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Cancer Risk Assessment for Less-Than-Lifetime Exposure at Contaminated Sites

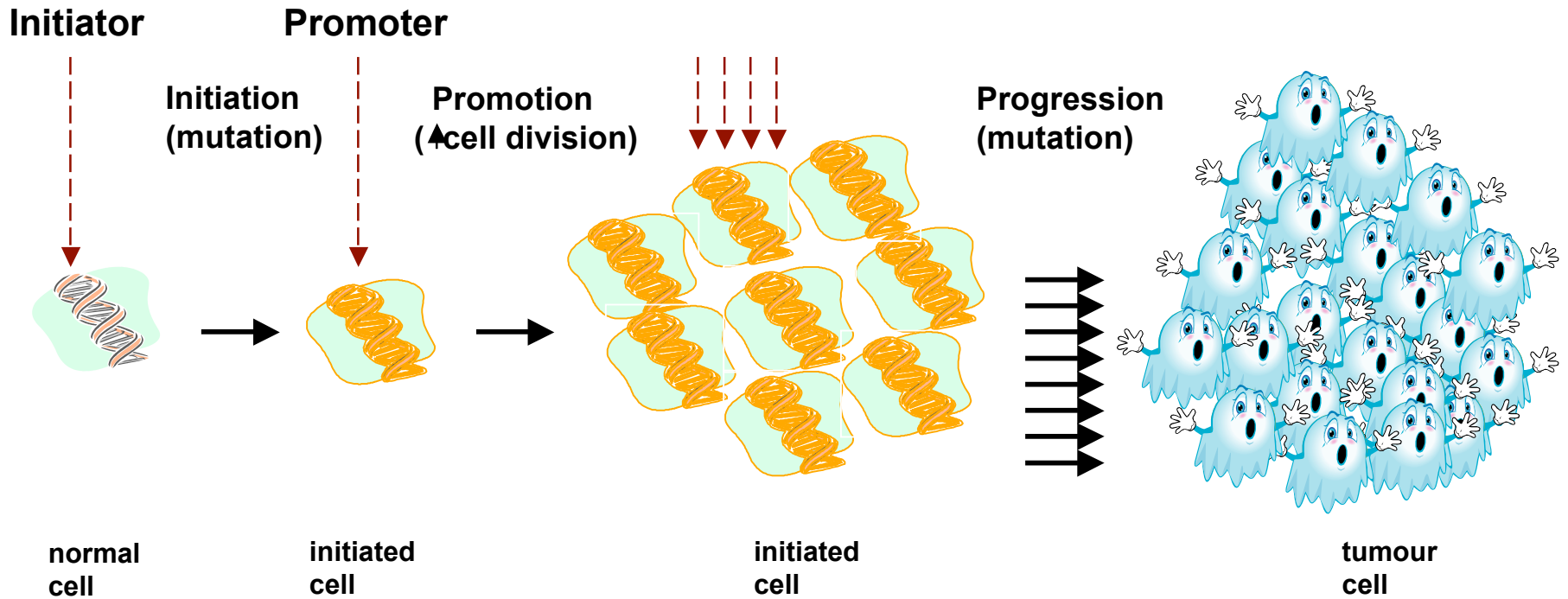
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Contaminated Sites Division, Health Canada***

***Federal Contaminated Sites National Workshop
Vancouver, April 28-May 1, 2008***



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What do we know about cancer process?



Initiated cell ≠ tumour cell



Cancer Induction by Cancer Causing Agents

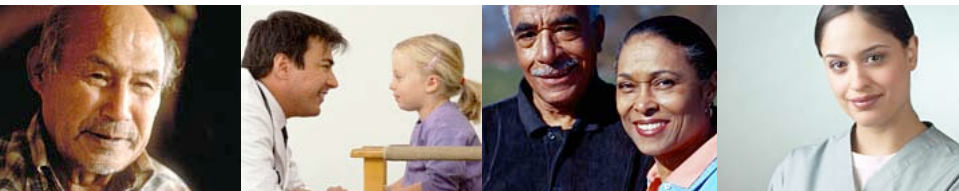
➤ Multistage sequential process

- **Initiation** – alter cell, irreversible, can be single exposure
- **Promotion** – stimulate cell division, reversible, repeated exposure
- **Progression** – initiated cell turns neo-plastic, mutational event

