the development of a cancer slope factor for the risk of skin cancer from dermal BaP exposure.

Disclaimer: This presentation does not represent and should not be construed to represent any Agency determination or policy.

History

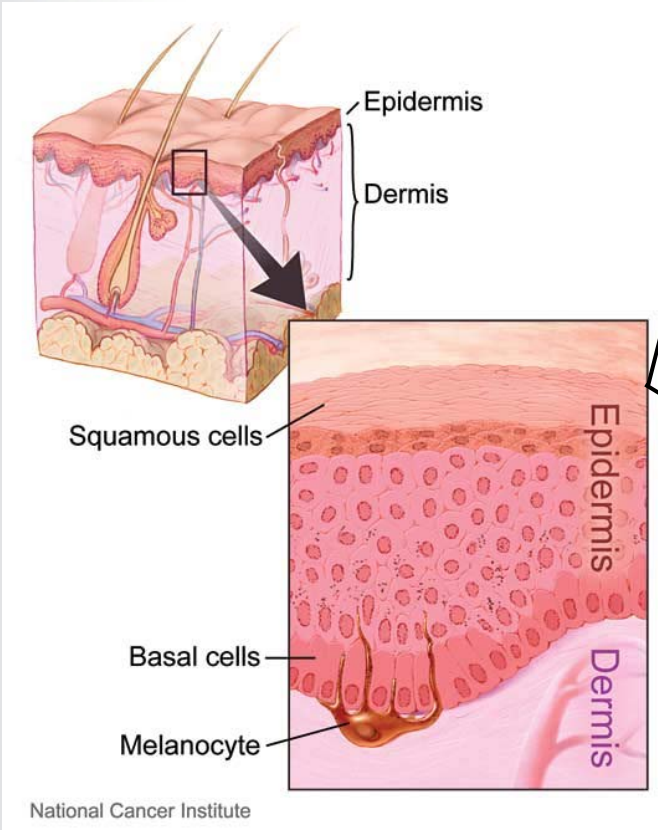
The BaP draft IRIS assessment included an approach for estimating the risk of skin cancer following dermal exposure.

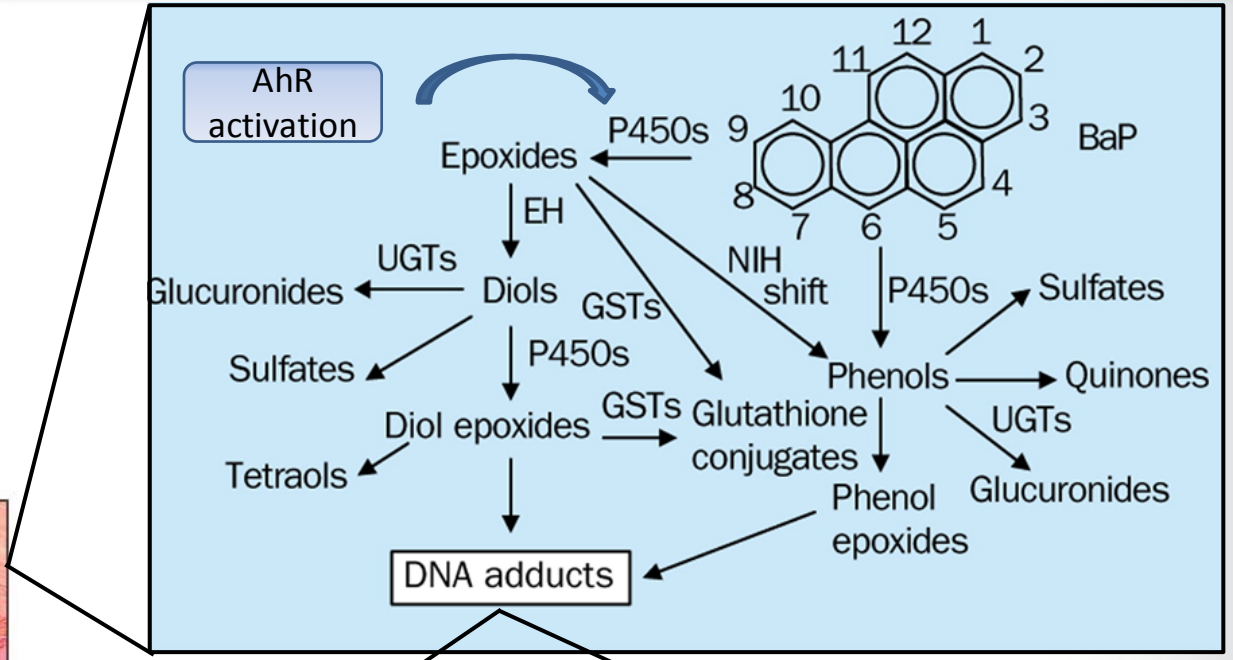
- Released for Public comment: August 2013
- Released for External peer review: September 2014
- EPA's Science Advisory Board (SAB) face-to-face meeting: April 2015
  - Final SAB report released: April 2016

