Water Quality Standards
Human Health Criteria Workgroup

December 17, 2020

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Dec 17, 2020 Meeting Agenda
Human Health Criteria (HHC) Workgroup

- Next Steps: finding new data & finding consensus
- Benzo(a)pyrene IRIS Update, **Ross Brittain**
- Look at remaining WV criteria
- Finalized Workgroup Goals
- Plan for next meeting

Agenda uploaded on 12/15/20 to
https://dep.wv.gov/WWE/Programs/wqs/Pages/WQSpublicmeetings.aspx

Next Steps

Where do we go from here?

In next few meetings will be looking at:

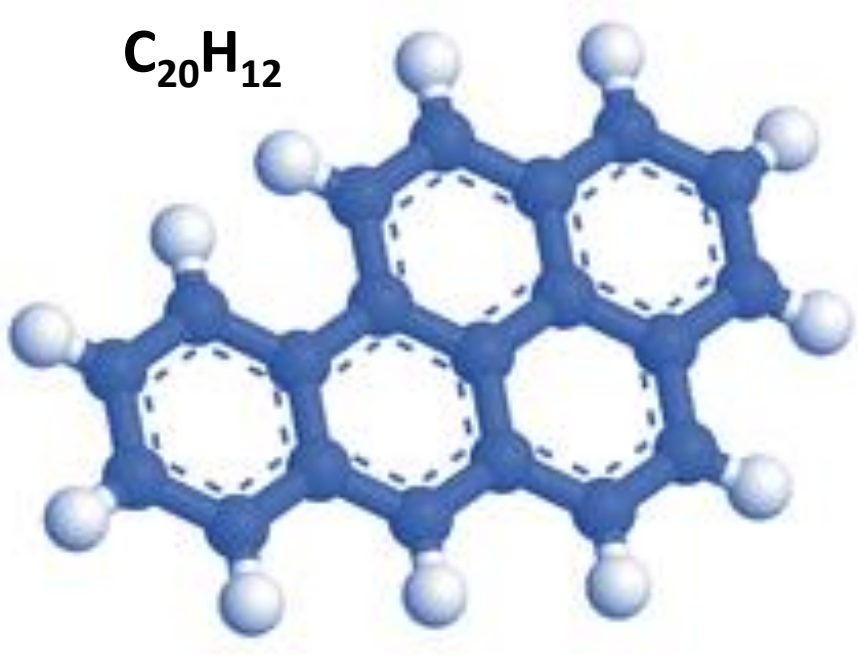
- Remaining WV criteria, looking for consensus
- Newer toxicity data
- Additional bioaccumulation factor studies
- Any info to better inform Relative Source Contribution

Benzo(a)pyrene Toxicity Summary

Human Health Criteria Workgroup
12/17/2020

Ross Brittain
Environmental Toxicologist
WVDEP-OER

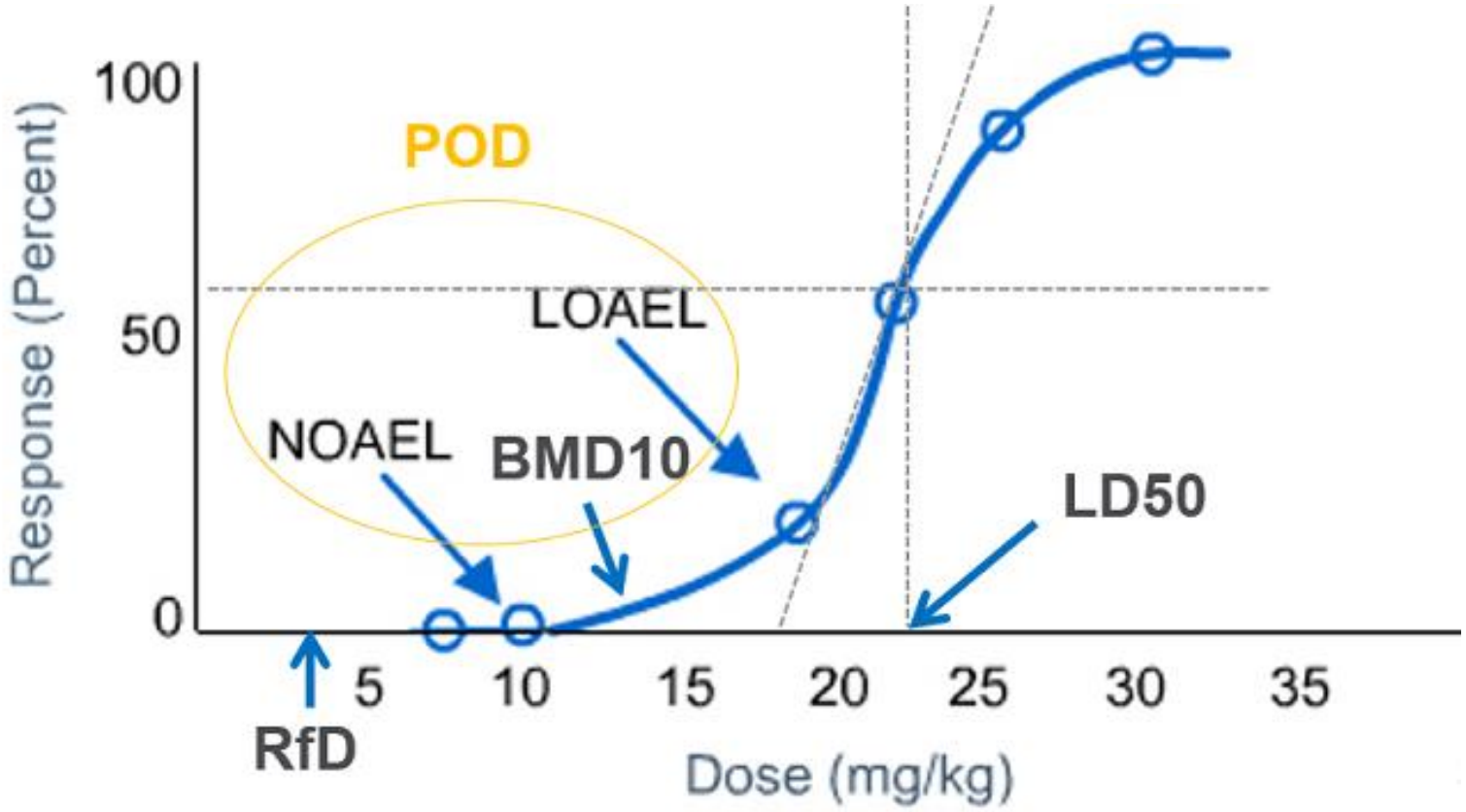
Benzo(a)pyrene



- A five-ring polycyclic aromatic hydrocarbon (PAH)
  Resulting from incomplete combustion of organic matter at 300°C to 600°C
- Group A: Known human carcinogen
- Soot with PAHs were known to cause
  "chimney sweeps' carcinoma" scrotal cancer as early as the 18th Century.
- Important to remember that exposures to PAHs do not occur in isolation
  PAHs come in mixtures!
- There are over 40 PAHs but 16 are considered the "core" PAHs that are regularly found together.

Toxicology 001

- Calculate Benchmark Dose (BMD) to estimate Reference Dose (Rfd)
  Replaced NOAEL method to determine Point of Departure (POD)



BMD is a range of values based on the lower and upper confidence limits.