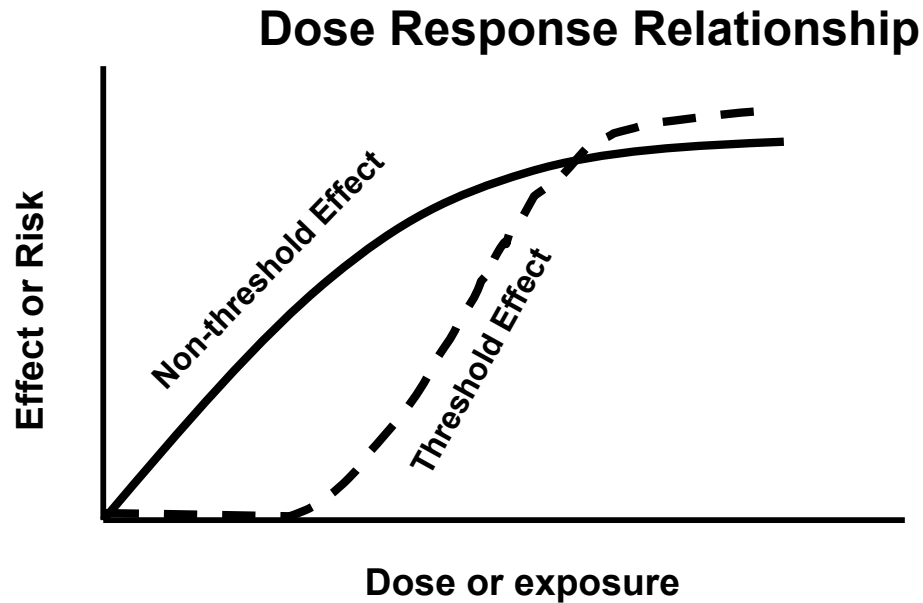
Result from multiple failure of repair mechanisms

➤ Generally long latency

➤ Generally long-term exposure



How do we evaluate cancer risk ?



mutagenic carcinogens = non-threshold

risk = cancer slope factor x dose



Current Risk Characterization Practice

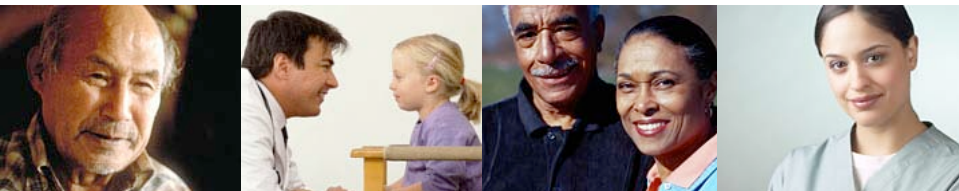
Incremental Lifetime Cancer Risk = cancer slope factor x exposure

Cancer slope factor

- **Based on empirical data**
 - **Animal bioassay – near lifetime exposure**
 - **Human epi study – long-term exposure**
- **Lifetime risk per mg/kg-d**
- **Involved process**

