ICH Q3D(R1): Cadmium Inhalation PDE Revision (Step 2)

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Outline

• This presentation will provide a summary of the proposed revision to the Cadmium Inhalation PDE in ICH Q3D.

Guideline Objectives

• The objectives and scope remain the same as indicated in the ICH Q3D Guideline finalized in December 2014.

• The Guideline revision (R1) is focused on an error correction of the PDE for Cadmium by the inhalation route.
Summary of Guideline Content

• The original PDE for cadmium by the inhalation route was identified as 2 µg/day in Table A.2.1 and the individual safety assessment in Appendix 3.

• The ICH Secretariat was notified of an error in the PDE calculation.

• Based upon the original approach used, the PDE should have been 0.2 µg/day, a level 10-fold below that identified in the finalised Guideline.

Summary of Guideline Content

• The Expert Working Group re-evaluated the data supporting the cadmium inhalation PDE and concluded that a modifying factors approach, similar to that used for calculating the oral and parenteral PDEs, was appropriate for the inhalation PDE.
Summary of Guideline Content

• The revised calculation is based on a Permitted Exposure Level of 5 µg/m³ developed by the United States Department of Labor Occupational Safety and Health Administration.

• The PDE calculation is as follows:

  For continuous dosing:
  \[ \frac{5 \, \text{µg/m}^3 \times 8 \, \text{hr/d} \times 5 \, \text{d/wk}}{24 \, \text{hr/d} \times 7 \, \text{d/wk}} = \frac{1.19 \, \text{µg/m}^3}{1000 \, \text{L/m}^3} = 0.00119 \, \text{µg/L} \]

  Daily dose = \[ 0.00119 \, \text{µg/L} \times 28800 \, \text{L} = 0.685 \, \text{µg/kg} \]
  \[ \frac{50 \, \text{kg}}{50 \, \text{kg}} \]

  PDE = \[ 0.685 \, \text{µg/kg} \times 50 \, \text{kg} / 1 \times 10 \times 1 \times 1 \times 1 = 3.43 \, \text{µg/day} \]

Guideline for Implementation

• The guideline revision will be implemented immediately upon finalisation.
Conclusions

- The PDE originally identified for cadmium by the inhalation route (2 µg/day) was incorrect due to a calculation error.
- The EWG re-evaluated the relevant data and concluded that a modifying factors approach was appropriate in determining the revised PDE.
- The revised PDE is identified as 3 µg/day.