Framework for Human Health Risk Assessment of Noncancer Effects Resulting from Short-duration and Intermittent Exposures to Chemicals

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Outline

• The problem and the framework
• Testing the framework and case study
• Future directions, issues and applications
The Challenge
Pragmatic framework

Generic PBPK model

Chronic TRV, LADD

Data intensity

Exposure profile, time-varying PBPK modeling
Objectives & Definitions

• Scientifically defensible approach (framework) for evaluating shorter- or longer-term health effects from:
  • A single short-term exposure
  • Repeated or intermittent short-term exposures
  • “Intermittent” = long periods of no exposure, e.g., exposed 1 day/month
  • “Near continuous” = exposure that occurs on some days, but not others or for a portion of each day. For example, 8 hours/day 5 days/week for 6 months is near-continuous for 6 months
Common Scenarios for Contaminated Sites

• 6 months continuous exposure,
• 2 months continuous exposure, or 1 month exposure twice a year separated by 2 to 3 months non-exposure,
• 1 week twice a year or 2 weeks continuous in a year,
• 2 days per week for 4 weeks, for 35 weeks or for a year,
• 1 day or 1 day per month for 4 months or longer, and
• Other possible scenarios

• Which toxicity reference value (TRV) should be used? E.g. – 2 weeks/year for 40 years – use a 2-week TRV or a chronic one?
Key principles in Framework Development

• A tiered approach, requiring increasing levels of information and toxicological understanding and expertise

• The use of TRVs chosen to be as consistent as possible with the ‘actual’ exposure period

• Use of dose averaging (also called “amortization”) only under limited, specified conditions
Why Use this Approach?

- Addresses both **duration** and **intermittency** of exposure
- Pragmatic tiered analysis
- Addresses implications of both toxicokinetics (half-life) and toxicodynamic (persistence of effect)
- Provides key data and sources for less than chronic exposures.
Mode of Action Analysis

Mode of Action analysis involves identification of several key events between exposure and effect.

Toxicokinetics

Toxicodynamics
Exposure: Monthly
Half-life: 1 day

aTRV – acute toxicity reference value; cTRV – chronic toxicity reference value
Figure 1
Key Determinants to Address Duration & Intermittency

Use of Chemical-Specific TRV-long or short-term

Duration

Comparison with Tox Study of Relevant Duration

Concentration related? Peak or AUC?

Chemical- or Group-Specific Biological $T_{1/2}$

Intermittency

Effect-Specific Repair Rate

Chemical-Specific Information on Key Events – (including PBPK, BBDR)
Sources of TRVs

**Chronic TRVs**
- Health Canada
- USEPA IRIS
- IPCS
- JECFA
- EFSA
- RIVM
- ICH
- ITER (compilation)
- Etc.

**Acute and/or subchronic TRVs**
- ATSDR
- USEPA PPRTV
- USEPA Office of Water
- CalEPA REL
- USEPA PALs
- TCEQ
- Etc.
Tier I-a
Comparison with published TRV - Is TRV available for the scenario of interest or a sufficiently similar scenario? (principally duration)

Tier I-b
Study that forms the basis for published TRV similar to scenario?

Tier II-a
Compare with toxicity study of relevant duration

Decisions
Modify adjustment for duration (including extrapolation and uncertainty factors)

Tiers I-a, I-b, & II-a
Primary determinant of toxic effect

3-b
Comparison of the short-duration exposure with published TRV - Is TRV available for the scenario of interest or a sufficiently similar scenario? (principally duration)

4-b
No

4-a
Study that forms the basis for published TRV similar to scenario?

5-a
No

5-b
Compare with toxicity study of relevant duration

9-a
Is toxicity primarily related to concentration (c)?

9-b
Is toxicity primarily related to concentration (c)?

10-a
Is toxicity primarily related to total dose (c x t)?

10-b
Is toxicity primarily related to total dose (c x t)?

