PPHASE III: INTEGRATED TESTING STRATEGY (ITS) FOR PRECIOUS METAL CYANIDES: ADDENDUM 1

DRAFT REPORT TO PRECIOUS METALS AND RHENIUM CONSORTIUM FROM WCA

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EXECUTIVE SUMMARY

The Precious Metals and Rhenium Consortium commissioned wca to design an Integrated Testing Strategy (ITS) involving the recommendation of any enabling tests or test waiving based on category read-across and weight of evidence arguments for precious metal cyanide substances.

The final ITS report was completed in April 2012. However, a tiered testing approach is used for many endpoints under REACH and therefore further iterations of the ITS are required following the initial recommendation for use of existing data, waivers and further testing outlined in the original ITS report. This ITS addendum outlines the additional data that has become available since the 2012 ITS report, provides updated proposals for completing REACH endpoints or for any further testing that is required, and gives a record of decisions made regarding the REACH strategy for precious metal cyanides since the 2012 ITS report.

The substances covered by this ITS addendum, along with their registration intentions, are provided in the table below. There have been no changes to the substance inventory or declared tonnages since the 2012 ITS report. A fourth precious metal cyanide substance, potassium tetrakis (cyano-C)aurate was removed from the scope of the project in December 2011.

Name of substance	CAS number	Volume (tpa)	Substance status	REACH Registration deadline	PMC registration date
Potassium dicyanoargentate	506-61-6	10-100	Mono-constituent substance	2018	2015 / 2016
Silver cyanide	506-64-9	10-100	Mono-constituent substance	2018	2015 / 2016
Potassium dicyanoaurate	13976-50-5	10-100	Mono-constituent substance	2018	2015 / 2016

The following updates have been agreed since the ITS report was finalised in 2012:

- Remaining physico-chemical tests have been conducted at Harlan Laboratories. All physico-chemical endpoints are now complete.
- It has been agreed to conduct a limited OECD 106 adsorption / desorption study with potassium dicyanoaurate. Testing is ongoing at Fraunhofer.

- Remaining ecotoxicity endpoints have been completed using mixture toxicity modelling and some direct testing for silver cyanide substances, and direct testing only for gold cyanide substances.

- Dustiness testing and respiratory tract deposition modelling has been conducted with all precious metal cyanide substances. Following this it was concluded that the oral route of administration is appropriate for hazard assessment, and that a route-to-route extrapolation could be performed for assessment of inhalation risk.

- Testing has been conducted for potassium dicyanoaurate and silver cyanide to complete all toxicological endpoints for which existing data was not available, and data waivers could not be used.

- The toxicological testing with potassium dicyanoaurate and silver cyanide showed differences in behaviour between the two substances, particularly with the positive results for potassium dicyanoaurate in the LLNA and *in vitro* micronucleus assay, suggesting that the metal ion contributes to toxicity, in addition to the free cyanide.

- Due to the differences observed in the testing with the other precious metal cyanide substances, read across from free cyanide is no longer considered to be appropriate for potassium dicyanoargentate. Testing has therefore been proposed for this substance, instead of read across.

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1 INTRODUCTION

The Precious Metals and Rhenium Consortium commissioned wca to design an Integrated Testing Strategy (ITS) involving the recommendation of any enabling tests or test waiving based on category read-across and weight of evidence arguments for precious metal cyanide substances.

The final ITS report was completed in April 2012. However, a tiered testing approach is used for many endpoint under REACH and therefore further iterations of the ITS are required following the initial proposals for use of existing data, waivers and further testing outlined in the ITS report. This ITS addendum outlines the additional data that has become available since the 2012 ITS report, provides updated proposals for completing REACH endpoints or for any further testing that is required based on this new data and provides a record of decisions made regarding the REACH strategy for precious metal cyanide substances since the initial ITS report.

1.1 Substances in scope

The precious metal cyanide substances covered in this ITS, and their tonnage requirements, are presented in Table 1.1.

Table 1.1 Substances in Scope

Name of substance	CAS number	Volume (tpa)	Substance status	REACH registration deadline	PMC registration date
Potassium dicyanoargentate	506-61-6	10-100	Mono-constituent substance	2018	2015 / 2016
Silver cyanide	506-64-9	10-100	Mono-constituent substance	2018	2015 / 2016
Potassium dicyanoaurate	13976-50-5	10-100	Mono-constituent substance	2018	2015 / 2016

All precious cyanide substances are being registered at 10-100 tpa, and therefore require an Annex VIII dataset under REACH.

A fourth precious metal cyanide substance, potassium tetrakis (cyano-C)aurate was removed from the scope of the project in December 2011.

2 TESTING STRATEGY FOLLOWING 2012 ITS REPORT

This section outlines the decisions that have been made with regard to the testing strategy since the 2012 ITS report was finalised. It details the latest status of the Annex III assessment, test programmes and decisions regarding read across and data waiving. A data matrix accompanies this ITS addendum (PM CN_Phase III_Data gap matrix_VIII_2014_12_18) and outlines how each REACH-required endpoint will be completed.

