Integrated Testing Strategy for Precious Metal Cyanides

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Original approach

- Classified according to EU harmonised classification for simple salts of hydrogen cyanide for CLP Notification
- Harmonised classification driven by perceived significant bioavailability of hydrogen cyanide
- Originally suggested a Letter of Access could be obtained for hydrogen cyanide registration data to fulfil REACH endpoints
- Following PMRC comments the approach was reviewed to take into account the binding affinity and solubility of the cyanide substances

SILVER CYANIDES

Annex III exemptions

- 1-10 tpa substance:
  - Silver cyanide
- PBT assessment not applicable for inorganic substances
- Not considered CMR on the basis of available data
- Require confirmation that the substance does not have wide dispersive uses
- Assume Annex III exemption applies until further information becomes available

PHYSICO-CHEMICAL ENDPOINTS

Physico-chemical Properties

- Annex VII dataset required for all substances
- Testing carried out for CLP for some endpoints

Physico-chemical endpoints

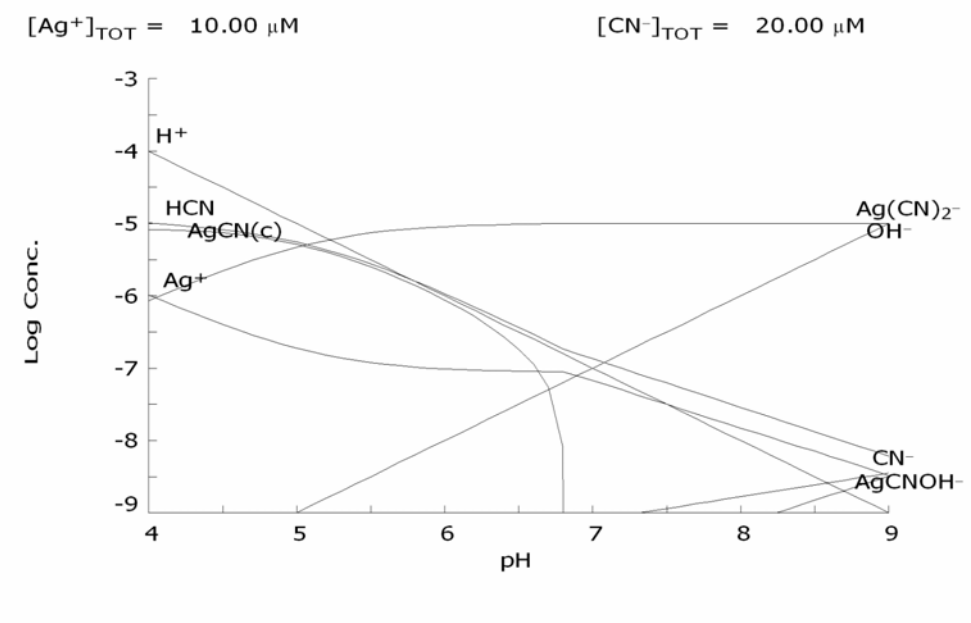
- Potassium dicyanoargentate – Testing proposed:
  - Density
  - Water solubility
- Silver cyanide – No testing proposed

ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL ENDPOINTS

Environmental fate

- Biodegradation and hydrolysis waived as the substances are inorganic

- Adsorption / desorption:
  - Potassium dicyanoargentate: HPLC screening study not suitable for metals
  - Partitioning information available for silver and cyanide
  - Dissociation would affect partitioning behaviour
  - May need to consider testing at the risk assessment stage, if required



Ecotoxicology – Potassium dicyanoargentate

- Testing proposed for potassium dicyanoargentate with *Daphnia*, algae and microorganisms
- Short-term toxicity to fish endpoint may be filled using toxicity data for silver and cyanide and mixture toxicity modelling
- Speciation would need to be considered to predict levels of free cyanide
- *Daphnia* and algae test results would be used to confirm modelling assumptions

Silver cyanide

- No testing currently proposed for silver cyanide on the basis of an Annex III exemption
- If the Annex III exemption is shown not to apply it may be possible to read across the results from potassium dicyanoargentate, refined using mixture toxicity assumptions

