What if you have carcinogens at your sites but the exposure is short?

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How do guidelines handle carcinogens?

• Guidelines are based on typical sites, e.g. residential, commercial or industrial land uses (long-term exposures)

• It is acceptable to calculate lifetime average daily dose (LADD) for long-term exposure to estimate cancer risk
What if people don’t use your site very often?

• What if exposure is short-term and infrequent?

• **Is it OK to average the short exposures over a lifetime and use LADD to estimate cancer risk?**
Why is this an important question?

Due to potential cost implications and uncertainties in the science

- risk assessment could be more conservative than required, resulting in higher clean-up cost

BUT

- Averaging short exposure over a lifetime may not be scientifically valid, or protective of human health
Comparison of ‘risk-based levels’ for long-term and short-term exposures

- Table assumes lifetime exposure or 2-week exposure for adults (averaged over a lifetime)
- Need to ensure levels are protective of human health

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Risk-based level* - lifetime exposure (mg/kg)</th>
<th>Risk-based level* - 2-week exposure (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>17</td>
<td>35,000</td>
</tr>
</tbody>
</table>

*excluding background
Short-term exposure to carcinogens

• Dose-averaging over a lifetime (LADD) for a short-term exposure (e.g., 2 weeks or 6 months) may be unrealistic and unsupportable

• Guidance required for assessments to be technically acceptable, protective of human health, and not overly conservative
We have some answers for the time being, but…

- limited information
- some patterns
- enough information to provide interim guidance
- interim guidance not to be used as a substitute for professional judgement
CSD interim guidance for adult exposures

- LADD may overestimate risk as much as it underestimates risk depending on timing and mode of action
- Variance is small in most cases
- Limited data on which to make chemical-specific adjustments
- For adult exposure, averaging short exposures over a lifetime can be done with sufficient scientific evidence
- Short-term exposure must consider non-carcinogenic endpoints with no averaging beyond actual exposure period
CSD interim guidance for early life exposures

- Short early-life exposures tend to produce higher responses than same adult exposures
- Account for higher sensitivity for early lifestages by applying suitable adjustment factors
And now for the science that backs it up…

CSD analysis focused on three lines of evidence to identify whether short-term exposure to carcinogens may have variable effects, dependant on lifestage of exposure

• Animal studies
• Epidemiological evidence
• Theoretical studies using mathematical models
Assessment of Cancer Risk for Adult Exposure: Short-Term vs Long-Term Exposure
Adult animal toxicity data with chemicals

- Mixed results from bioassays that exposed adult animals for a short term (A) then waited a lifetime as compared to animals that were exposed for a lifetime (B)

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>unexposed</td>
<td>exposed</td>
</tr>
</tbody>
</table>

- Tumour response rate
  - A > B for 46% chemical/sites
  - A = B for 44% chemical/sites
  - A < B for 5% chemical/sites

- LADD generally under-predicted potency by 2-fold (median value)
Adult animal toxicity data with radiation

- Similar radiation dose was 3-fold less effective in elderly rodents (6-12 or 19-21 months) than young adults (3-3.5 months)
- For some agents, it matters when exposure happens; early adulthood may be more sensitive than later years
Adult Epidemiological Data

- Asbestos & Lung cancer –
  - LADD underestimates risks when remaining lifespan exceeds latency period
  - LADD overestimates risks when remaining lifespan is shorter than latency period

- Sunlight & Skin cancer –
  - Acute high dose > chronic low level exposure
  - by up to 2-fold
Modelled data for adult short-term exposure

Ratio of cancer risk estimates from a 6 stage LMS AD model of carcinogenesis to LADD equivalent for an initiator (green) and a completer (blue). Ratio of 1 (red) indicates equal estimates.
Assessment of Cancer Risk for Exposure During Early Lifestages
Evidence for early life susceptibility

• Several factors indicate possibility of increased susceptibility to cancer early in life…

• When compared to animals exposed only as adults, animals exposed also perinatally show
  – higher tumour frequency, or
  – reduced latency period
US EPA age-dependent adjustment factors (ADAFs)

**Early Lifestages**
- 10 - 0 to < 2yrs
- 3 - 2 yrs to <16 yrs

**Adult Stage**
- 1 - 16+ yrs

- Applied to slope factor, *only* if no age-specific slope factor
- *Mutagenic* carcinogens only (e.g. carcinogenic PAHs)
- Lifestage (i) exposures averaged over lifetime (LADDi)
- Lifestage-specific intake rates
CSD Interim Guidance for Cancer Risk Assessment at Contaminated Sites: The Specifics
CSD Interim Guidance: Carcinogenic effects via a mutagenic mode of action

Adapted the US EPA approach, where:

Lifetime Cancer Risk

\[ \sum (SF \times ADAF_i \times LADD_i) \]

SF = cancer slope factor
ADAF\(_i\) = age-dependent adjustment factors for lifestage \(i\)
LADD\(_i\) = dose received during lifestage \(i\) averaged over a lifetime
CSD Interim Guidance: ADAFs for carcinogenic effects via mutagenic MOA

<table>
<thead>
<tr>
<th>Lifestage</th>
<th>Ages</th>
<th>Default ADAFs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>0 – 6 mo.</td>
<td>10</td>
</tr>
<tr>
<td>Toddler</td>
<td>7 mo. – 4 yrs.</td>
<td>5</td>
</tr>
<tr>
<td>Children</td>
<td>5 – 11 yrs.</td>
<td>3</td>
</tr>
<tr>
<td>Teenager</td>
<td>12 – 19 yrs.</td>
<td>2</td>
</tr>
<tr>
<td>Adult</td>
<td>20 +</td>
<td>1</td>
</tr>
</tbody>
</table>

* US EPA’s ADAFs adjusted to fit CSD’s age groups, to be used if no chemical-specific slope factor
CSD Interim Guidance: Carcinogenic effects via an unknown mode of action

• Unknown MOA, or those where threshold mode of action has not been proven → treat as non-threshold
• Apply same risk equation as for mutagenic carcinogens
• Chemical-specific data to adjust for early-life exposure
• No default age-dependent adjustment factors
CSD Interim Guidance: Carcinogenic effects via threshold mode of action

- Use TDI*; do not average beyond actual exposure period unless supported by scientific rationale
- Age-specific adjustment can be made - chemical-specific basis
- Default age-specific adjustment not recommended

* tolerable daily intake or tolerable concentration (TC) in the case of inhalation
Check mechanism for non-cancer effects

- Check for potential short-term and chronic non-carcinogenic effects
- Ensure no adverse health effects with short-term exposure
- Use short-term TRVs* where applicable

*toxicity reference values
Bottom Line

- Dose averaging is a necessary part of many risk assessments

- Ensure good scientific rationale to be applied on a chemical-specific basis for any amortization in risk assessments