The Benchmark Dose Lower Confidence Limit (BMDL, based on 90% LCL) is frequently used as conservative POD

Advantages:
Account for variability and shape of response curve
Can compare across other chemicals and studies

Limitations: Time consuming

BMD Derivation

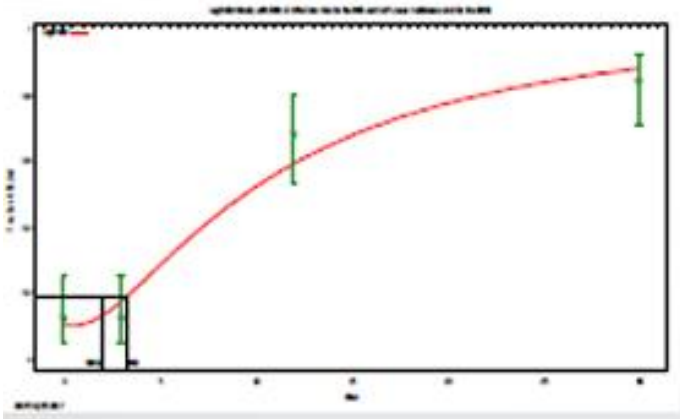
Typically, EPA's Benchmark Dose Software

Data must meet key criteria:
- either quantal or continuous data
- clear dose-response trend
- sufficient dose groups
  (at least 3 plus 1 control),
  response in ≥ 2 groups
- dose-response model should fit
  by predetermined criteria
  (e.g., p-value > 0.1)

Establish BMDL criteria (5%, 10% or 1SD)
aka Benchmark Response (BMR)

Software fits the model
highest p-value
lowest AIC

Model	# parameters	p-value	AIC	BMD	BMDL
Gamma	3	0.0095	192.99	2.688	1.422
Logistic	2	0.0007	198.47	4.029	3.313
Log-logistic	3	0.0535	189.81	3.200	1.841
Probit	2	0.0006	199.07	4.003	3.370
Log-probit	3	0.0566	189.73	3.313	1.976
Weibull	3	0.0076	193.55	2.291	1.383
2° Multistage	3	0.0063	194.20	1.684	1.346



The reported BMDL is the POD!

Establishing Non-Carcinogenic RfD from POD

Once POD (e.g., BMDL) is established, apply Uncertainty (UF) and Modifying Factors (MF)

$$RfD\ or\ RfC = \frac{Point\ of\ Departure\ (POD)[Modification\ if\ necessary]}{UF1 * UF2 * UF3 * UF4 *\ Modifying\ Factor\ (MF)}$$

Modification based on differences in bioavailability, units of exposure in route-to-route extrapolation, exposure conditions, and respiratory volumes

UF1 = 10; Account for variation in sensitivity among human populations

UF2 = 10; Account for uncertainty extrapolating from animals to humans

UF3 = 1 to 10 (default 1); Account for uncertainty extrapolating from sub-chronic POD to chronic POD

UF4 = 1 to 10 (default is 1); Account for uncertainty when using LOAEL as POD

MF = 1 to 10; Account for additional uncertainty such as data quality and confidence in data set

Benzo(a)pyrene Non-carcinogenic effects

- Found in both animal and human studies…
- Developmental toxicity (from gestational exposures)
  - neurobehavioral changes
  - cardiovascular changes
- Reproductive toxicity (from oral exposures in adults)
  - decreased sperm count
  - decreased ovary weight
  - decreased follicle numbers
- Immunotoxicity (from oral exposures in adults)
  - decreased immunoglobulin and B cell numbers
  - decreased thymus weight
- Developmental toxicity is considered the most sensitive

Reference Dose (RfD)

The BMD for BaP ranged from 0.092 mg/kg/day to 0.16 mg/kg/day for the three modes of toxicity

0.092 mg/kg/day for developmental toxicity was conservatively chosen as POD (Chen et al. 2012)

This POD was divided by a UF of 300

- 10 for variability in sensitive human populations (UF1)
- 10 for extrapolation from humans to animals (UF2)
- 3 for deficiencies in the database (MF)

Resulting **RfD = 3×10^{-4} = 0.0003 mg/kg/day**

IRIS overall confidence was medium

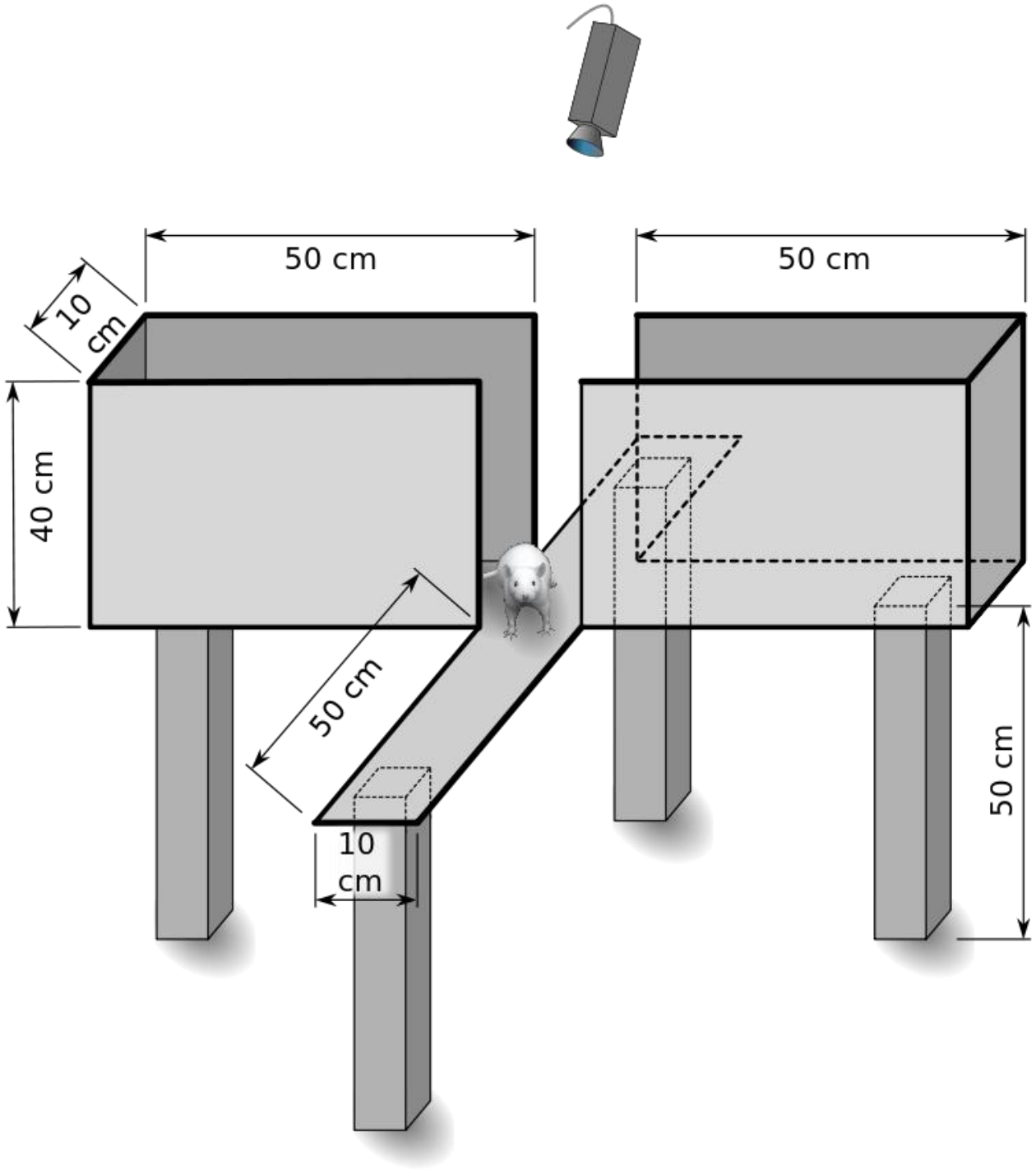
- potentially introduced maternal stress
- missing sensitivity of some assays at developmental stages
- lack of individual or gender-specific data for all outcomes
- multigeneration throughout development and across generations is not available