11
Is toxicity primarily related to concentration and total dose?

Compare to longer-duration TRV
Dose averaging not appropriate,

Compare to longer-duration TRV
Dose averaging may be appropriate

Compare to longer-duration TRV
Dose averaging may be appropriate

TRV is expressed as tolerable weekly or monthly intake.
Tier 0

Is highest exposure < chronic TRV? Yes

Decisions
No appreciable risk
Tier I – Comparison with TRV for Relevant Exposure Duration

1. Is the exposure intermittent?
   - Yes
      3-a. Comparison of short-duration exposure with published TRV - is TRV available for the scenario of interest or a sufficiently similar scenario? (principally duration)
   - No
      4-a. Study that forms the basis for published TRV similar to scenario?
         - Yes
            Modify adjustment for duration (including extrapolation and uncertainty factors)
         - No
            Tier I-b
   - No
      5-a. Compare with toxicity study of relevant duration
      6. Is exposure > relevant short-duration TRV?
         - Yes
            Potential for health effects
         - No
            Tier II-a

Decisions
- Tier I-a
  - Yes: Compare TRV with Exposure
  - No: Modify adjustment for duration (including extrapolation and uncertainty factors)
- Tier I-b
  - Yes: Modify adjustment for duration (including extrapolation and uncertainty factors)
  - No: Study that forms the basis for published TRV similar to scenario?
    - Yes
      3-b. Compare with published TRV - is TRV available for the scenario of interest or a sufficiently similar scenario? (principally duration)
    - No
      4-b. Study that forms the basis for published TRV similar to scenario?
         - Yes
            Modify adjustment for duration (including extrapolation and uncertainty factors)
         - No
            Tier II-a
    - No
      5-b. Compare with toxicity study of relevant duration
      6. Is exposure > relevant short-duration TRV?
         - Yes
            Potential for health effects
         - No
            Tier II-a

Primary determinant of toxic effect
- 9-b. Is toxicity primarily related to concentration (c)?
   - Yes
      Compare TRV and Exposure Dose averaging not appropriate
   - No
      10-b. Is toxicity primarily related to total dose (c x t)?
         - Yes
            Compare TRV and Exposure Dose averaging appropriate
         - No
            Tier II-a

Tiers I-a, I-b, & II-a
Tier I-a - Direct Application of Existing TRVs

3-b
Comparison with published TRV - Is TRV available for the scenario of interest or a sufficiently similar scenario? (principally duration)

Decisions
Yes
Compare TRV with Exposure
Tier I-b - Modify Adjustment for Duration an Existing TRV

- Ex: Remove subchronic to chronic uncertainty factor
- Ex: Remove adjustments made to extrapolate from a multiple day study to a 1-day TRV
- Caution: If remove a UF, need to consider whether another endpoint might become the critical effect for the duration of interest.
  - Data arrays of endpoints by duration and effect level, (e.g. – ATSDR) can help in evaluating whether other endpoints might be critical for the duration of interest.
Tier II-a – Comparison with Toxicity Study of Relevant Duration – de Novo TRV

De novo TRV or Margin of Exposure approach
Dose Averaging – Near-Continuous (Non-Intermittent) Exposure

• E.g – occupational exposure – 6 hours/day, 5 days/week
• Is toxicity *primarily* due to concentration?
• Or toxicity primarily related total dose?

Primary determinant of toxic effect

9-b
Is toxicity primarily related to concentration (c)?

Yes

10-b
Is toxicity primarily related to total dose (c x t)?

Yes

Compare TRV and Exposure
Dose averaging not appropriate

Compare TRV and Exposure
Dose averaging appropriate
Questions to Ask – Concentration vs. Total Dose

• Do authoritative reviews indicate that toxicity for the duration of interest is driven by concentration?
• Does a ceiling OEL exist for the chemical?
• Is the chemical reactive?
• Do critical effects occur at the portal of entry?
• Is the critical effect narcosis or asphyxia or an irritant or allergen?
• Is there evidence of a greater effect after bolus versus continuous dosing?
More on Dose Averaging

• Generally not done for developmental toxicity, but consider relative duration of the window of susceptibility and the proposed averaging time, the chemical’s kinetics and dynamics, and the degree of variability within that window.

• Dose averaging of *exposure* is a non-conservative approach – reduces exposure compared with TRV
  – Dose averaging in development of the TRV is a health-protective approach
Tier 0

1. Is highest exposure < chronic TRV?
   - Yes
   - No, or no chronic TRV available

   No appreciable risk

   Is the exposure intermittent?
   - Yes
   - No

   Tier 1-a

   3-a. Comparison of the short-duration exposure with published TRV - is TRV available for the scenario of interest or a sufficiently similar scenario? (principally duration)
   - Yes
   - No

   Tier 1-b

   4-a. Study that forms the basis for published TRV similar to scenario?
   - Yes
   - No

   Tier II-a

   5-a. Compare with toxicity study of relevant duration
   - Yes
   - No

   Tier I-a, I-b, & II-a

   6. Is exposure > relevant short-duration TRV?
   - Yes
   - No

   Potential for health effects

   7. Is half-life sufficiently short to permit elimination of chemical/active metabolite from the body between exposures?
   - Yes
   - No

