A Curation and Data Extraction for Peer-Reviewed Reference Doses

Inclusion Criteria

- Chronic oral non-cancer toxicity value (e.g., chronic RfD or MRL).
- Point of departure based on experimental data in mammalian, non-human species exposed orally, expressed as mg/kg-d.
- Required data and metadata available for extraction (see below).

Exclusion Criteria

- Duplicate records.
- RfDs based on human data, because the WHO/IPSC (2014) framework has not yet been extended to apply to points of departure from human studies.
- Reporting inconsistencies (e.g., composite UF is not equal to product of individual UFs; reported critical effect not consistent with dose-response data).
- Used a chemical-specific extrapolation (e.g., physiologically-based pharmacokinetic modeling) or non-standard UF (e.g., a "modifying factor").

Data and metadata extracted

- Chemical identification (name, CASRN).
- Source and reported value of RfD.
- Species and (if reported) body weight.
- Point of departure (type [e.g., LOAEL, NOAEL, BMDL] and value in mg/kg-d).
- For BMDLs, BMR and (if reported) BMD.
- Type of effect (e.g., organ weight, clinical chemistry) and (if reported) type of data (e.g., continuous, dichotomous). The effect categories were standardized to one of the following: body weight, clinical chemistry, enzyme activity, food and/or water consumption, hematology, neurotransmitter, organ weight, urinalysis, clinical signs, gross pathology, mortality/survival, nonneoplastic histopathology, development, multiple, neurobehavior, none, other, reproduction.
- For continuous effects with a BMDL based on 1SD change, data on control animals (number of animals, the mean and SD or SE response).
- Individual UFs (animal-to-human, human variability, subchronic-to-chronic, LOAEL-to-NOAEL, database) and composite UF.

B Conceptual Models and Magnitudes of Effect for Different Types of Endpoints

Continuous Endpoints

- Description: Used when the endpoint is reported as a continuous measurement.
- Endpoints included: body weight, clinical chemistry, development (e.g., fetal weights), enzyme activity, food and/or water consumption, hematology, neurobehavior (e.g., grip strength), neurotransmitter (e.g., cholinesterase inhibition), organ weight, reproduction (e.g., sperm counts), urinalysis.
- Magnitude of effect: If a % change is reported, then that value is used. In cases where BMD modeling is used and a 1SD change from the control group mean is reported, the 1SD change is converted to a % change based on the reported SD in the control group. This change is made so that the BMD is interpretable as a magnitude of effect in humans. If only NOAELs or LOAELs are reported, it is adjusted to an equivalent BMD for a 5% change (see Figure 4).

Quantal-Deterministic Endpoints

- Description: Used when the endpoint is reported as incidence (number or fraction affected), but is judged to reflect an underlying (unreported) continuous endpoint that has been dichotomized using a cut-point; for the purposes of dose–response data analysis, the ED50 from the incidence data would be used to estimate the dose at which the underlying continuous response crosses the cut-point (see WHO/IPCS 2014 and Chiu and Slob 2015 for detailed discussions of this point).
- Endpoints included: clinical signs, gross pathology neurobehavior (e.g., ataxia), nonneoplastic histopathology.
- Magnitude of effect: Reflected in the severity of the effect for which the incidence is reported. If the ED50 for incidence is reported, it is used. Otherwise, the reported POD is adjusted to the ED50 (see Figure 4).

Quantal-Stochastic Endpoints

- Description: Used when the endpoint is reported as a dichotomous measurement (i.e., as incidence), but is judged to reflect a stochastic process so that the incidence is an estimate of the probability of the effect occurring at the individual level.
- Endpoints included: Mortality/survival, development (e.g., skeletal variations), reproduction (e.g., conception rate).
- Magnitude of effect: If an extra risk value is reported (e.g., 5% extra risk), it is used. Otherwise, the reported POD (i.e., NOAELs or LOAELs) is adjusted to an equivalent BMD for a 10% extra risk (see Figure 4).

Multiple Endpoints

- For reproductive or developmental endpoints that do not specify a continuous or dichotomous measure (e.g., reported as NOAEL), both "Continuous" and "Quantal-Stochastic" models are implemented, reflecting both possibilities.
- For non-reproductive and non-developmental endpoints that do not specify a continuous or dichotomous measure (e.g., reported as NOAEL), both "Continuous" and "Quantal-Deterministic" models are implemented, reflecting both possibilities.