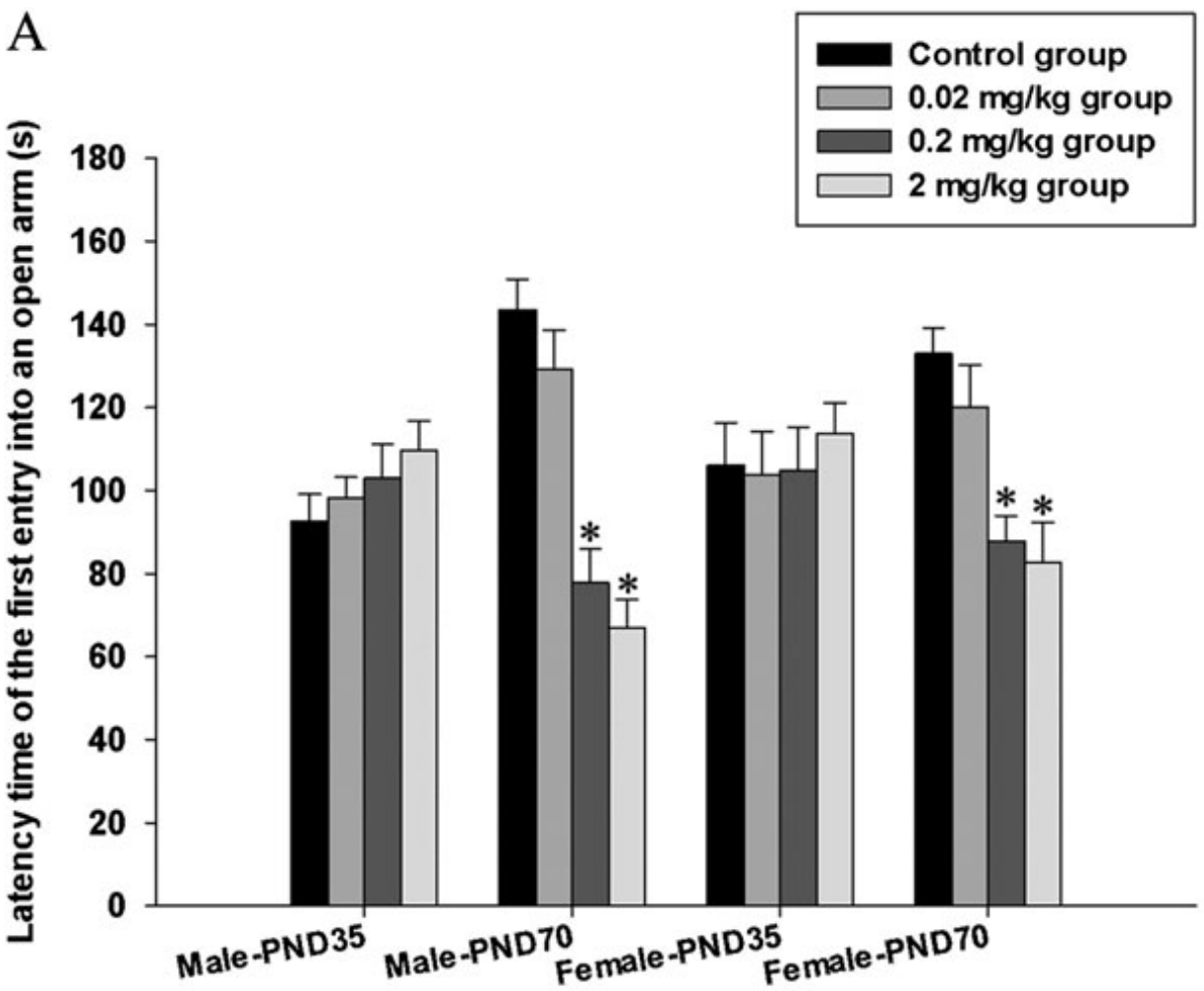
If exposure is less than the RfD then non-carcinogenic effects are unlikely!