GOLD CYANIDES

Annex III exemptions

- 1-10 tpa substance:
  -Potassium tetrakis(cyano-C) aurate
- PBT assessment not applicable for inorganic substances
- Not considered CMR on the basis of available data
- Require confirmation that the substance does not have wide dispersive uses
- Assume Annex III exemption applies until further information becomes available

PHYSICO-CHEMICAL ENDPOINTS

Physico-chemical endpoints

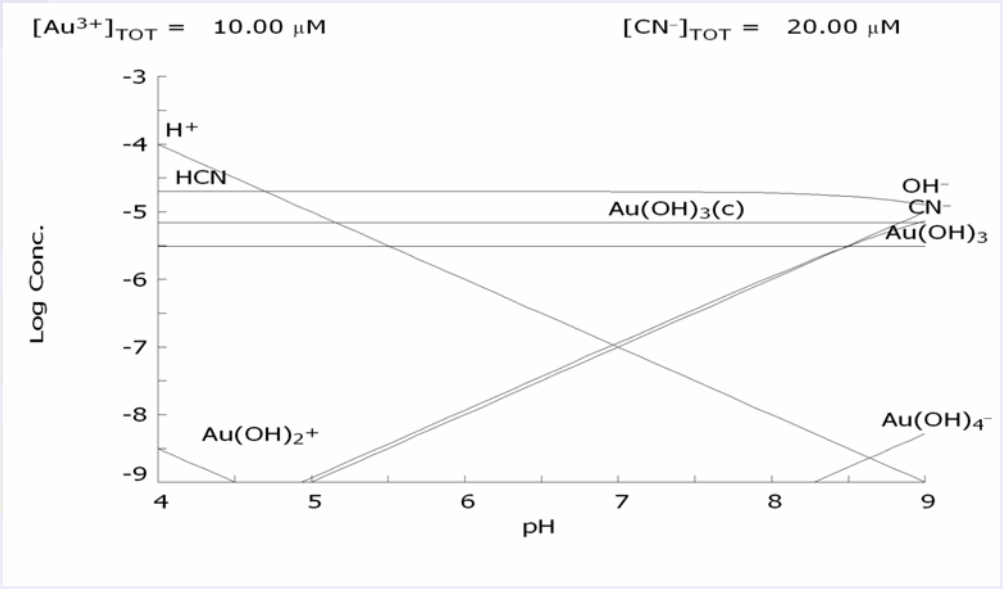
- Potassium dicyanoaurate - Testing proposed:
  - Density
- Potassium tetrakis(cyano-C) aurate – Testing proposed:
  - Density
  - Water solubility

ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL ENDPOINTS

Environmental fate

- Biodegradation and hydrolysis waived as the substances are inorganic

- Adsorption / desorption:
  - HPLC screening test not suitable for metals
  - Dissociation and stability data can be used to assess behaviour in the environment
  - Testing may be considered at the risk assessment stage, if required



Ecotoxicology – Potassium dicyanoaurate

- Testing proposed for potassium dicyanoaurate with *Daphnia*, algae and microorganisms
- Short-term toxicity to fish endpoint may be filled using data for gold and cyanide and mixture toxicity modelling
- Speciation would need to be considered to predict levels of free cyanide
- Algae and *Daphnia* test results would be use to refine modelling assumptions

Potassium tetrakis (cyano-C) aurate

- If Annex III exemption does not apply for potassium tetrakis (cyano-C) aurate, testing on *Daphnia* would be recommended to determine if read across is appropriate

TOXICOLOGICAL ENDPOINTS

wca environment

Potassium dicyanoargentate

- Soluble in cold water and weak acids
- Expected to be easily solubilised under acidic stomach conditions
- Under normal equilibrium conditions only half the cyanide would be expected to dissociate

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Silver cyanide

• AgCN tends to be soluble in hot acid; increased heat shifts the equilibrium to the right

• Solubility of AgCN may be complicated by formation of the cyanoargentate complex ion in the presence of excess cyanide

• Expected to be partially soluble under acidic stomach conditions leading to some release of HCN