Support for the Development of a Dermal Toxicity Value for BaP

- Increased risk of non-melanoma skin cancer in occupations exposed to PAH mixtures (reviewed in IARC 2010 and Baan 2009).
- BaP is carcinogenic in all animal species tested, at multiple sites, by all routes of exposure, and evidence supports a mutagenic MOA.

Overview of mechanisms involved in BaP-induced skin tumorigenesis





Mutation (e.g. Ha-Ras, p53)

Repair

Promotion → Progression → **Cancer**

Adapted from NCI 2016 and Hecht 2002

Agency Need for a Dermal Toxicity Value for BaP

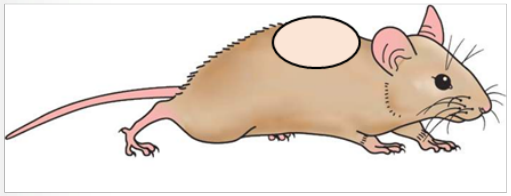
- BaP is a common soil contaminant and there is a programmatic need for toxicity values for dermally active chemicals such as BaP (US EPA 2004).

Lifetime mouse dermal bioassays

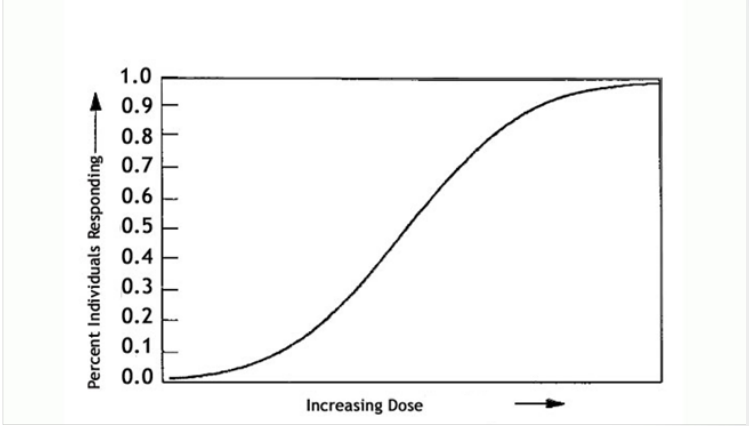
Poel (1959) C57L mice: male (13–56/dose) 0, 0.15, 0.38, 0.75, 3.8, 19, 94, 188, 376, or 752 µg 3 times/wk for up to 103 wks	Habs et al. (1980) NMRI mice: female (40/group) 0, 1.7, 2.8, or 4.6 µg 2 times/wk until natural death
Poel (1963) SWR, C3HeB, or A/He mice: male (14–25/dose) 0, 0.15, 0.38, 0.75, 3.8, 19.0, 94.0, or 470 µg 3 times/wk until natural death	(Grimmer et al. (1984); Grimmer et al. (1983)) CFLP mice: female (65–80/group) 0, 3.9, 7.7, or 15.4 µg (1983 study) 0, 3.4, 6.7, or 13.5 µg (1984 study) 2 times/wk for 104 wks
Roe et al. (1970) Swiss mice: female (50/dose) 0, vehicle, 0.1, 0.3, 1, 3, or 9 µg 3 times/wk for up to 93 wks	Habs et al. (1984) NMRI mice: female (20/group) 0, 2, or 4 µg 2 times/wk until natural death
Schmidt et al. (1973) NMRI mice: female (100/group) Swiss mice: female (100/group) 0, 0.05, 0.2, 0.8, or 2 µg 2 times/wk until natural death	(Sivak et al. (1997); Arthur D Little, 1989; NIOSH (1989)) C3H/HeJ mice: male (30/group) 0, 0.05, 0.5, or 5 µg 2 times/wk for up to 104 wks
Schmähl et al. (1977) NMRI mice: female (100/group) 0, 1, 1.7, or 3 µg 2 times/wk until natural death	