   Tier II-b Intermittent Exposure

   8. Does the effect persist beyond the no-exposure interval to allow the effects to accumulate?
   - Yes
   - No

   No appreciable risk

   Tier I-a

   3-b. Comparison with published TRV - is TRV available for the scenario of interest or a sufficiently similar scenario? (principally duration)
   - Yes
   - No

   Tier I-b

   4-b. Study that forms the basis for published TRV similar to scenario?
   - Yes
   - No

   Tier II-a

   5-b. Compare with toxicity study of relevant duration
   - Yes
   - No

   Tiers I-a, I-b, & II-a

   9-b. Is toxicity primarily related to concentration (c)?
   - Yes
   - No

   Compare to longer-duration TRV Dose averaging not appropriate*

   10-b. Is toxicity primarily related to total dose (c x t)?
   - Yes
   - No

   Compare to longer-duration TRV Dose averaging may be appropriate

   11. Is toxicity primarily related to concentration and total dose?
   - Yes
   - No

   Compare to longer-duration TRV Dose averaging may be appropriate

* Dose averaging over short durations may be appropriate when the TRV is expressed as tolerable weekly or monthly intake.
Intermittent Exposure – Tiers I-a, I-b, & II-a

• First comparison – Exposure vs. Short-Duration TRV

| Is exposure > relevant short-duration TRV? | Yes | Potential for health effects |
Tier II-b – Intermittent Exposure

7. Is half-life sufficiently short to permit elimination of chemical/ active metabolite from the body between exposures?
   - No: Compare to longer-duration TRV; Dose averaging is not appropriate
   - Yes: 8.

8. Does the effect persist beyond the no-exposure interval to allow the effects to accumulate?
   - No: No appreciable risk
   - Yes: 9-a.

9-a. Is toxicity primarily related to concentration (c)?
   - Yes: Compare to longer-duration TRV; Dose averaging not appropriate
   - No: 10-a.

10-a. Is toxicity primarily related to total dose (c x t)?
   - Yes: Compare to longer-duration TRV; Dose averaging may be appropriate
   - No: 11.

11. Is toxicity primarily related to concentration and total dose?
    - Yes: Compare to longer-duration TRV; Dose averaging may be appropriate
Tier II-b - Kinetics

• Key question: Is half-life sufficiently short to permit elimination of chemical/active metabolite from the body between exposures?

• Reasonable rule of thumb: 5 half-lives = “complete” elimination (95%)

• If biphasic, need to consider amount of chemical in terminal phase

Is half-life sufficiently short to permit elimination of chemical/active metabolite from the body between exposures?

No

Compare to longer-duration TRV Dose averaging is not appropriate*
Tier II-b - Toxicodynamics

• Key question: Does the effect persist beyond the no-exposure interval to allow the effects to accumulate?
• Exposure is below the level that would cause adverse effects.
• Prefer to evaluate reversibility of precursors - early and intermediate key events
• In practice - conservative approach – look at adverse effects
• Early key events (except mutation) are likely to be reversible – e.g., oxidative stress, irritation

• “Long” persistence effects
  • generally later stage (e.g., cytotoxicity) or
  • the result of impact during a sensitive period (developmental toxicity)

Does the effect persist beyond the no-exposure interval to allow the effects to accumulate? No
No appreciable risk
• Dose averaging across intermittent exposures would mean averaging periods of exposure with periods of non-exposure, substantially decreasing the exposure level compared with the TRV.

– In practice, intermittent exposure scenarios where dose averaging is appropriate are rare.
TESTING THE FRAMEWORK AND
CASE STUDY
Rounds of Input

• Initiated as Alliance for Risk Assessment “Beyond Science and Decisions” case study – expert panel input
• Developed in work funded by API
• Further enhanced in work funded by Health Canada
  – Two rounds of peer consultation within Health Canada
  – Practical testing by team of toxicologists
Testing the Framework

• Applied to 17 chemicals or mixtures (organics and metals) in four exposure scenarios

• Objectives:
  – Experienced toxicologists identify potential areas for framework modification
  – Advise on chemical-specific assessments for specific conditions
Lessons Learned and Challenges

• Significantly restructured the overall framework
• One of the biggest challenges is identifying consistent rules for choosing TRVs from multiple agencies; importance of problem formulation
• Evaluating persistence of effect
  – May need to consider not only whether the exposure exceeds the TRV, but by how much. Exposures close to the TRV may result in the occurrence of later key events that can accumulate with repeated exposure.
Case Study - Alkyl Hydrocarbon

