ICH HARMONISED GUIDELINE

GUIDELINE FOR ELEMENTAL IMPURITIES

ICH Q3D(R1) 指引之意見彙整表

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<tr><td>3-10</td><td>Introduction</td><td>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.</td><td></td></tr>
<tr><td>12-15</td><td rowspan="2">Safety Limiting Toxicity</td><td>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.</td><td></td></tr>
<tr><td>16-18</td><td>A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity (Buchet et al. 1990). Skeletal and</td><td></td></tr>
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		renal effects are observed at similar exposure levels and are a sensitive marker of cadmium exposure (ATSDR, 2012).	
19-26		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).	
27-37	**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.	
38-55	**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.	
56-73	**PDE – Inhalation Exposure**	The United States Department of Labor Occupational Safety and Health Administration has developed a Permitted Exposure Level of 5 µg/m3 for cadmium. Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as: For continuous dosing = $\frac{5\ \mu g/\ m^3 \times 8\ hr/d \times 5\ d/wk}{24\ hr/d \times 7\ d/wk} = \frac{1.19\ \mu g/m^3}{1000\ L/m3} = 0.00119\ \mu g/L$ 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.	