Overview of Dermal Slope Factor Derivation

BaP in solvent



2-3 x /week for lifetime



Dermal Slope Factor- mouse

Interspecies extrapolation

Dermal Slope Factor- human

Dermal Slope factor X Absorbed Dermal Dose = Dermal Cancer Risk

Session 1: Determining the appropriate dose-metrics for expressing absorbed BaP dose

Session 1

Previous publications that derived a dermal slope factor expressed BaP dose in various ways:

- mass/day
- mass/kg bw-day
- mass/cm^2-day
  - None of the lifetime BaP dermal bioassays reported cm^2 of dorsal skin treated
  - Treatment area estimated from 6 cm^2 (Knafla 2011) to 30 cm^2 (Sullivan et al 1991)
- The Draft EPR DSF was expressed as mass/day
  - The Draft EPR DSF assumed that risk at *low doses* of BaP is dependent on absolute dermal dose
  - At *high* dermal doses, mechanisms in addition to direct genotoxicity are seen such as inflammation and necrosis (Albert et al., 1996)

Session 1: continued

- The SAB noted that there does not appear to be any empirical data available to inform a choice between dose metrics.

- Whichever dose metric is selected, it will need to be paired with an exposure equation for estimating an average daily dose of BaP absorbed into human skin, which expresses dose in the same units (see Session 2).

The IRIS Program is seeking public input on points that are important to consider and would be informative in selecting a dose metric.

Session 2: Estimating absorbed dose as a function of exposure parameters

Mouse-absorbed dose, laboratory conditions

- The SAB noted that for the mouse study used to derive the dermal slope factor, applied dose closely approximated absorbed dose because:
  - the mass of the chemical was too small to completely cover the application area,
  - the time between dose applications was long, and
  - metabolism in the viable epidermis (the target tissue) was likely not saturated.

Humans-absorbed dose, environmental conditions

- The SAB also recommended that 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 based on the exposure scenario.

Session 2: continued

Estimation of human absorbed dose

- An example equation was included in the EPR draft for calculating the average daily dermal dose of BaP. This example equation was a modified version of equation 3.11 and 3.12 from US EPA Risk Assessment Guidelines for Superfund, Volume 1, Part E (US EPA 2004)
- *Lifetime Average Daily Dose (ug/day):*

$$LADD_{dermal} = \frac{C_{soil} \times CF \times SA \times AF \times ED \times EF \times ABS}{AT}$$

C_{soil} = Soil Concentration (ug/kg)
CF = Conversion Factor (kg/ug)
SA = Surface Area of Skin Exposed (cm^2)
AF = Soil Adherence Factor (ug/cm^2-day)
ED = Exposure Duration (years)
EF = Exposure Frequency (days/year)
ABS= Dermal Absorption Fraction
AT = averaging time (days)

The IRIS Program is seeking public input on factors to consider in developing a model of absorbed dose of BaP as a function of exposure parameters.

Session 3: Scaling absorbed dose between mouse skin and human skin

Session 3

- An established methodology does not exist to adjust for interspecies differences in dermal toxicity at the point of contact.
- After consideration of limitations in the available toxicokinetic data, EPA selected allometric scaling (i.e., body-weight$^{3/4}$).
  - Based on empirical evidence supporting more rapid distribution, metabolism, and clearance in small animals (U.S. EPA, 2005; U.S. EPA 2011).
  - BaP metabolism is known to occur in the dermal layer.
  - Viewing skin as an organ, and without evidence to the contrary, metabolic processes in the skin were assumed to scale allometrically (similarly to whole body toxicokinetics).
- The SAB noted that the science is uncertain for choosing the best approach for scaling absorbed dose from mouse skin to human skin.

Session 3: Biological Considerations for Interspecies Extrapolation

- The SAB recommended consideration of **thickness of the viable epidermis** and **metabolic rates** in the skin.
- Are there other factors that would be important to consider for scaling between mice and humans?
  - Skin permeability
  - Thickness of the stratum corneum (between anatomical sites and between species)
  - Toxicokinetic processes
    - Rate of formation of DNA adducts in skin
    - Rate of detoxification and elimination of reactive metabolites
    - Rate and fidelity of DNA repair
    - Others?

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.

Session 4: General Discussion on the BaP Dermal Slope Factor