Use of Safety Factors in Human Health Risk Assessment

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What is a Safety Factor?

- Two types of factors:
  - safety factor, uncertainty factor - subtle differences
  - for this presentation will be considered as one
- Multiple applied to an endpoint in the toxicity data base
- Ensures a wide margin or gap (Margin of Safety) between animal toxicity and human exposure to ensure protection of humans

Standard/Traditional/Default Safety Factors

- **Intraspecies 10x (4x TK x 2.5x TD)**
  - compensates for uncertainties/variations in TK/TD within species- intended to cover differences in absorption, dose in circulation, tissue distribution, distribution at target tissues, intracellular changes, interactions within cells, hormonal status, general health,age
- **Interspecies 10x (3.16 TK x 3.16 TD)**
  - compensate for differences in TK/TD between animals and humans and the uncertainty in extrapolating from animals to humans; in absence of data, humans always considered most sensitive species
- 100x - internationally accepted minimum default

Additional Safety Factors

What is magnitude of additional factor?

- Generally additional 3-10x above standard 100x
  - Sliding scale dependent on severity of endpoint
  - Higher factors for severe endpoints such as mortality, malformations, failure to produce viable offspring
  - Lower factors for other less serious effects – immunotoxicity, endocrine disruption
- New PCPA – focus on children's health
  - codifies application of additional 10x factor
  - account for pre/post natal toxicity concerns for infants and children unless data/information to show otherwise; consistent with USEPA

Additional Safety Factors

- When are additional factors applied?
  - **Data base uncertainties**
    - key studies missing or inadequate – incomplete hazard identification
    - use of short term study to extrapolate to chronic exposure
    - extrapolating from LOAEL to a surrogate NOAEL
  - **Severity of effect**
    - Severe endpoints that are life-threatening or incompatible with life – mortality, malformations, other endpoints – endocrine modulation
    - Considers nature of response and dose-response curve
  - **Sensitivity of young - SF/UF**
    - fetus/young animals affected preferentially or more severely at same dose or effects of a different type with greater consequences
    - some cases sensitivity of young/severity of effect cannot be independently defined eg. malformations in absence of maternal toxicity

Decision Process for Additional Safety Factors

- Weight of evidence approach
- Recommendations based on findings during hazard characterization
  - Nature and severity of endpoints
  - Potential sensitive subpopulations – pre/post natal effects
  - Slope of dose response curve
  - Adequacy of data base i.e. are all core studies present and acceptable
  - Residual uncertainties in data base use of a LOAEL
- Level of confidence in all components of risk characterization
  - Includes hazard identification and exposure assessment

Example of Application of Safety Factors

- **Effect: Neurotoxicity in data base**
- **Exposure Duration: chronic,**
- **Source of Exposure: food/water, residential**
  - Signs and symptoms and neuropathology observed in several studies: 90 d rat, 1 year dog, chronic rat and mouse, reproductive toxicity
  - Treatment related neurotoxic symptoms in young when not observed in maternal animal – sensitivity of young
  - No repeated dose neurotoxicity study available
  - No developmental neurotoxicity study available
  - Chronic exposure – chronic rat study (adult liver toxicity); NOAEL 2 mg/kg bw/d
  - Standard 100x UF applied to account for intra/interspecies differences
  - Additional 10x SF applied for sensitivity of young and lack of repeated dose and DNT studies to fully define true NOAEL; RfD for population would be 0.002 mg/kg bw/d
  - Conduct aggregate exposure for food/water and residential
  - Conduct cumulative exposure assessment for chemicals with same MOA

Challenges

- Ongoing controversy regarding 100x default
- Intraspecies (4.0 TK x 2.5 TD)
  - Paucity of data to facilitate TK/TD approach to derive chemical specific safety factor; definitive data limited; currently only available for drugs
  - Based on drug data, intraspecies 10x - generally protective for healthy adults
  - Elderly population with declining renal function, ~ 20% TKxTD > 10x; not adequately protected; lots of variation with drug class
  - Children vs adults - about 10% exceeded 10x
  - Almost complete lack of data for pregnant females/fetus
  - Calabrese study– 300 diverse chemicals;
    - generally children more susceptible
    - where children more susceptible, 10% exceeded 10x difference

Challenges

- Interspecies (3.1 TK x 3.1 TD)
  - Generally rat/mouse exceed 4x TD vs humans
  - Emerging data demonstrating rat/mouse to human differences > 10x; e.g. theophyline, lidocaine
  - 10x default not protective in numerous cases
- Controversy regarding FQPA 10x SF
  - NAS/NRC recommendation to protect infants and children, women of childbearing age vs JMPR
  - NAS/NRC findings supported by emerging data
- Need for data to derive appropriate adjustment factors

Challenges

- Application of SF/UF
  - PMRA applies additional SF/UF to food/water and residential risk assessments as per USEPA
  - PMRA applies additional SF/UF to risk assessment for occupational/bystander - protect pregnant female
  - USEPA – no additional SF/UF use for risk assessments for occupational/bystander
  - Differences lead to different risk assessments and decisions of acceptability
  - New PCPA requires application of extra factors to protect infants/children; currently have scientifically defensible framework that respects intent of new PCPA

Challenges

- Next Steps
  - NAFTA project initiated
    - Each country will define analyze and document SF/UF approach
    - Examine similarities and differences in occupational/bystander SF/UF approach
    - Develop approach that is scientifically defensible
    - Option of independent review panel to provide impartial opinion
    - Inclusion of public comment
  - Need for willingness to explore existing approaches and clearly define current activities followed by change in policy