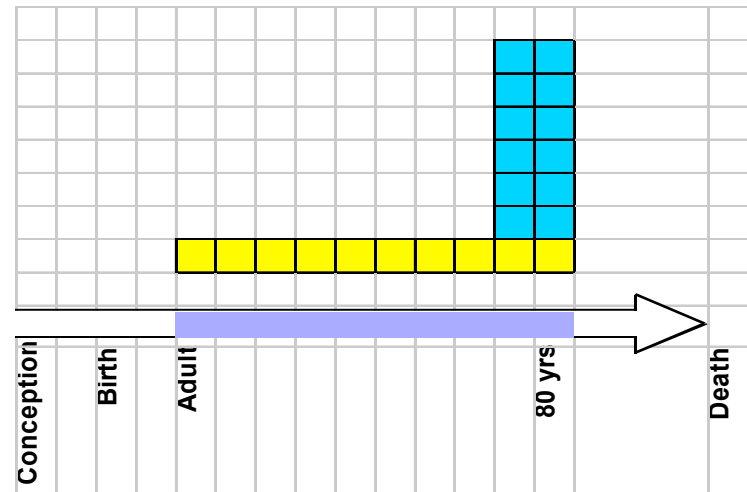
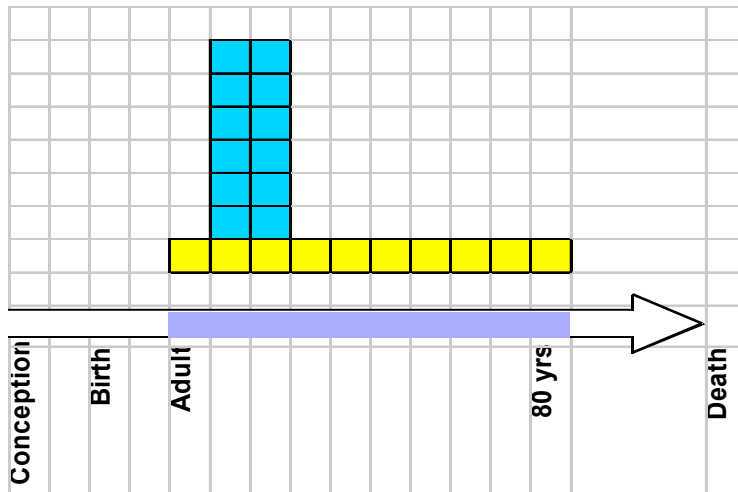
Exposure

- **Site-specific, receptor-specific**
- **mg/kg/d**
- **LADD**
- **More certain when exposure duration \approx lifetime (empir. data source)**





Questions



Are the risks equivalent?

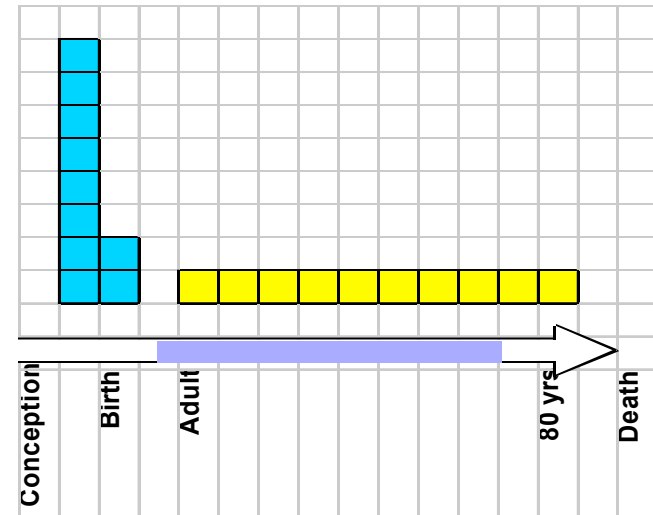
Does only “total exposure” matter?

Is timing important?





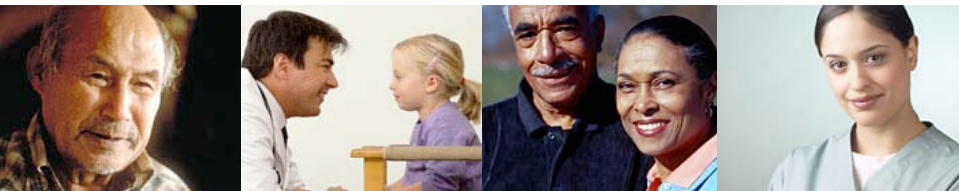
Questions



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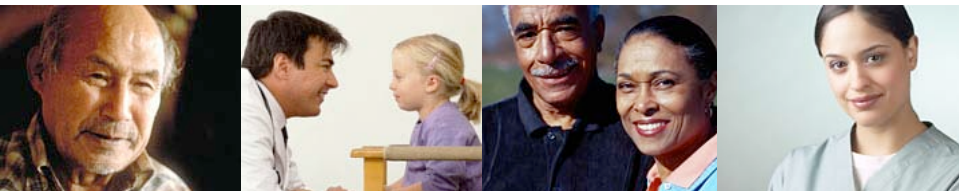
Contractor Reports