• Critical effect for acute and chronic – neurotoxicity
• Acute – dizziness, numbness of extremities; recovery is rapid
• Chronic – Peripheral neuropathy’ toxicity related to cumulative dose of the toxic metabolite
  – Repair rate for the critical effect of peripheral neuropathy is slow.
• Decreased fetal body weight and intrauterine survival in the absence of maternal toxicity at doses above critical effect.
• Metabolites (including the key toxic metabolite) are eliminated with a half-life of approximately 13 to 14 hours.
Scenarios

• Inhalation exposure of 221 mg/m$^3$
• Subchronic TRV is 2 mg/m$^3$
• Chronic TRV is 0.7 mg/m$^3$
• Exposure scenarios:
  – 2 months continuous exposure
  – 1 week exposure twice a year
2-month exposure

Is exposure > relevant short-duration TRV?

Yes

Potential for health effects

221 mg/m³ > 2 mg/m³
Intermittent Exposure – 1 week 2x/year

6. Is exposure > relevant short-duration TRV? Yes → Potential for health effects

7. No → Is half-life sufficiently short to permit elimination of chemical/active metabolite from the body between exposures? No → Compare to longer-duration TRV Dose averaging is not appropriate*

8. Yes → Does the effect persist beyond the no-exposure interval to allow the effects to accumulate? No → No appreciable risk
1 week twice per year repeated yearly for a lifetime

- No 1-week TRV
- Consider deriving a 1-week TRV based on the developmental toxicity data
- Dose averaging in this scenario not appropriate
- Resulting TRV 7 mg/m$^3$
- Exposure (221 mg/m$^3$) > TRV, so there is potential for effects from the short-term exposure alone, so don’t need to finish framework
- Will continue for illustrative purposes
Addressing intermittency – 1 week, 2x/year

• Half-life of 14 hours - completely eliminated between exposures
• Effect on peripheral nerves persists past 6 months, therefore would compare to chronic TRV if exposure were < 1-week TRV
• Dose metric is cumulative exposure, so dose averaging may be appropriate
• Avg exposure: 221 mg/m$^3$ x 2/52 = 8.5 mg/m$^3$
  – Still above the chronic TRV of 0.7 mg/m$^3$
Does the effect persist beyond the no-exposure interval to allow the effects to accumulate?

Yes

10-a

Is toxicity primarily related to total dose \((c \times t)\)?

Yes

Compare to longer-duration TRV
Dose averaging may be appropriate

No

No appreciable risk

Tier II-b Intermittent Exposure

Primary determinant of toxic effect

Yes

9-a

Is toxicity primarily related to concentration \((c)\)?

Yes

Compare to longer-duration TRV
Dose averaging not appropriate,

No

Compare to longer-duration TRV
Dose averaging may be appropriate

10-a

Is toxicity primarily related to total dose \((c \times t)\)?

Yes

Compare to longer-duration TRV
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Is toxicity primarily related to concentration and total dose?

Yes

Compare to longer-duration TRV
Dose averaging may be appropriate
Summary

• Pragmatic tiered approach
• Considers toxicokinetics and toxicodynamics
• Considers both duration and intermittency
FUTURE DIRECTIONS AND ISSUES
Potential Enhancements and Issues

• Slow dermal absorption may complicate evaluation of elimination half-life
• Chemicals with long half-life, but that is sequestered in a tissue
• Rhomberg (2009) - refine guidance for dose averaging for non-intermittent inhalation exposures
• Impact of periodicity for the near-continuous exposure
• Implications of difference of timescales for interspecies extrapolation.
Complex Time Variation – Rule of Thumb for OELs

• Exceedances of TLV-TWA should not exceed 3 times the TLV for more than 30 minutes, and should never exceed 5x the TLV (ACGIH)

• By analogy, short-duration excursions should not exceed 5 times the longer-duration TRV, even if dose-averaging is applied
Data Needs

• Reversibility of common intermediate key events
• Less than chronic TRVs
Other Applications

• Manufacturing – chemical, pharma

• Consumer product exposures

• Food safety
Big Data in Food Safety

Federal roundtable on current interest in use of big data in food intake assessment
- November 18, 2015 – organized by USDA OS/Office of Chief Economist
- Invited speakers, then round the table of USG agencies with interest
  - Linda Abbott, Director, Office of Risk Assessment and Cost-Benefit Analysis
  - LAbbott@oce.usda.gov

Society for Risk Analysis symposium on use of big data in food intake assessment
- December 8, 2015 – SRA Annual Meeting
  - http://sra.org/

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