Development of safe levels of elemental impurities

ICH Q3D

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Safe Levels or exposure Limits: Definition

A safe Level is a toxicological index that, when compared with exposure, is used to qualify or quantify a risk to human health.

Safe levels are widely used in quantitative health risk assessment, a decision-making process designed to provide the scientific evidence essential for proposing corrective measures.
The Exposure limits : two Approaches

- Based on an increase of risk per dose
  - Safety value that defines quantitatively the relationship between dose and response (i.e., the slope factor)
  - Risk at low exposure levels is difficult to measure directly either by animal experiments or by epidemiologic studies
  - Based on a data set and using the model to extrapolate

- Based on critical effect for a specific substance in animal or in Human and apply uncertainty factors
The Exposure limit: Which one?

- There are two types of Exposure Limit in ICH guidelines.
- ICH guidelines (Q3x) use the Permitted Daily Exposure Method (PDE).
- ICH M7 uses the TTC concept and Stage TTC.

**TTC Concept**
- Based on simple linear extrapolation from the dose giving a 50% tumor incidence (TD50) to a 1 in 10^6 incidence, using TD50 data for the most sensitive species and most sensitive site of tumor induction.

**PDE Concept**
- Based on a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

Many heavy metals are known to accumulate, and there are extensive databases on most heavy metals and these should be used for risk assessment.
Calculation of a permitted Daily Exposure
PDE : General methods

- **STEP 1**: Hazard identification by reviewing all relevant data
- **STEP 2**: Identification of “critical effects”,
- **STEP 3**: Determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects,
- **STEP 4**: Use of several adjustment factors to account for various uncertainties (Uncertainty Factors)

\[
PDE = \frac{\text{NOEL} \times \text{Weight Adjustment}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}}
\]

(50 kg) PDE apply for all population
The Exposure limit: Other exposure limits

- **MRL**: Minimal Risk Level: An estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk. (ATSDR), ATSDR uses the no observed adverse effect level/uncertainty factor (NOAEL/UF) express in (mg/kg/day)

- **Rfd** Reference Dose US EPA

<table>
<thead>
<tr>
<th>TABLE 1. Comparison of Methodology Used in Deriving ATSDR MRLS and USEPA RfDs/RfCs</th>
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<td>Exposure duration</td>
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<td>Route of exposure</td>
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<td>Uncertainty Factors (UFs) used:</td>
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<td>Human variability</td>
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<td>Animals to humans extrapolation</td>
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<td>Extrapolation from a LOAEL to a NOAEL</td>
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<td>Extrapolation across exposure durations</td>
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Occupational exposure limits

- PEL: Permitted Exposure Limit.
- TVL: Threshold Limit Value: The concentration in air to which it is believed that most workers can be exposed daily without an adverse effect (ACGIH)
- TWA: Time Weighted Average: As defined by ACGIH, time-weighted average concentration for a conventional 8-hour workday and a 40-hour workweek. (IUPAC)
- URF: Unit Risk Factor
Calculation of a permitted Daily Exposure
PDE : ICH Q3D

Elements evaluated in this guideline were assessed by reviewing publicly available data contained in scientific journals, government research reports and studies, international regulatory standards (applicable to drug products) and guidance, and regulatory authority research and assessment reports.

- The factors considered are:
  - The likely oxidation state of the element in the drug product;
  - Human exposure and safety data when it provided applicable information;
  - The most relevant animal study;
  - Route of administration;
  - The relevant endpoint(s)
Calculation of a permitted Daily Exposure
PDE : ICH Q3D

- international regulatory standards
- Where appropriate, these standards were considered in the safety assessment and establishment of the PDEs.
- The longest duration animal study was generally used to establish the PDE.
- Inhalation studies using soluble salts (when available) were preferred over studies using particulates for inhalation safety assessment and derivation of inhalation PDEs.
- The PDEs established in this guideline are considered to be protective of public health for all patient populations
Exemple Oral PDE of As

◆ Critical effects
  ❖ Inorganic arsenic has shown to be genotoxic, but not mutagenic and has been acknowledged as a human carcinogen
  ❖ most part the effects of arsenic in humans have not been reproduced in animals
  ❖ Oral exposure has been linked to cancers of the skin, liver, lung, kidney and bladder.
  ❖ Following inhalation exposure there is evidence for an increased risk of lung cancer

◆ Sources
  ❖ Agency for Toxic Substances and Disease Registry (ATSDR)
Exemple Oral PDE of As

- Agency for Toxic Substances and Disease Registry (ATSDR)
- MRL = 0.0003 mg/kg/d

\[
15 \mu g/d = \frac{0.0003 \times 50}{1 \times 1 \times 1 \times 1 \times 1}
\]

PDE = 0.0003 mg/kg/d x 50 kg = 0.015 mg/d = 15 \mu g/day
Inhalation PDE of As

- Critical effects
  - Increased risk of lung cancer and other respiratory disorders have been reported following inhalation exposure to workers in the occupational setting.
  - The rationale for using a cancer endpoint for inhalation to set the PDE is the relative lack of information on linear-dose extrapolation, as compared to the oral route.