Contaminated Sites Division

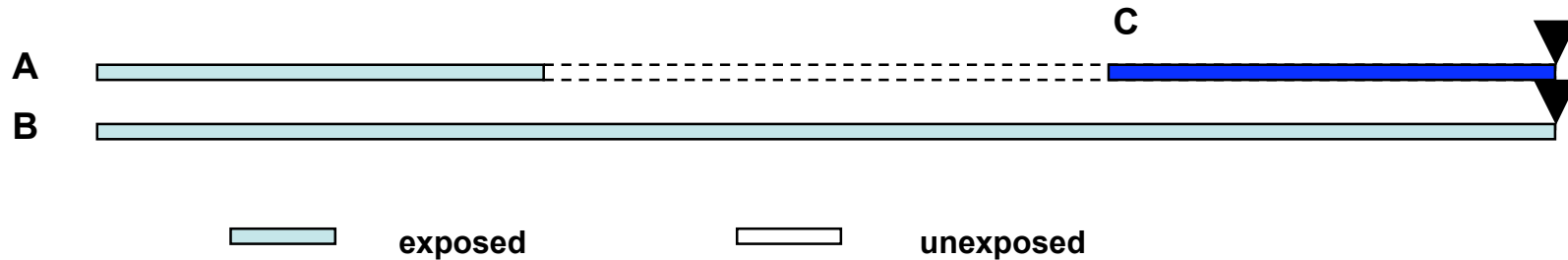
- Brand 2004
- GlobalTox 2005
- Wilson 2006
- Orr 2007
- Al-Zoughool and Krewski 2008

Other Reports

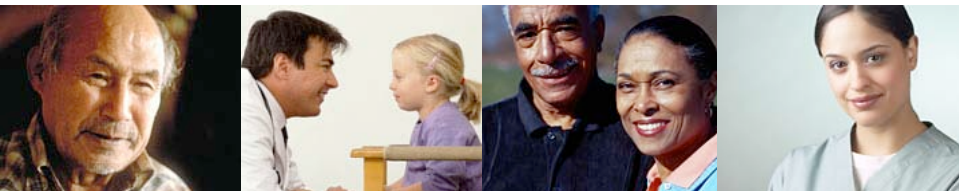
- Reviewed reports available from various sources



Dose Averaging: Adult Animal Data



- **NTP chronic bioassay + stop exposure (11 chemicals) (Halmes *et al.* 2000)**
 - Response rate: $A > B$ for more than half of chemical/sites, 46% same response rate
 - When A included in ED_{01} estimate - effect varied (47 sites)
 - 79% ↓ (50% by > 2-fold)
 - 21%↑
 - Median equiv. ave. time $\approx \frac{1}{2}$ lifetime (LADD under predicts potency by 2-fold)
- **Similar radiation dose 3-fold less effective in elderly rodents (19-21 mo - C) than young adults (4-6 mo) (Hattis *et al.* 2004)**



Adults: Epidemiological data

➤ **Asbestos & lung cancer:**

LADD underestimates risks when remaining lifespan exceeds latency period (Hauptmann et al. 2002)