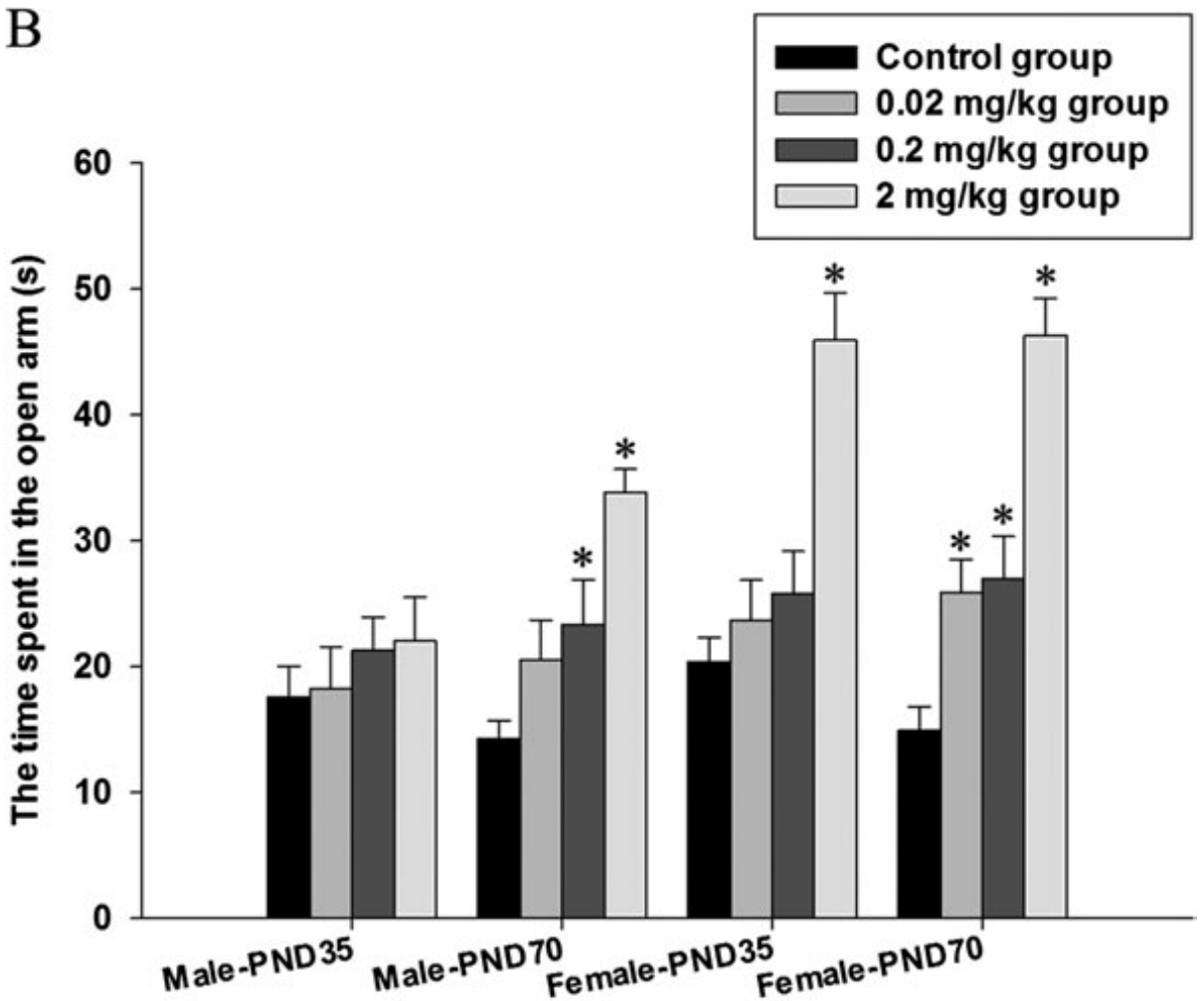
Elevated Plus Maze

used by Chen et al.

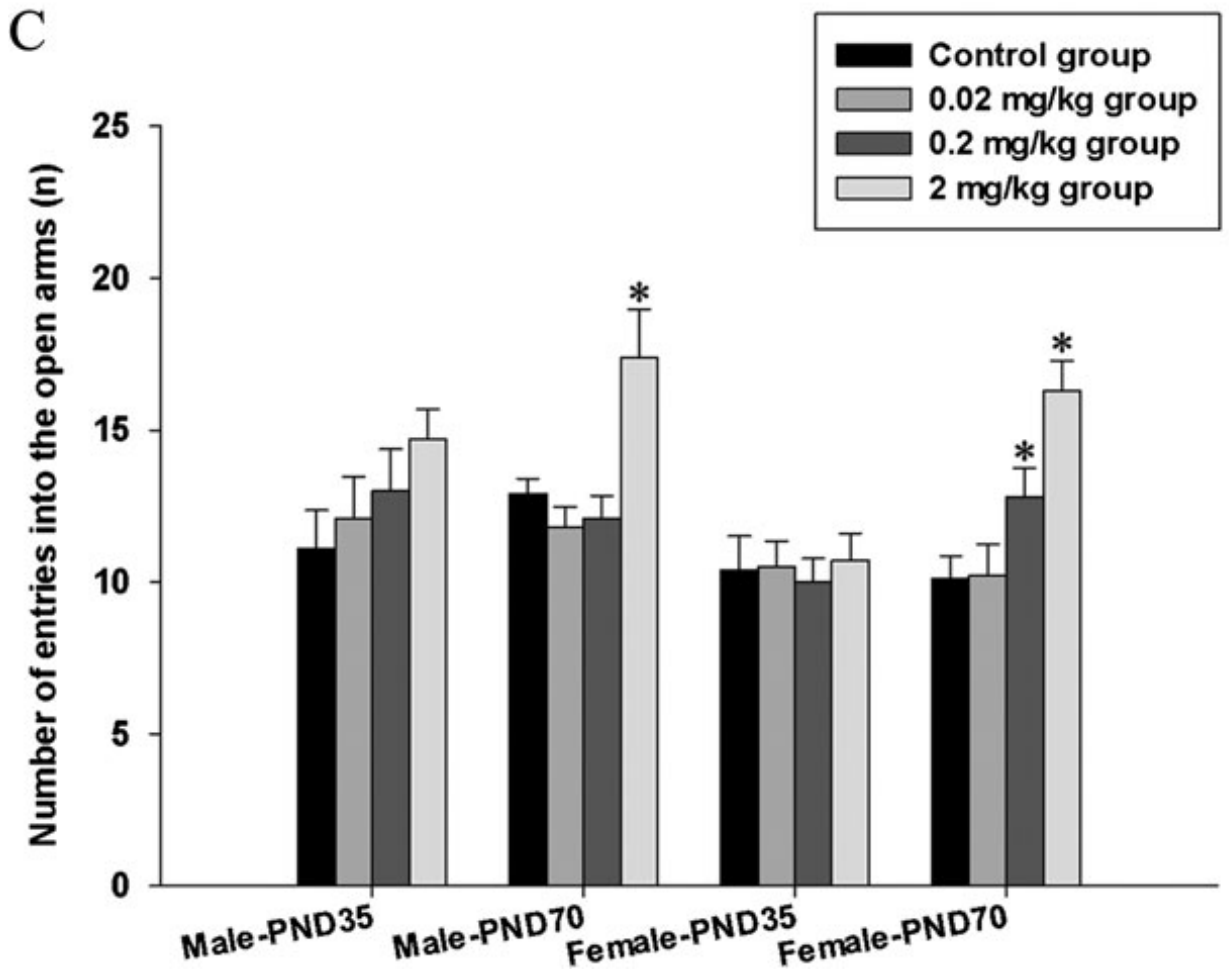
- Time spent in closed arms indicates higher anxiety
- Time spent in open arms indicates reduced anxiety