- Source
- URF (Unit Risk Factor) = for 0.067 µg/m3 => 1/100,000
- Inhalation PDE =

  \[
  \frac{0.067 \, \mu g/m^3 \times 28800 \, L/d}{1000 \, L/m^3} = 1.9 \, \mu g/day
  \]

  No modifying factors were applied. PDE is based on a URF derived from the multiplicative relative risk model described by Erraguntla et al. (2012).
Oral PDE for Hg

- Critical effects
  - inorganic mercury is not carcinogenic in human
  - neurological, corrosive, hematopoietic, and renal effects and cutaneous disease (acrodynia).
- Source
  - The 6-month gavage study in rats was selected because it had more detailed clinical pathology assessment and a wider range of doses, nephropathy was noted from 0.625 mg HgCl2.
  - BMDL10 of 0.06 mg Hg/kg/day
Oral PDE for Hg (cont.)

\[ 30 \, \mu g/d = \frac{0.006 \times 50}{5 \times 10 \times 2 \times 1 \times 1} \]

Rat inter individual 6 month study finding not significant BMDL10 = NOAEL
In the absence of data or where data are not considered sufficient for a safety assessment for the parenteral and or inhalation route of administration, modifying factors based on oral bioavailability were used to derive the PDE from the oral PDE:

- Oral bioavailability <1%: divide by a modifying factor of 100;
- Oral bioavailability ≥ 1% and <50%: divide by a modifying factor of 10
- Oral bioavailability ≥50% and <90%: divide by a modifying factor of 2
- Oral bioavailability ≥ 90%: divide by a modifying factor of 1.

If no bioavailability data or occupational inhalation exposure limits

Oral PDE divided by a modifying factor of 100
Table A.2.1: Permitted Daily Exposures for Elemental Impurities

<table>
<thead>
<tr>
<th>Element</th>
<th>Class</th>
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Derivation of an Acceptable Level (AL) for element impurity (EI) not in Q3D

- Needs to follow the principles to derive a PDE as outlined in the Guideline (Appendix 1)
- Literature review is needed to find safety information
- Information needs to be judged for quality and applicability
- Note: example does not represent an ICH Q3D-derived PDE; example is for illustrative purposes only
Example 1: Safety Qualification of an EI not in Q3D

- Drug Product in a pre-filled syringe (PFS)
- Stopper is a sulfur cured elastomer
  - Elemental sulfur (S) detected from a leachable study of the container closure system and not S from mAb
  - Based on shelf-life of DP, S level determined to be 2.3 µg/dose
- DP is a mAb that has a SC dose regimen (1 dose every 8 weeks)
- Quality attributes
  - Determined that S does not affect the quality of the mAb
Determinations of an acceptable level

- Using Q3D principles an AL for elemental S in a parenteral DP can be developed
  - Note: not an ICH Q3D-derived PDE; example for illustrative purposes only

- Limited parenteral data available – use oral study data to calculate an AL
  - Reported human data suggests that S is relatively nontoxic but an MRL is not available
  - Rabbit iv study; single dose level, limited number of animals, non-GLP, used colloidal sulfur containing polysulfide (Greengard and Woolley, 1940; Studies on colloidal sulfur-polysulfide mixture. Toxicity J.Am.Pharmaceut.Assoc. 29: 289-292)
  - The oral bioavailability of S is unknown
  - A feed study in calves with dietary administration of 2 concentrations of sulfur (as Calcium sulfate) for 85 days showed no effects in health, body weight, Cu and Se levels and activity of Cu and Se dependent enzymes up to a dose of 16 mg/kg/day. Thus the no observed adverse effect level (NOAEL) is 16 mg/kg/day.
  - \[ S \text{ intake (oral)} = 16 \text{ mg/kg/d} \times 50 \text{ kg} \div (10 \times 10 \times 10 \times 1 \times 1) = 0.8 \text{ mg/day (800 \mu g/day)} \]
  - This study was considered the most appropriate to determine an AL
Determination of an acceptable level (cont)

- Parenteral AL
  - Using the most conservative modifying factor of 100 (section 3.1 of Q3D, oral bioavailability < 1%), a parenteral AL for S is:
    \[ 800 \, \mu g/day \div 100 = 8 \, \mu g/day \]

- S in PFS DP
  - The calculated AL for S is 8 \, \mu g/day
  - PFS DP contains worst case level of 2.3 \, \mu g/dose
    - Patient dosed once every 8 weeks
  - The level of S in the DP is considered acceptable
  - ALs are subject to review and approval by regulatory agencies/authorities

- Note: This is not an ICH Q3D-derived AL. It is an example for illustrative purposes only.
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