Contaminated Media Forum

Consideration of Early Life Exposure to Carcinogens (ADAFs)

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Background

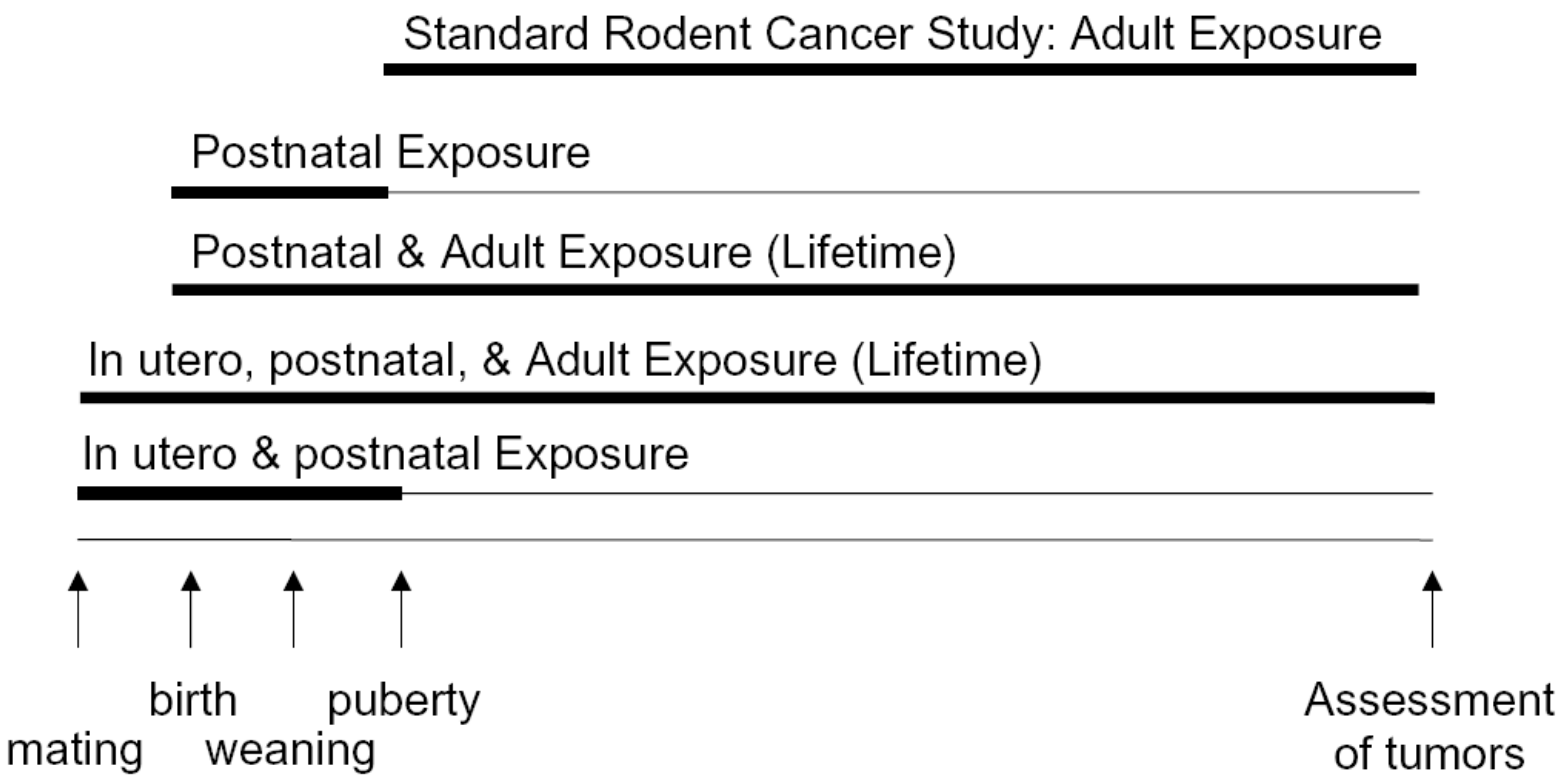


Figure 1. Study designs.