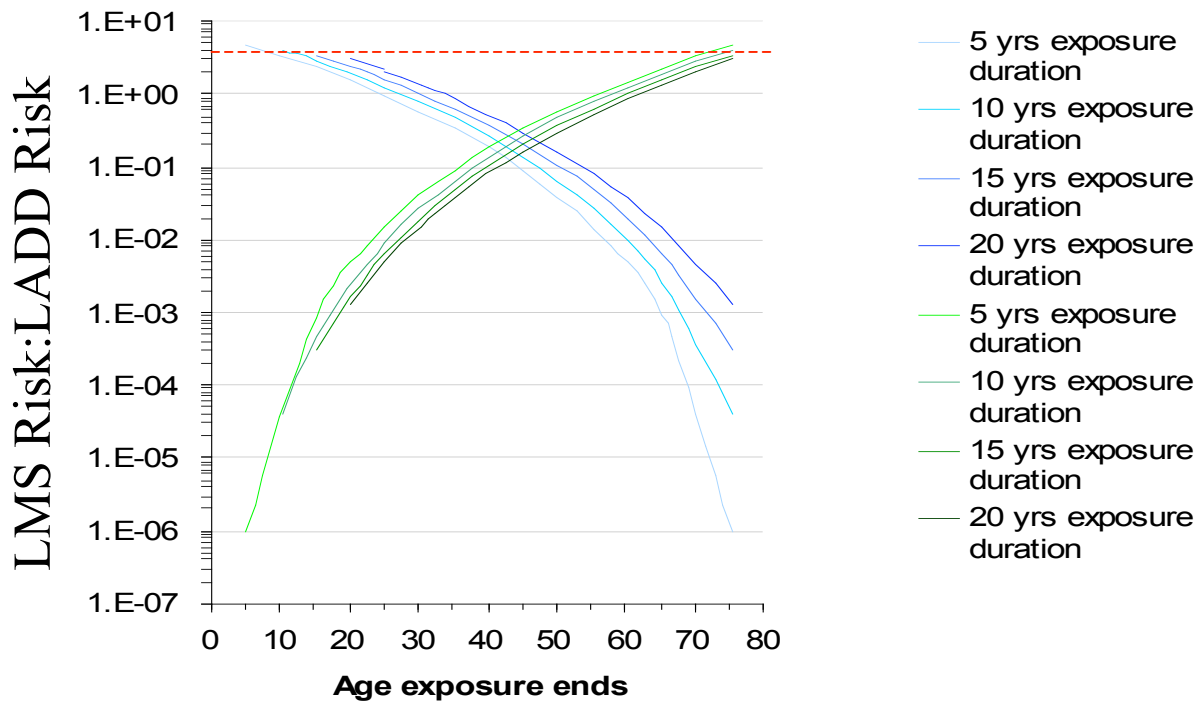
➤ **Sunlight & skin cancer:**

acute high dose exposure risks > chronic low level (Kricker et al. 1995; Elwood et al., 1985)



Adults: Modeling

Cancer risk estimates for initiator (blue) and completer (green) using 6 stage LMS AD model of carcinogenesis Vs LADD

