INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GUIDELINE FOR ELEMENTAL IMPURITIES

Q3D(R1)

Draft *v*ersion

Endorsed on 18 May 2018

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Q3D(R1)
Document History

Code	History	Date
Q3D(R1)	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation (document dated 23 February 2018).	18 May 2018
Q3D	Corrigendum to correct: the modifying factor in the text of the safety assessment for Selenium (changed to 2 instead of 10 consistent with Section 3.1); and two references for consistency in the safety assessments for Barium (deleted reference) and Vanadium (revised reference).	16 December 2014
Q3D	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the ICH regulatory bodies.	12 November 2014
Q3D	Addition of line numbers to facilitate the provision of comments by stakeholders.	30 September 2013
Q3D	Post sign-off minor editorial corrections including: removal of references to Appendix 5 (pgs i & 13); deletion of redundant text (pg 4); change of Option 2 to Option 2a (pg 10); insertion of omitted text under Safety Limiting Toxicity (pg 35); removal of duplicated redundant text (pg 41); replacing references to "metals" in text and "metal" in Table A.4.7 title with "elementals" and "elements" (pg 73); and deletion of header Table A.4.10 (pg 75).	26 July 2013
Q3D	Post sign-off corrigendum in: • Table 4.1 W and Al were removed from the list of included elemental impurities in Class 2B and 3 respectively. • Table A.2.1 the Class for Ni was changed to read 3 instead of 2.	14 June 2013
Q3D	Approval by the Steering Committee under *Step 2b* and release for public consultation.	6 June 2013
Q3D	Approval by the Steering Committee under *Step 2a*.	6 June 2013

CADMIUM

Summary of PDE for Cadmium

Cadmium (Cd)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	5.0	1.7	3.4

Introduction

Cadmium (Cd) is a transition metal whose most abundant naturally-occurring isotope is non-radioactive. It is found in nature in mineral forms and is obtained for commercial uses principally from cadmium ore (ATSDR, 2012). Cadmium exists as a salt form in the +2 oxidation state only. Some cadmium salts such as cadmium chloride, cadmium sulfate and cadmium nitrate are water soluble; other insoluble salts can become more soluble by interaction with acids, light or oxygen. Cadmium, cadmium oxide, cadmium salts on borosilicate carrier are used as catalysts in organic synthesis. Silver cadmium alloy is used in the selective hydrogenation of carbonyl compounds.

Safety Limiting Toxicity

Cadmium has shown to be genotoxic, but not mutagenic and has been acknowledged as a human carcinogen (Group 1; IARC, 2012). Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity (Buchet *et al*. 1990). Skeletal and renal effects are observed at similar exposure levels and are a sensitive marker of cadmium exposure (ATSDR, 2012).

Evidence from numerous epidemiologic studies assessing inhalation exposures to cadmium *via* both occupational and environmental routes has demonstrated an increased risk of developing cancer (primarily lung) that correlates with inhalation exposure to cadmium (IARC, 2012; NTP, 1995). ATSDR (2012) concluded that lung carcinogenesis due to occupational exposure was not unequivocal. Cadmium was clearly positive for lung tumours in rats; non-significant, non dose dependent in mice; and not observed in hamsters. An inhalation unit risk estimate of 0.0018/µg/m^3 has been derived by the US EPA (1992); however, a modifying factor approach may be used for non-mutagenic carcinogens. The US Department of Labor has a reported a Permitted Exposure Level of 5 µg/m^3 for cadmium (Cadmium OSHA, 2004).

PDE – Oral Exposure

A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity (Buchet *et al*, 1990). Skeletal and renal effects are observed at similar exposure levels and are a sensitive marker of cadmium exposure (ATSDR, 2012). A number of oral exposure studies of cadmium in rats and mice showed no evidence of carcinogenicity. Therefore, the renal toxicity endpoint was used to establish the oral PDE for cadmium, following the recommendations of ATSDR, an MRL of 0.1 µg/kg for chronic exposure is used to set the oral PDE. This is consistent with the WHO drinking water limit of 0.003 mg/L/day (WHO, 2011).

PDE = 0.1 µg/kg/d x 50 kg = 5.0 µg/day

No modifying factors were applied because they are incorporated into the derivation of the MRL.

PDE – Parenteral Exposure

A 12-week study in rats given daily subcutaneous injections of 0.6 mg/kg Cd, 5 days per week showed renal damage at week 7 and later (Prozialeck *et al*, 2009). A single dose level was used in this study. The

LOAEL of this study is 0.6 mg/kg based on decreased body weight, increased urine volume and urinary biomarkers seen at this dose level. This study was used to set the parenteral PDE. In a separate single dose study where rats were administered 0, 1, 2, 4, 8, 16 or 32 µmol/kg cadmium chloride by the subcutaneous route, sarcomas were noted at the injection site at the two highest doses at the end of the 72 week observation period (Waalkes *et al*, 1999). It is uncertain whether the granulomas at the sites of injection over time trap an unspecified amount of the administered cadmium dose at the injection site. This phenomenon may decrease the actual parenteral cadmium dose, compared with the calculated parenteral cadmium dose. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), and correcting for continuous dosing from 5 days to 7 days per week (factor of 5/7), the parenteral PDE is calculated as:

PDE = 0.6 mg/kg x 5/7 x 50 kg / 5 x 10 x 5 x 5 x 10 = 1.7 µg/day

A factor of 5 was chosen for F4 because cadmium is carcinogenic by the inhalation route and granulomas were observed by the subcutaneous route. These findings are of uncertain relevance. A factor of 10 was chosen for F5 because a LOAEL was used to set the PDE.

PDE – Inhalation Exposure

The United States Department of Labor Occupational Safety and Health Administration has developed a Permitted Exposure Level of 5 µg/m^3 for cadmium.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

$$\text{For continuous dosing} = \frac{5\ \mu g/\ m^3 \times 8\ hr/d \times 5\ d/wk}{24\ hr/d \times 7\ d/wk} = \frac{1.19\ \mu g/m^3}{1000\ L/m^3} = 0.00119\ \mu g/L$$

$$\text{Daily dose} = \frac{0.00119\ \mu g/L \times 28800\ L}{50\ kg} = 0.685\ \mu g/kg$$

PDE = 0.685 µg/kg x 50 kg / 1 x 10 x 1 x 1 x 1 = 3.43 µg/day

A modifying factor for F4 of 1 was chosen based on the potential for toxicity to be mitigated by the possible species specificity of tumorigenesis, uncertain human occupational tumorigenesis, ambient exposure levels not expected to be a health hazard, and workplace exposure levels expected to be safe. A larger factor F4 was not considered necessary as the PDE is based on a PEL.

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