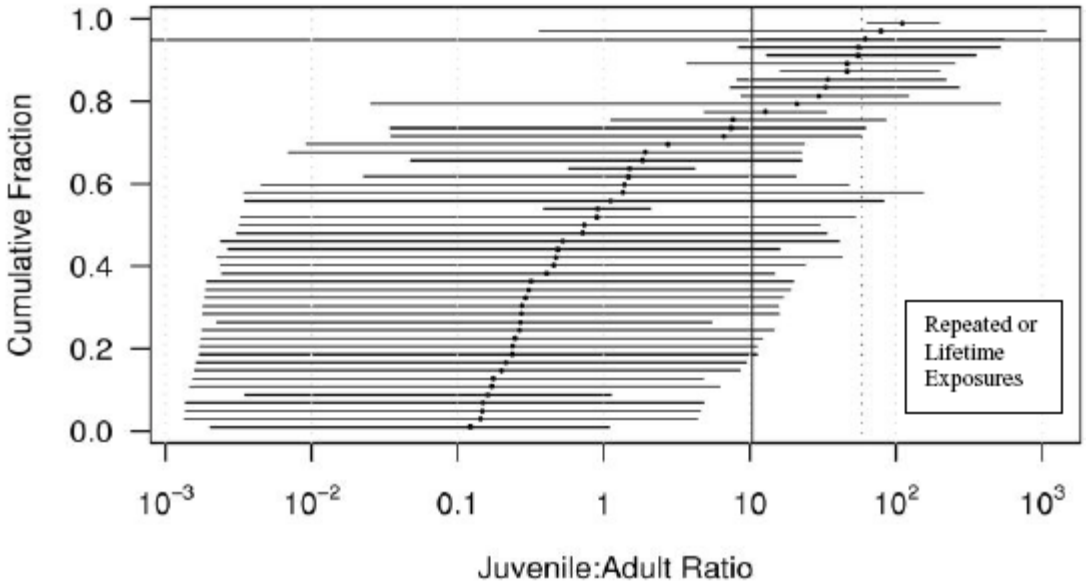
(EPA, 2005)

Exposure Averaging

- Animal Studies
  - Dose (mg/kg body weight) calculated as average amount of chemical divided by average body weight over exposure
- FDEP Residential Methods
  - Intake soil 120 mg/day (200 mg/day child and 50 mg/day adult)
  - Body weight 51.6 kg (15 kg child and 76.1 kg/day adult)
- EPA Residential Methods
  - Exposure broken down into child and adult age groups

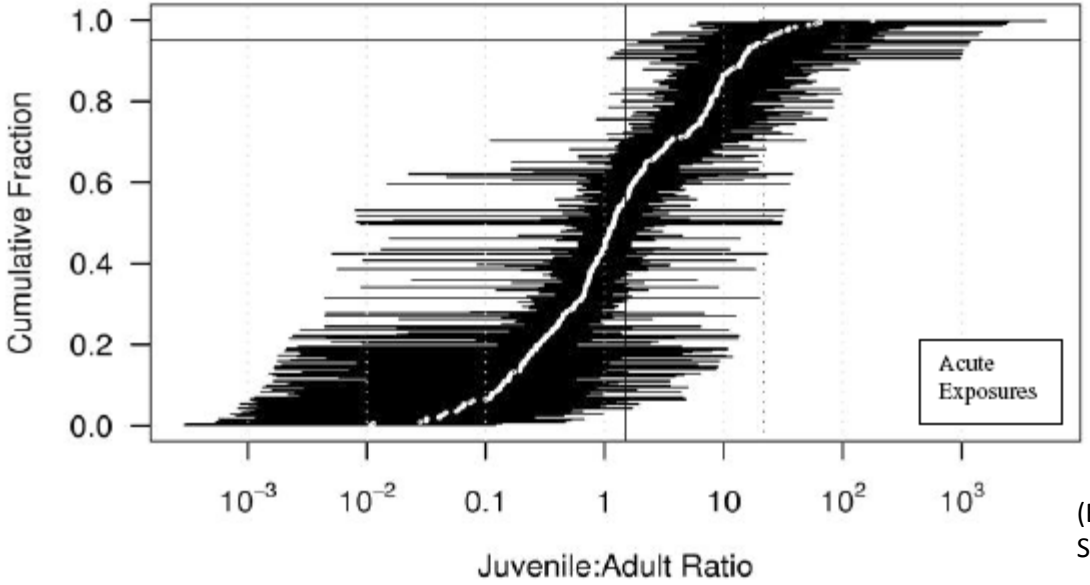
$$IFS_{res\text{-}adj}\left(\frac{36{,}750\ mg}{kg}\right) = \left(\frac{EF_{res\text{-}c}\left(\frac{350\ days}{year}\right) \times ED_{res\text{-}c}\left(6\ years\right) \times IRS_{res\text{-}c}\left(\frac{200\ mg}{day}\right)}{BW_{res\text{-}c}\left(15\ kg\right)} + \frac{EF_{res\text{-}a}\left(\frac{350\ days}{year}\right) \times \left(ED_{res}\left(26\ years\right) - ED_{res\text{-}c}\left(6\ years\right)\right) \times IRS_{res\text{-}a}\left(\frac{100\ mg}{day}\right)}{BW_{res\text{-}a}\left(80\ kg\right)}\right)$$

ADAF Guidance



45% of endpoints juvenile more sensitive

but… when more sensitive tend to be much more sensitive



Lifetime and repeated exposures show effect but not so much acute exposures.

