Agence nationale de sécurité du médicament et des produits de santé

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 heath risk assessment, a decision-making process designed to provide the scientific evidence essential for proposing corrective measures

The Exposure limits : two Approachs

- 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 uncertainity factors

The Exposure limit : Which one ?

- There are two type of Exposure Limit in ICH guideline
- ICH guidlines (Q3x) uses Permitted Daily Exposure Method (PDE)
- ICH M7 uses TTC concept and Stage TTC

DO NOT APPLY

TTC Concept is 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

Many heavy metals are known to accumulate,

PDE concept is 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

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 (Uncertainity Factors)

$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

(50 kg) PDE apply for all population

F1 Inter species
F2 Inter individual
F3 Tox. EP vs Time exp
F4 Severity Tox. Effect
F5 NOEL not established

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 1. Comparison of Methodogy Used in Deriving ATSDR MRLS and USEPA RfDs/RfCs

	MRL	RfD/RfC
Exposure duration	Acute Intermediate Chronic	Chronic
Route of exposure	Oral, Inhalation	Oral, Inhalation
Uncertainty Factors (UFs) used:		
Human variability	Yes	Yes
Animals to humans extrapolation	Yes	Yes
Extrapolation from a LOAEL to a NOAEL	Yes	Yes
Extrapolation across exposure durations	Yes	Yes
Incomplete database	No	Yes
Across exposure route extrapolation	No	Yes
Modifying Factor (MF)	Yes	Yes

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 = 0.0003mg/kg/d

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

Humans

Include in MRL

Include in MRL

Include in MRL

MRL

PDE = 0.0003 mg/kg/d x 50 kg = 0.015 mg/d = 15 µg/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 =

0.067 µg/m3 / 1000 L/m3 x 28800 L/d = 1.9 µg/day

No modifying factors were applied PDE is based on a URF derived from the multiplicate 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

Calculation of a permitted Daily Exposure PDE : Routes of Administration

- 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[1]

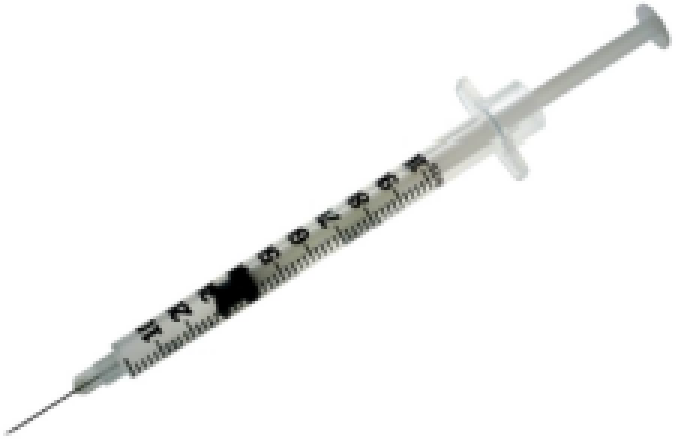
Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

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



Determination 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 intake (oral) = 16 mg/kg/d x 50 kg ÷ (10 x 10 x 10 x 1 x 1) = 0.8 mg/day (800 µg/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 µg/day ÷ 100 = 8 µg/day

- S in PFS DP
  - The calculated AL for S is 8 µg/day
  - PFS DP contains worst case level of 2.3 µg/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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