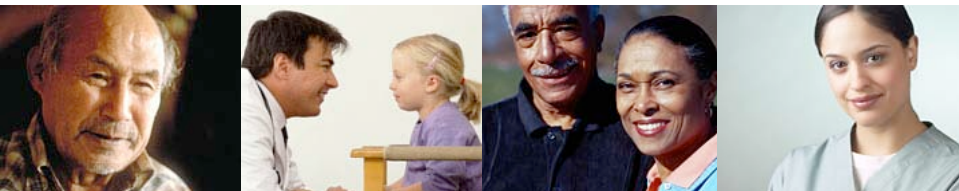


Adults: Health Canada interim position

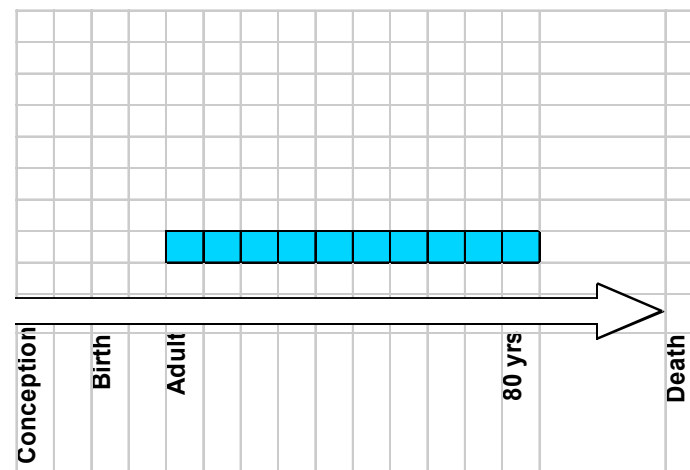
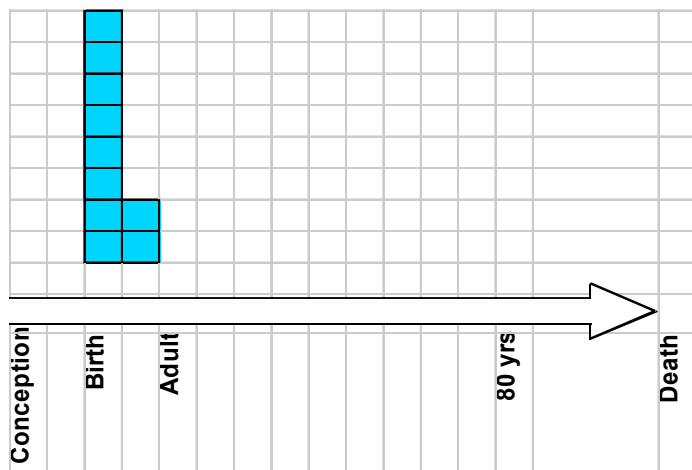
➤ Status quo (LADD)

➤ Because:

- Present (limited) evidence (animals, epi, modelling studies) suggests LADD overestimates risk as likely as it underestimates; depends on timing and mode of action
- Variance is small in most cases
- Limited data on which to make chemical-specific adjustments

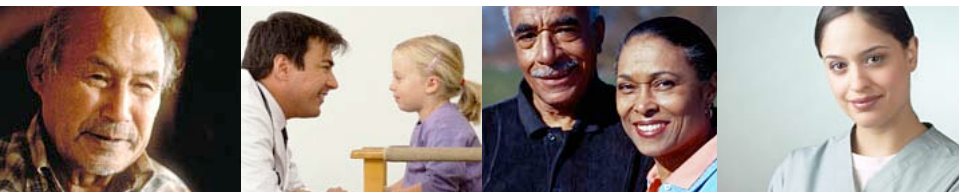


Early life stages – Cancer risk



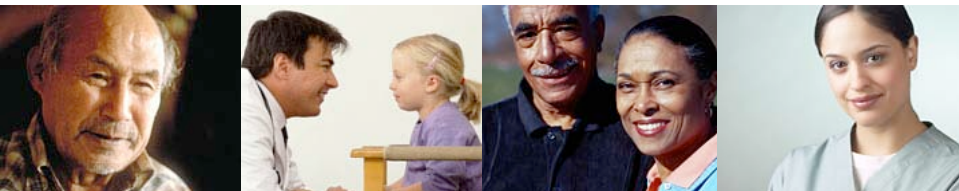
Same lifetime total dose:

- Is risk from early-life exposure equivalent to risk for late-life exposure?



Early Life Susceptibility

- Pharmacokinetic differences
- More frequent cell division
- Some embryonic cells, lack key DNA repair enzymes
- Immature immune system
- Hormonal differences
- Developmental abnormalities → carcinogenic effects later in life
- Initiation can occur relatively rapidly
- Long latency before tumour development



Early Life Susceptibility: Evidence

Perinatal + adult vs adult-only exposure (same study)