Silver cyanide

- pH in the small intestine is around 8.5
- Expected that AgCN will not dissolve to a great extent in the small intestine as it is not sufficiently reducing

Potassium dicyanoaurate

- Soluble in cold water and weak acids
- Expected to be easily solubilised under acidic stomach conditions
- Since the cyanoaurate complex is very stable partial dissolution (ie half the cyanide contained in the complex) is considered for a reasonably conservative approach

Potassium tetrakis (cyano-C)aurate

- Sparingly soluble in cold water and weak acids
- Expected to be readily solubilised under strongly acidic stomach conditions
- Tetrakis (cyano-C)aurate complex is stable therefore partial dissociation (ie one fourth of the cyanide in the complex) presents a reasonably conservative approach

Oral toxicity

- Information on acute oral toxicity has been extrapolated following desk-based assessment of HCN release. Oral LD50 of HCN is reported as 3-4 mg/kg for rats (using HCN, KCN or NaCN). Using an upper value of 4 mg/kg the equivalent cyanide dose is 3.85 –CN mg/kg
- Potassium dicyanoargentate: An equivalent oral lethal dose of 29.5 mg/kg body weight as potassium dicyanoargentate derived based on theoretical availability

Oral toxicity

- Potassium dicyanoaurate: An equivalent oral lethal dose of 42.54 mg/kg bodyweight as potassium dicyanoaurate is derived
- Silver cyanide: An oral LD50 of 123 mg/kg has been reported for rats exposed to silver cyanide
- Potassium tetrakis (cyano-C)aurate: An equivalent oral lethal dose of 50.33 mg/kg bodyweight as potassium tetrakis (cyano-C)aurate is derived

Oral toxicity

- An oral LD50 is available for potassium dicyanoaurate of 29.2 mg/kg
- This is comparable to the calculated value and both would result in classification as Acute category 2, the same as the harmonised classification for HCN and salts of HCN
- If it is assumed this is driven by free HCN a similar result and classification for potassium dicyanoargentate would be expected

Oral toxicity

- The calculated LD50 for potassium tetrakis (cyano-C)aurate is borderline for classification as Acute category 2
- The published LD50 for silver cyanide would result in classification as Acute category 3
- Using theoretical calculation of HCN availability from the substances the classification is consistent with the harmonised Annex VI classification, except for silver cyanide

Inhalation

- Particle size distribution determined that all substances except potassium tetrakis (cyano-C)aurate have >10% particles < 100 µm
- It is recommended that potassium dicyanoargentate and potassium dicyanoaurate are subjected to particle size distribution to determine Mass Median Aerodynamic Diameter and Geometric Standard Deviation
- Respiratory tract particle deposition modelling can then be performed

Inhalation

- Inclusion of PSD with dustiness testing should be considered
- Also consider testing the two substances with Annex III exemptions – may modify the CLP inhalation classification

Bioaccessability tests

- The following bioaccessability tests are recommended for potassium dicyanoargentate and potassium dicyanoaurate:

Artificial skin surface liquid (*simulates fluid excreted from body through sweating*)

Artificial gastric fluid (*mimics harsh digestive milieu of low pH (1.5) in stomach*)

Gambles' solution (*mimics interstitial fluid within deep lung in normal health*)

Phosphate-buffered saline (*standard physiological solution mimicking human blood serum*)

Artificial lysosomal fluid (*simulates relatively harsh intracellular conditions in lung cells occurring in conjunction with phagocytosis*)

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Bioaccessability testing

- Bioaccessability testing would allow assessment of the substances in relation to existing data on the toxicity of HCN
- Consider testing the 2 substances with Annex III exemptions to validate current CLP classifications
- When the results of the bioaccessibility tests are available, a full Annex VIII toxicology test plan will be defined for the two substances.

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Other endpoints

- Sensitisation and mutagenicity not usually associated with HCN
- These endpoints need to be considered in relation to the presence of undissociated cyanide molecule and metal speciation
- Repeat dose toxicity and reproductive screening - need to consider relative contributions by free HCN and undissociated components