(EPA, 2005 Supplemental Guidance for Assessing Susceptibility from Early-life Exposures to Carcinogens)

ADAF Guidance

Table 8. Summary of quantitative estimates of ratio of early-life to adult cancer potencies

Dose	Tissue	Number of chemicals	Inverse-weighted geometric mean ratio	Unweighted Minimum	Unweighted Maximum	Number of ratios	Percentage >1
Chemicals with mutagenic mode of action							
Repeated		4	10.5	0.12	111	45	42
Lifetime		3	8.7	0.18	79	6	67
	Combined repeated and lifetime	**6**	**10.4**	**0.12**	**111**	**51**	**45**
Acute	**Combined**	11	1.5	0.01	178	268	55
	Forestomach	3	0.076	0.01	1.9	32	16
	Harderian	2	0.48	0.06	0.8	20	0.0
	Kidney	2	1.6	0.17	7.1	18	78
	Leukemia	1	5.9	5.1	6.7	2	100
	Liver	5	8.1	0.10	40	70	77
	Lung	7	1.1	0.04	178	77	56
	Lymph	2	1.8	1.1	2.7	3	100
	Mammary (wk 5 vs wk 26)	1	7.1	NA	NA	1	100
	Mammary (wk 2 vs wk 5–8 or 26)	1	0.071	NA	NA	2	0
	Nerve	2	2.3	0.24	64	8	75
	Nerve (Day 1 comparison)	2	10	0.24	64	3	67
	Ovarian	1	0.033	0.01	0.13	3	0
	Reticular tissue	1	6.5	1.96	8.6	2	100
	Thymic lymphoma	1	2.8	1.01	7.9	6	100
	Thyroid	1	0.05	0.03	0.08	2	0
	Uterine/vaginal	1	1.6	0.03	8.6	3	67
	Day 1	7	1.7	0.01	178	127	55
	Day 15	3	1.5	0.06	52	74	65
Chemicals with nonmutagenic mode of action							
Repeated		6	2.2	0.06	13	22	27
Lifetime		5	3.4	0.15	36	38	21

ADAFs

0-2 = 10X

2-16 = 3X

16+ = 1X

(EPA, 2005)

Compounds Identified with Lifetime or Repeated Dose Studies

Diethyl Nitrosamine
Safrole
Urathane

Benzidine
3-Methyl Cholanthrene
Safrole
Vinyl Chloride

Vinyl Chloride already considered more potent for lifetime exposure (same study used in ADAF guidance)

Mutagenic Compounds

benzidine
benzo[a]pyrene (BaP)
dibenz[a,h]anthracene (DBA)
diethylnitrosamine (DEN)
n-nitrosodiethylamine (NDEA)
n-ethyl-n-nitrosoethanamine
dimethylbenz[a]anthracene (DMBA)
dimethylnitrosamine (DMN)
nitrosodimethylamine (NDMA)
n-methyl-n-nitrosomethanamine ethylnitrosourea (ENU)
3-methylcholanthrene (3-MC)
methylnitrosourea (NMU)
Safrole
Urethane
vinyl chloride

EPA ADAF Method

$$SL_{res\text{-}soil\text{-}mu\text{-}ing}\left(\frac{mg}{kg}\right) = \frac{TR \times AT_{res}\left(\frac{365\ days}{year} \times LT\left(70\ years\right)\right)}{CSF_o\left(\frac{mg}{kg\text{-}day}\right)^{-1} \times RBA \times IFSM_{res\text{-}adj}\left(\frac{166{,}833\ mg}{kg}\right) \times \left(\frac{10^{-6}\ kg}{mg}\right)}$$

where:

$$IFSM_{res\text{-}adj}\left(\frac{166{,}833\ mg}{kg}\right) = \left(\begin{array}{l} \frac{EF_{0\text{-}2}\left(\frac{350\ days}{year}\right) \times ED_{0\text{-}2}\left(2\ years\right) \times IRS_{0\text{-}2}\left(\frac{200\ mg}{day}\right) \times 10}{BW_{0\text{-}2}\left(15\ kg\right)} + \\ \frac{EF_{2\text{-}6}\left(\frac{350\ days}{year}\right) \times ED_{2\text{-}6}\left(4\ years\right) \times IRS_{2\text{-}6}\left(\frac{200\ mg}{day}\right) \times 3}{BW_{2\text{-}6}\left(15\ kg\right)} + \\ \frac{EF_{6\text{-}16}\left(\frac{350\ days}{year}\right) \times ED_{6\text{-}16}\left(10\ years\right) \times IRS_{6\text{-}16}\left(\frac{100\ mg}{day}\right) \times 3}{BW_{6\text{-}16}\left(80\ kg\right)} + \\ \frac{EF_{16\text{-}26}\left(\frac{350\ days}{year}\right) \times ED_{16\text{-}26}\left(10\ years\right) \times IRS_{16\text{-}26}\left(\frac{100\ mg}{day}\right) \times 1}{BW_{16\text{-}26}\left(80\ kg\right)} \end{array}\right)$$

Options

- Adopt EPA methods completely
  - Ease of implementation
  - Would impact all carcinogens (~ 2x lower)
- Use EPA age grouping for mutagenic carcinogens only
  - Not technically consistent
- Use ADAFs for specific compounds with data support
  - Complicated to ID chemicals
  - Not technically consistent
- Don't use ADAFs

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