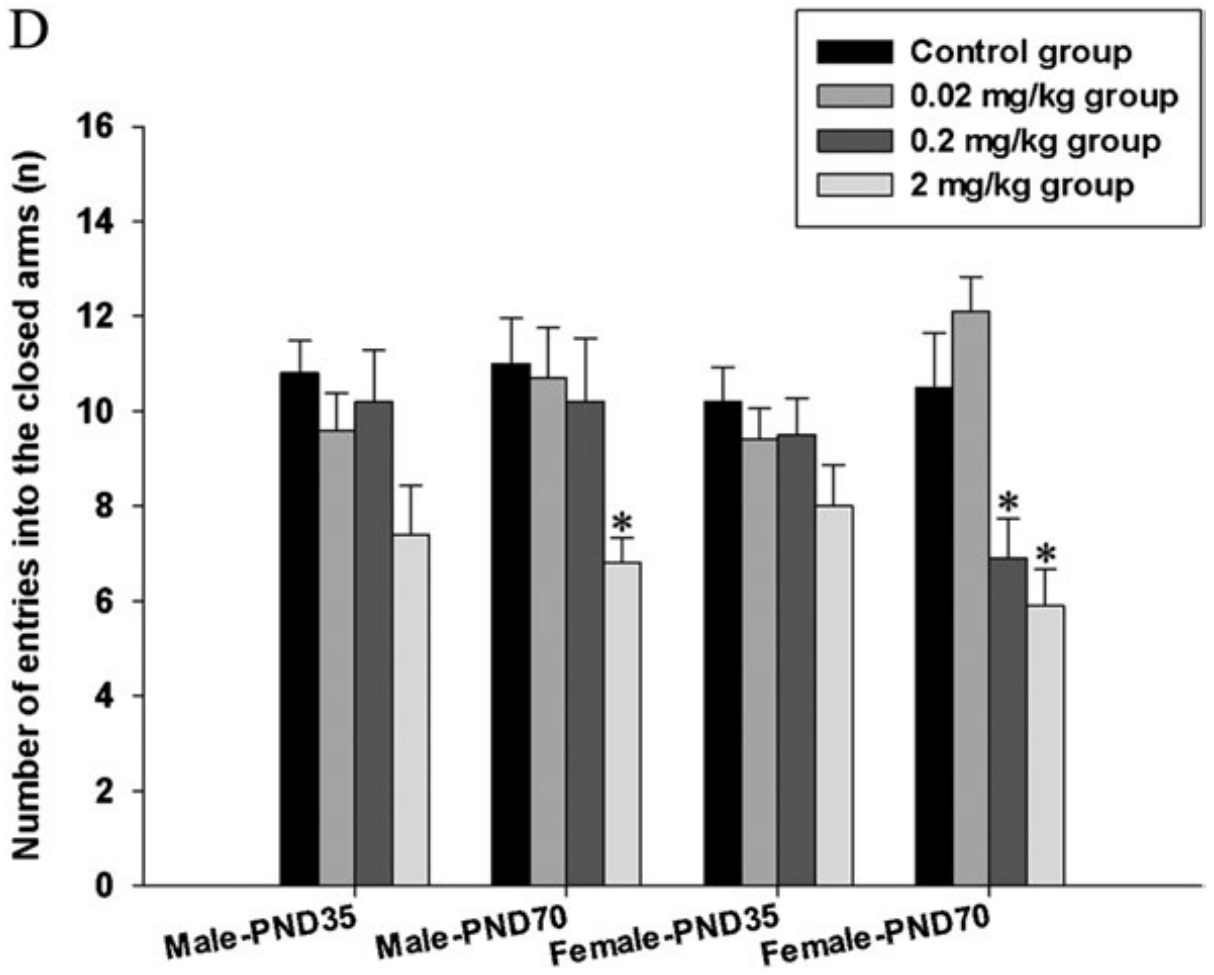






Chen et al. 2012





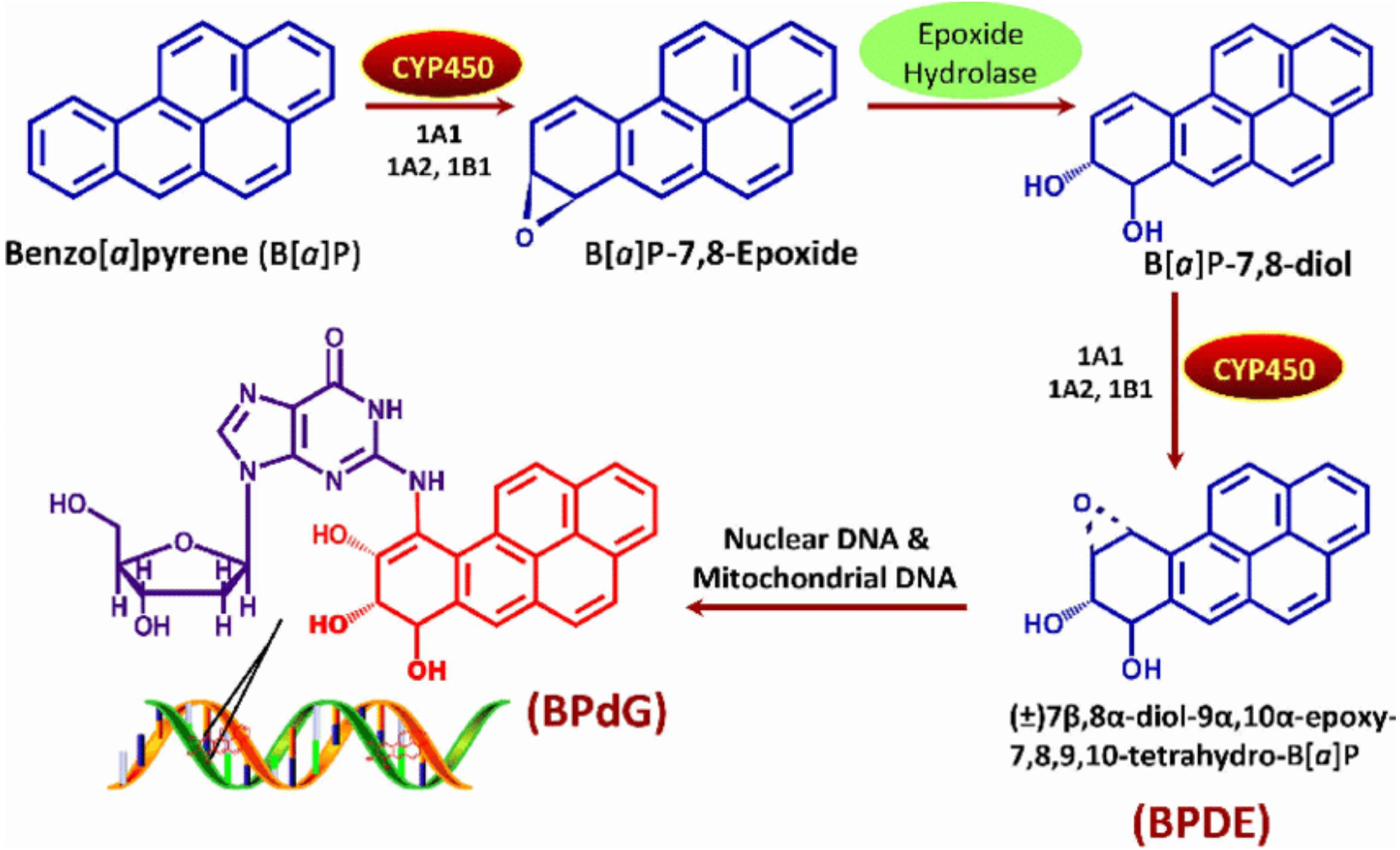
- Note that Chen and others did not calculate the BMD.
- EPA acquired their data to calculate it themselves for IRIS.

