

# **Age-Dependent Child Protective Factors: Overview of Agency Guidance and Practice**

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# Goals and Objectives of Presentation

- EPA's tools for assessing early-life susceptibility
- EPA's Supplemental Cancer Guidelines
- Guidance implementation

## *The National Research Council*

**"EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults."** *Science and Judgment in Risk Assessment  
National Research Council, 1994*

- "Children's risk" can mean different things to different people:
  - Effects manifested during childhood.
  - Early-life exposures that can contribute to effects at any time later in life.
- In the cancer guidelines, EPA is interested in both.



# Guidance and Tools for Evaluating Risks to Children

- Guidelines for Carcinogen Risk Assessment (2005)
- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (2005)
- Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Contaminants (2005)
- A Framework for Assessing Risks of Environmental Exposures to Children (2006)
- Child-Specific Exposure Factors Handbook (2008)

# Key Features of US EPA's 2005 *Cancer Guidelines*

- Increased emphasis on analyzing data before invoking default options.
- Emphasis on understanding underlying mode of action throughout the guidelines.
- Weight-of-evidence narrative replaces the previous “A-B-C-D-E” classification scheme.
- Two-step dose-response process separates modeling the observed data, from extrapolation to lower doses.
- Linear and nonlinear extrapolations are considered.
- Differential risks to children are addressed.

# Framework for Evaluating a Hypothesized Mode of Action

- Description of the hypothesized mode of action.
- Discussion of experimental support for the hypothesized mode of action.
- Consideration of the possibility of other modes of action.
- Conclusions about the hypothesized mode of action:
  - a. Is the hypothesized mode of action sufficiently supported in the test animals?
  - b. Is the hypothesized mode of action relevant to humans?
  - c. Which populations or lifestages can be particularly susceptible to the hypothesized mode or action?
    - *Question is both qualitative and quantitative*
    - *Quantitative differences are used in the dose-response assessment*

# Key Features of US EPA's 2005 *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*

- When chemical-specific data permit, develop separate potency estimates for early-life exposure.
- When such data are absent, adjust risk for carcinogens with a mutagenic mode of action using standard factors:
  - 10 for ages <2 yr
  - 3 for ages 2 to < 16 yr
  - 1 for ages ≥ 16 yr
  - ❖ Overall: 1.6-fold adjustment for constant lifetime exposure under certain standard exposures.
- Interest in identifying and characterizing attendant risk implications for:
  - Other modes of action
  - Uniquely susceptible lifestages
  - In utero/transplacental carcinogenesis

# Literature Review and Study Inclusion Criteria: Key Points

- Comparative data across ages for analysis available for 18 chemicals.
- Lifetime versus adult exposure comparisons.
- Postnatal exposure for juvenile rats and mice at ages younger than standard 6 - 8 week start for bioassays.
- Adult rats and mice exposure beginning at 6 to 8 weeks old, comparable to standard cancer bioassay.
- Same study or lab (if not concurrent) with multiple ages to control cross-lab experimental variables.
- Same strain/species to eliminate strain-specific responses.
- Approximately same dose across ages to eliminate dose-dependent responses confounding age-dependent responses.
- Similar latency period following exposures at different ages to control period for tumor expression.
- Number of affected animals and total number of animals examined was available or reasonably reconstructed for control, young, and adult groups.

# Chemicals Evaluated

- Chemicals with proposed mutagenic modes of action:
  - Benzidine
  - Benzo[a]pyrene
  - Dibenzanthracene
  - Diethylnitrosamine
  - Dimethylbenz[a]anthracene
  - Dimethylnitrosamine
  - Ethylnitrosourea
  - 3-Methylcholanthrene
  - N-Methylnitrosourea
  - Safrole
  - Urethane
  - Vinyl chloride
- Chemicals with proposed non-mutagenic modes of action:
  - Amitrole
  - DDT
  - Dieldrin
  - Diphenylhydantoin
  - Ethylenethiourea
  - Polybrominated biphenyls

# Final Recommendations

- Default adjustments only used when chemical-specific data not available to address early-life exposure.
- EPA considered advantages and disadvantages of extending application of ADAFs to carcinogens whose MOA is unknown.
- EPA's final recommendation is to apply ADAFs only for carcinogens acting through a mutagenic MOA.
- When MOA is unknown, use of linear, no threshold extrapolation is considered health protective.