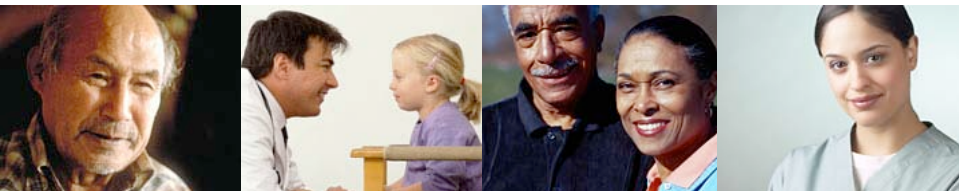
➤ Increased tumour frequency or

➤ Reduced latency

(Barton et al., 2005; Chhabra et al., 1993; Peto et al., 1984;
Vesselinovitch et al., 1979 and others)

➤ Tumours at same sites following either perinatal or adult exposure

(USEPA, 2005)



US EPA Age-Dependent Adjustment Factors (ADAFs)

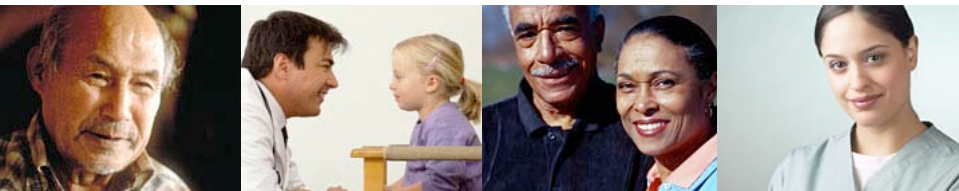
➤ for early-life stage

10 (0 to < 2 yrs)
3 (2 yr to < 16 yrs)

for adult stage

1 (16+ yrs)

- Applied to slope factor, *only* if no age-specific slope factor
- *Mutagenic* carcinogens only
- Life-stage(i) exposures averaged over lifetime (LADD_i)
- Life-stage specific intake rates



Health Canada Interim Position: Less-than-lifetime Exposure For Cancer RA

Lifetime cancer risk

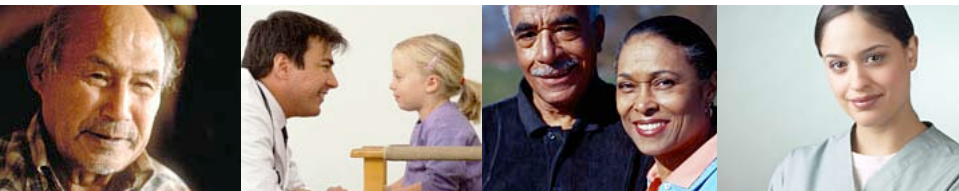
$$= \sum (SF * ADAF_i * LADD_i)$$

SF = cancer slope factor

ADAF_i = age-dependent adjustment factors for lifestage i

LADD_i = dose received during lifestage i averaged over a lifetime

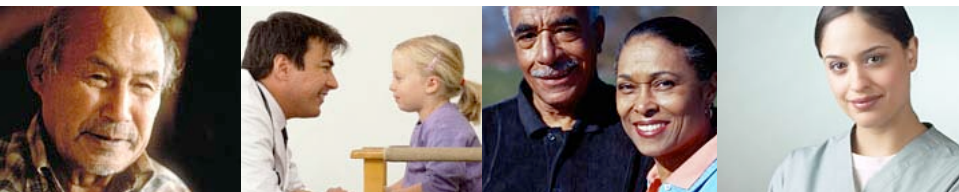
***ADAF is applied to slope factor for carcinogens with mutagenic mode of action**



Health Canada CSD Interim Position: ADAFs

Lifestage	Ages	Default ADAFs*
Infant	0 – 6 mo	10
Toddler	7 mo – 4 yrs	5
Children	5 – 11 yrs	3
Teenager	12 – 19 yrs	2
Adult	20+	1

***USEPA's ADAFs adjusted to fit Health Canada's age groups, to be used if no chemical-specific age-specific slope factor**



Interim position vs current practice

Exposure scenario	Risk ratio (interim: current)
• 6 mo from birth	10
• 2 yr from birth	5
• 2 yr as toddler	5
• 2 yr as adult	1
• 30 yr from birth	5
• 30 yr since 5 yr of age	4