Chen et al. 2012

Benzo(a)pyrene Carcinogenic Effects

- Evidence from numerous studies demonstrate carcinogenicity in multiple animals and humans exposed via all routes of administration.
- Forestomach, liver, oral cavity, jejunum, duodenum, auditory canal, esophagus and larynx tumors
- Metabolites of BaP linked to mutations in genes that can lead to cancer
  - formation of BaP-specific DNA adducts
  - oncogene mutation
  - tumor suppressor gene mutation

- BaP is carcinogenic via a mutagenic mode of action (mutagen)
- Early life stage exposures to mutagens are more likely to cause cancer
  - Not enough data on kids to determine chemical-specific cancer effects from mutagens
  - Use an Age-Dependent Adjustment Factor
    - Multiply Cancer Slope Factor (CSF) by 10 for years 0-2
    - Multiply CSF by 3 for years 2-16
    - Net effect is to multiply CSF by 3.1 or divide HHC by 3.1



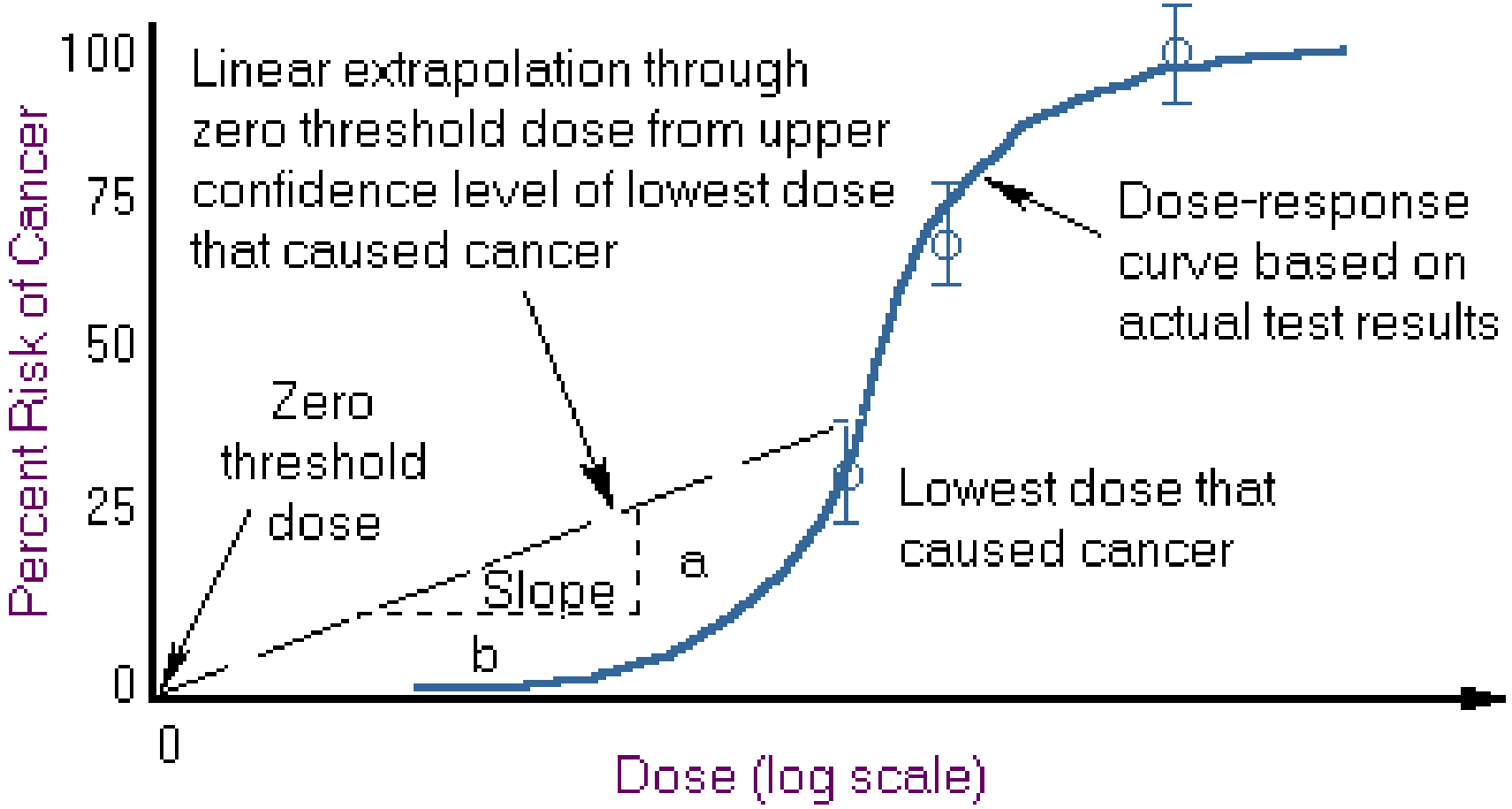
Source:
Barnes et al. 2018

BaP bioactivation process mediated by Cytochrome P450 enzymes that create BPDE.

BPDE targets primarily guanine (G) and adenine (A) DNA bases, creating BPgG DNA adducts that cause DNA mutations.

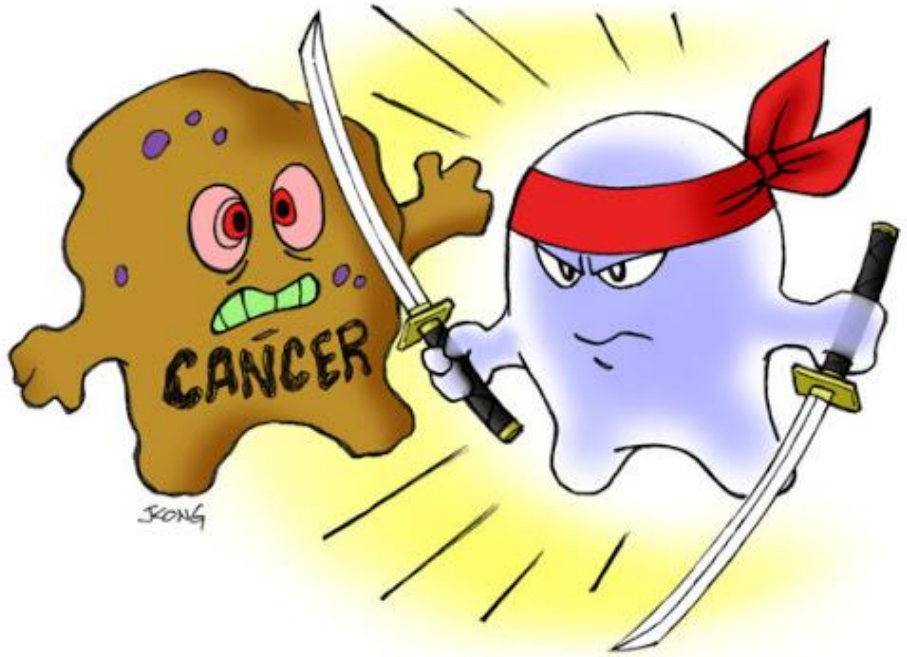
Oral Cancer Slope Factor (CSF) Development

- Dose-response is assumed linear for mutagens, based on existing studies
- Several models for low-dose extrapolation of high-dose responses:
  One hit
  Multihit
  Probit
  Multistage Weibull
  Linearized Multistage



Benzo(a)pyrene CSF model for IRIS

- Used the Multistage Weibull Model for BaP
  Predicts the probability of carcinogenic tumor by observation time (t) given the dose
- BMD calculated by finding a root of a nonlinear equation
- BMD is the estimate of a fatal risk response.
- BMDL is generally the 95% lower confidence limit of the BMD and typically used to generate the CSF. (IRIS used the 90% LCL for BaP.)



Adjust CSF for body mass

- Several approaches are available for adjusting human equivalent slope factors
  - $BW^{1/1}$ = direct proportionality
  - $BW^{2/3}$ = proportion based on skin surface area ratios
  - $BW^{3/4}$ = proportion based on the relative changes in proportions of organs as body mass increases (preferred)
- These adjustments are used to calculate a Human Equivalent Dose (HED)
- When the preferred $BW^{3/4}$ is used, then the Uncertainty Factor for animal to human toxicity is reduced to 3.