# Example Calculation

Risk = Exposure dose (mg/kg-d) × CSF (per mg/kg-d) × duration/lifetime × ADAF

Example 1: Unknown MOA

Risk  $2 \times 10^{-4} = 0.0001 \text{ mg/kg-d} \times 2 \text{ per mg/kg-d}$

Example 2: Mutagenic MOA for risk estimates from **lifetime** exposure

Risk for birth through < 2 yr = (2 per mg/kg-d) × **10** (ADAF) × (0.0001 mg/kg-d) × 2yr/70yr =  $0.6 \times 10^{-4}$

Risk for ages 2 until < 16 = (2 per mg/kg-d) × **3** (ADAF) × (0.0001 mg/kg-d) × (14yr/70yr) =  $1.2 \times 10^{-4}$

Risk for ages 16 until 70 = (2 per mg/kg-d) × **1** (ADAF) × (0.0001 mg/kg-d) × (56yr/70yr) =  $1.5 \times 10^{-4}$

Risk  $3.3 \times 10^{-4} = 0.6 \times 10^{-4} + 1.2 \times 10^{-4} + 1.5 \times 10^{-4}$

This example assumes the same exposure (mg/kg-d) at every age by the oral route.



# 2005 *Cancer Guidelines* Implementation Memos

The Cancer Guidelines and Supplemental Guidance should be used:

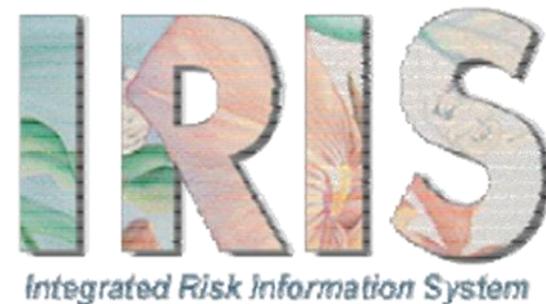
- for all carcinogenicity risk assessments that are newly initiated.
- recommendation to apply ADAFs for chemicals included in the Supplemental Guidance analysis for which IRIS assessments are available: benzidine, benzo[a]pyrene, diethylnitrosamine, and dimethylnitrosamine.
- recommendation to apply ADAFs when using the relative potency factor approach to estimate cancer risk associated with exposure to polycyclic aromatic hydrocarbon (PAH) mixtures since benzo[a]pyrene is used as the index chemical.

Implementation memos available at  
<http://epa.gov/cancerguidelines>

# EPA's Draft *Framework for Determining a Mutagenic Mode of Action for Carcinogenicity*

- External review draft released for public comment and peer review in September 2007.
- Summary Report of the Peer Review Meeting released in May 2008.
- Risk Assessment Forum (RAF) Technical Panel currently in the process of revising the report.
- Publicly released document available at <http://epa.gov/osa/mmoaframework/index.htm>

# Early-Life Susceptibility and EPA's Integrated Risk Information System



For all IRIS assessments with human or animal cancer data:

- 1) all mode of action data are evaluated with particular attention to early-life susceptibility,
- 2) early-life-specific cancer slope factors may be derived if data are available, regardless of the mode of action,
- 3) mutagenic mode of action determinations and recommendations for the application of ADAFs are made, as appropriate.

# IRIS Assessments with a Determination of a Mutagenic Mode of Carcinogenic Action

- Dichloromethane (2012)
- Trichloroethylene (2011)
- Chloroprene (2010)
- Acrylamide (2010)
- 1,2,3-Trichloropropane (2009)



# Examples: EPA Program Office and Regional Application of ADAFs in Risk Assessment

- Program and Regional Offices routinely incorporate ADAFs as appropriate for assessing risks when early-life exposure is of concern for chemicals identified on IRIS, etc., as having a mutagenic mode of carcinogenic action.
- Office of Solid waste and Emergency Response Implementation webpage -  
<http://www.epa.gov/oswer/riskassessment/sghandbook/chemicals.htm>