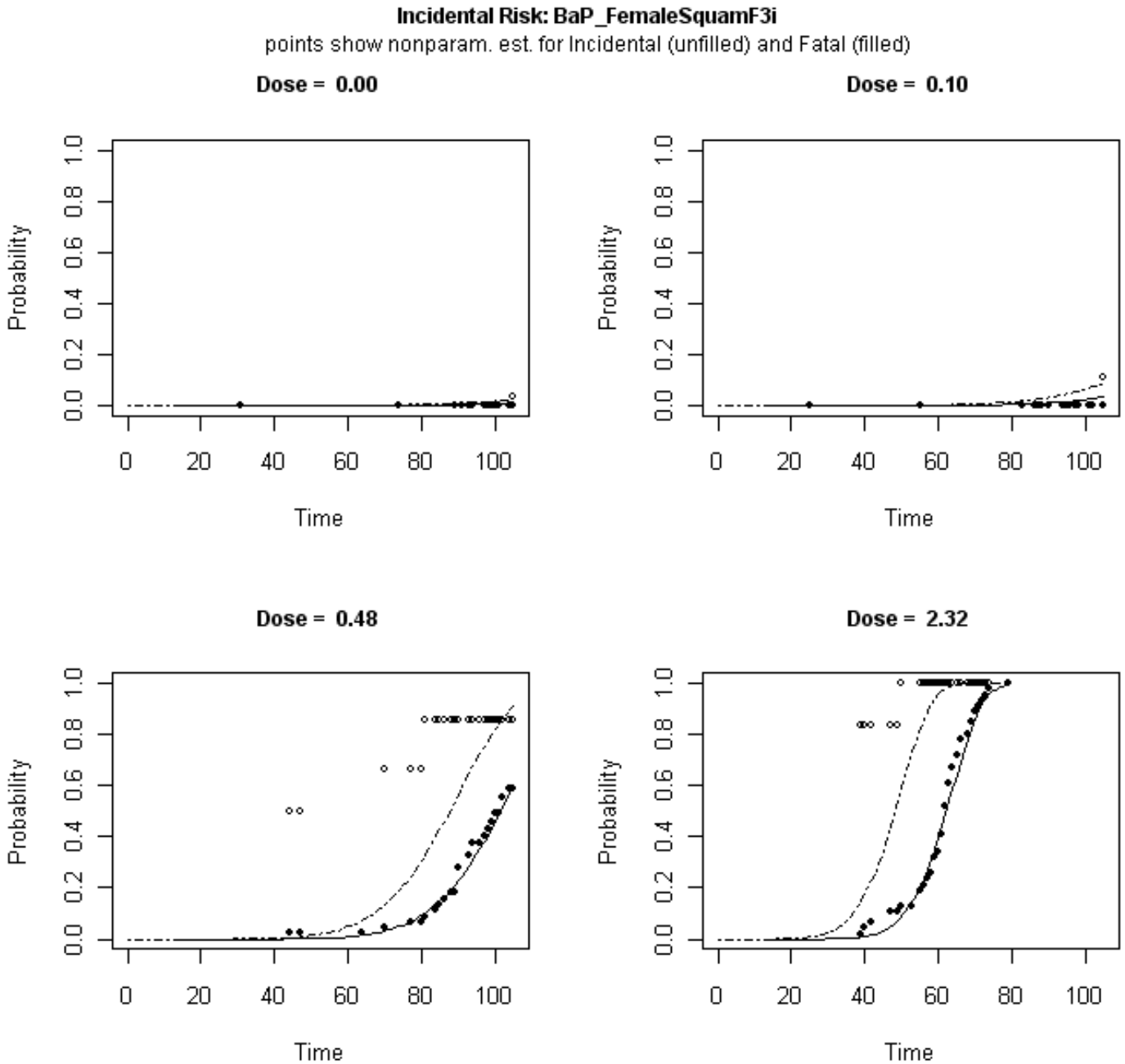
Benzo(a)pyrene CSF (2017)

- The current CSF is 1 per mg/kg*d, or $(1\ mg/kg*day)^{-1}$ based on Kroese et al. (2001) and Beland and Culp (1998)
  - Studied rats (Kroese et al.) and female mice (Beland and Culp)
  - Histological exams for tumors in many different tissues
  - Three exposure levels and controls
  - ~50 animals/sex/group
  - Treated for 2 years

- High dose treatment groups were all dead or moribund by week 79

- Significantly increasing trend in tumor incidence with increasing exposure

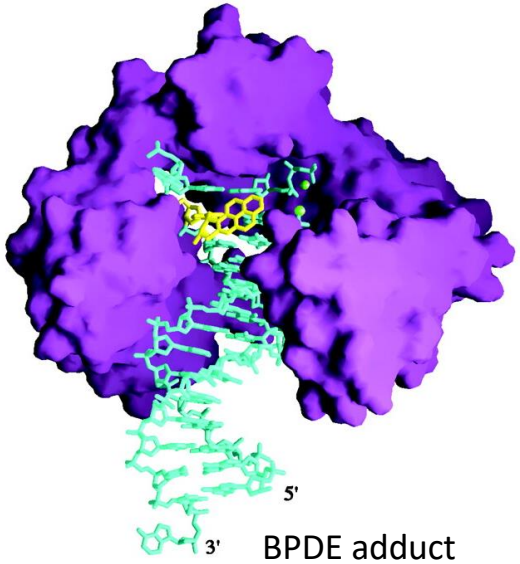
MGM/UA Entertainment Co. (1982)



- Probability of adenocarcinomas in duodenum or jejunum for female rats in Kroese et al. (2001).
- Solid circles mean the tumor was fatal

Dose = mg/kg
Time = days

Previous BaP CSF Assessment



BPDE adduct

- First IRIS CSF developed in 1992
- BaP was in Group B as probable human carcinogen (inadequate data)
- Developed four CSFs based on four different studies
  - 11.7 per mg/kg*d (Brune et al. 1981)
  - 5.9 per mg/kg*d (Neal and Rigdon 1967, 2-stage response model)
  - 9.0 per mg/kg*d (Neal and Rigdon 1967, linear extrapolation from 10% BMDL to background)
  - 4.5 per mg/kg*d (Neal and Rigdon 1967, Weibull model upper bound to reflect less than lifetime exposure)
- Each dataset had issues (less than optimal but were within 3-fold & equal merit)
- EPA used the geometric mean of these four CSF estimates :

Old BaP CSF = 7.3 per mg/kg*day

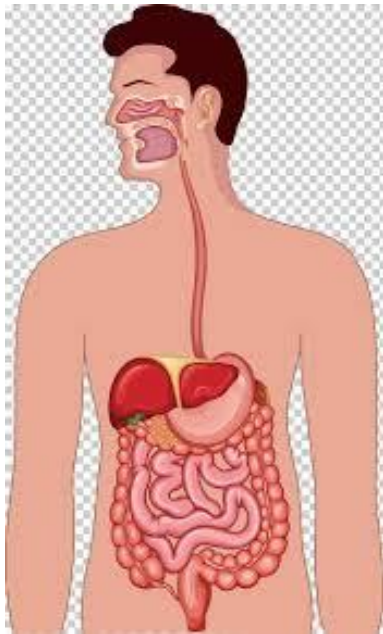
Brune et al. used only 32 rats/sex/group and variable dose timing
Neal and Rigdon only treated rats for one year

Determined POD and Slope Factor for each tumor type/location in Kroese et al. (2001) and Beland and Culp (1998)

Tumor	Species/Sex	Model	BMD (mg/kg*d)	POD = BMDL (mg/kg*d)	Slope Factor $(mg/kg*d)^{-1}$
Forestomach, squamous	Male rats	Multistage Weibull	0.453	0.281	0.36
Hepatocellular adenomas or carcinomas	Male rats	Multistage Weibull	0.651	0.449	0.22
Jejunum/duodenum adenocarcinomas	Male rats	Multistage Weibull	3.03	2.38	0.042
Kidney, urothelial carcinomas	Male rats	Multistage Weibull	4.65	2.50	0.040
Skin/mammary, basal cell squamous cell	Male rats	Multistage Weibull	 2.86 2.64	 2.35 1.77	 0.043 0.056
Forestomach, squamous	Female rats	Multistage Weibull	0.539	0.328	0.3
Hepatocellular adenomas or carcinomas	Female rats	Multistage Weibull	0.575	0.507	0.2
Jejunum/duodenum adenocarcinomas	Female rats	Multistage Weibull	3.43	1.95	0.05
Alimentary track, squamous	Female mice	Multistage Weibull	0.127	0.071	1.4

Uncertainties in the BaP CSF Development

- Humans do not have a forestomach so the duration of the exposure in the rodent forestomach would be longer
- Rat study used soybean oil and gavage compared with dietary for the mice
  - BaP is lipophilic so goes to lymph system, changing the exposure pathway
  - Gavage has higher peak concentrations that create nonlinear responses
- Rats dosed only 5 days/week (adjusted in calculations), mice dosed every day
- Alimentary tract tumors had 5-fold greater CSF, conservatively chosen
- Mouse study had 3-fold greater CSF compared to rats, conservatively chosen
- Used $BW^{3/4}$ scaling to extrapolate to humans, actual correlation is unknown
- Multistage Weibull model addressed additional data (time of death, etc.)
- Linear low-dose extrapolation increases cancer risk estimate,
  but data support linearity
- Assume mutagenic responses via ADAFs but actual responses
  may be different (no BaP-specific data)



Choosing the CSF

- Rat risk estimates spanned a 5-fold range
- No data to support any one result as most relevant to extrapolate to humans
- A geometric mean that gives equal weight to rats and mice would be:

  0.74 per mg/kg-day
- Lab studies do not account for sensitive populations,

  support use of highest value

  1.4 per mg/kg-day
- EPA chose the female mouse study

  (Beland and Culp 1998) to derive the CSF

BaP CSF = 1 per mg/kg/-day

CSF Conclusions

- Basically, IRIS split the difference between the highest value and the geometric mean to “hedge their bets” for sensitive populations.
- Multiply the CSF times the Exposure (Dose) and the product is the estimated ***probability of getting cancer in your lifetime*** due to those exposures.

  CSF x Dose = Risk

- In our case the probability is established as 1 in a million (1E-06) and we back calculate the dose to determine the concentration.

Questions?

What this means:

2015 CSF for BaP = 7.3 per mg/kg-d
2017 IRIS-revised CSF for BaP = 1 per mg/ kg-d

7.2 AWQC for Carcinogenic Toxicological Effects

For consumption of water and organisms:

$$\text{AWQC } (\mu g/L) = \frac{\text{toxicity value } (10^{-6} / \text{CSF}) \text{ [mg/kg-d]} \times \text{BW (kg)} \times 1{,}000 \text{ (µg/mg)}}{\text{DI (L/d)} + (\text{FCR (kg/d)} \times \text{BAF (L/kg)})}$$

$$= \frac{(10^{-6} / 7.3) \text{ mg/kg-d} \times 80.0 \text{ kg} \times 1{,}000 \text{ µg/mg}}{2.4 \text{ L/d} + (0.022 \text{ kg/d} \times 3{,}900 \text{ L/kg})}$$

$$= 0.0001243 \text{ µg/L}$$

$$= 0.00012 \text{ µg/L (rounded)}$$

With IRIS-revised CSF is
= 0.00091 µg/L

Or… 1.2×10^{-4} vs. 9.1×10^{-4}

WV's Remaining Criteria

We will be looking at data and info on these remaining WV criteria in upcoming meetings

Let's look at the spreadsheet…

Chemical	Units	WV Current Category A	EPA Recom. Criteria (ug/L)	Cat A WVMA* suggested Criteria (ug/L)
1,2-dichlorobenzene	mg/l	2.7	1	2
2,4,6-Trichlorophenol	µg/l	2.1	1.5	
2,4-Dichlorophenol	µg/l	93	10	17
2-Chloronaphthalene	µg/l	1000	800	1200
Acenaphthene	µg/l	670	70	200
Aldrin	ng/l	0.071	0.00077	0.097
alpha-BHC (alpha-Hexachlorocyclohexane)	µg/l	0.0039	0.00036	0.0034
Anthracene	µg/l	8300	300	1780
Benzo(a) Anthracene	µg/l	0.0038	0.0012	0.0038
Benzo(a) Pyrene	µg/l	0.0038	0.00012	0.0038
Benzo(b) Fluoranthene	µg/l	0.0038	0.0012	0.0038
Benzo(k) Fluoranthene	µg/l	0.0038	0.012	0.0038
beta-BHC (beta- Hexachlorocyclohexane)	µg/l	0.014	0.0080	0.012
Bis(2-Ethylhexyl) Phthalate	µg/l		0.32	
Butylbenzyl Phthalate	µg/l		0.10	6.5
Chlordane	ng/l	0.46	0.31	1.6
Chlorobenzene	mg/l	0.68	0.1	130
Chrysene	µg/l	0.0038	0.12	0.0038
Cyanide	µg/l	5.0	4	
DDT	ng/l	0.024	0.03	0.44
Dibenzo(a,h) Anthracene	µg/l	0.0038	0.00012	0.0038
Dieldrin	ng/l	0.071	0.0012	0.1
Diemethyl Phthalate	µg/l		2000	4100
Diethyl Phthalate	µg/l		600	58000
Di-n-Butyl Phthalate	µg/l		20	490
Ethylbenzene	mg/l	3.1	0.068	0.130
Fluoranthene	µg/l	300	20	46
Fluorene	µg/l	1100	50	270
gamma-BHC	µg/l	0.019	4.2	51
Heptachlor	ng/l	0.21	0.0059	0.17
Hexachlorobenzene	ng/l	0.72	0.079	0.89
Indeno(1,2,3-cd)Pyrene	µg/l	0.0038	0.0012	0.0038
Methoxychlor	µg/l	0.03	0.02	0.53
Methyl Bromide	µg/l	47	100	131
Pentachlorophenol	µg/l	0.28	0.03	0.08
Pyrene	µg/l	830	20	178

Additional discussion

HHC Workgroup Goals

- **Reasonable standards** – approvable by WV Legislature & EPA
- **Protective regulations** – to protect West Virginians
- **To Learn** – broaden horizons, gain a better understanding
- **To Reach Consensus** – agree on what to propose in 2021

January meeting

Does Wednesday Jan 27 at 10AM work for everyone?