2.1 Annex III exemptions

For substances that are manufactured or imported at 1–10 tpa only the REACH Annex VII physico-chemical endpoints are required, plus any existing data, if the substance does not meet the criteria of REACH Annex III. For clarity, a summary of the Annex III criteria is as follows (for an exact review of the Annex III regulatory text, see the REACH Regulation):

If substances **meet** the following criteria:

a) Prediction (e.g. by QSARs) that they are likely to meet the criteria for category 1 classification for carcinogenicity, mutagenicity, or reproductive toxicity under the CLP Regulation (category 1 or 2 under the Dangerous Substances Directive (DSD)), or PBT/vPvB,

OR b)

i) Have dispersive or diffuse use(s), particularly where such substances are used in consumer preparations or incorporated into consumer articles; AND

ii) predicted (e.g. by QSARs) that they are likely to meet the classification criteria for human or environmental effects endpoints under the CLP Regulation or DSD.

then all Annex VII test endpoints are required.

All of the precious metal cyanide substances are being registered at greater than 10 tpa and therefore Annex III exemptions do not apply for any of these substances.

2.2 Physico-chemical testing recommendations

Physico-chemical endpoints are completed for precious metal cyanide substances using existing data, data waivers and new test data carried out as part of the CLP and REACH test programmes. All physico-chemical endpoints are now complete for precious metal cyanide substances. The test results obtained as part of the REACH physico-chemical testing programme are provided in Tables 2.1 and 2.2. The data matrix accompanying this ITS addendum outlines how each REACH-required endpoint will be filled.

Table 3.1 Physico-chemical test results conducted for the CLP test programme

Test material	Test	Results or test status	Reference
Potassium dicyanoargentate	OECD 101/ A1 Melting/Freezing Temperature	Revised conclusion: Decomposed with melting from approximately 368°C (641 K).	Harlan (2011a)
	N1 Readily Combustible Solid	Negative	Harlan (2011a)
	N.4 (modified method) Self-Heating Substances	There were no signs of self ignition or self-heating when the test item was held at 140°C for 24 hours. However, when the test item was heated from 140 to 400°C, the sample temperature did exceed the oven temperature by greater than 60°C at an oven temperature of approximately 400°C.	Harlan (2011a)
	OECD 110 Granulometry (Screening Test)	16.8% <100 µm.	Harlan (2011a)
Silver cyanide	N.1 Readily Combustible Solids	The test item is not classified as a readily combustible solid under Division 4.1, as it ignited but then failed to propagate combustion in the preliminary screening test.	Harlan (2011b)
	N.4 (modified method) Self-Heating Substances	There were no signs of self ignition or self-heating when the test item was held at 140°C for 24 hours. However, when the test item was heated from 140 to 400°C, the sample temperature exceeded the oven temperature by greater than 60°C at an oven temperature of approximately 355°C.	Harlan (2011b)
	OECD 110 Granulometry (Screening Test)	46.4%<100 µm	Harlan (2011b)
Potassium dicyanoaurate	OECD 101/ A1 Melting/Freezing Temperature	(Revised Conclusion): The test item has been determined to decompose from approximately 390°C (663 K), with no definitive signs of melting below 450°C (723 K). As the test item decomposed, no value for melting temperature could be determined.	Harlan (2011c)
	N1 Readily Combustible Solid	The test item is not classified as a readily combustible solid under Division 4.1 as it failed to ignite in the preliminary screening test.	Harlan (2011c)
	N.4 (modified method) Self-	There were no signs of self ignition or self-heating when the test item was	Harlan (2011c)

Test material	Test	Results or test status	Reference
	Heating Substances	held at 140°C for 24 hours. Additionally, when the test item was heated from 140 to 400°C, the sample temperature did not exceed the oven temperature by greater than 60°C.	
	OECD 110 Granulometry (Screening Test)	17.6%<100 µm	Harlan (2011c)

Table 3.2 Physico-chemical test results conducted for the REACH test programme

Test material	Test	Results or test status	Reference
Potassium dicyanoargentate	Relative density	2.43 at 20 ± 0.5°C	Harlan (2012a)
	Water solubility	20.0 to 21.9% w/w of solution at 20 ± 0.5°C	Harlan (2012a)
Potassium dicyanoaurate	Relative density	3.60 at 20 ± 0.5°C	Harlan (2012b)
Potassium tetrakis (cyano-C)aurate	Relative density	2.89 at 20 ± 0.5°C	Harlan (2012c)
	Water solubility	14.8 to 16.0% w/w of solution at 20 ± 0.5°C	Harlan (2012c)

2.3 Environmental fate testing recommendations

All precious metal cyanide substances require Annex VIII environmental fate endpoints to be completed. Biodegradation and hydrolysis endpoints can be waived as the substances are inorganic.

For silver cyanide and potassium dicyanoargentate the adsorption / desorption endpoint can be completed using available data for silver and cyanide. In the 2012 ITS report it was proposed that modelled speciation data may be able to be used for potassium dicyanoaurate, but if not testing would be required. The standard test for adsorption / desorption under REACH is an OECD 121 screening study (K_{OC} estimation by HPLC). However, this study is not appropriate for inorganic substances; the method has not been validated for any inorganic compounds and none of the recommended reference substances are inorganic compounds. In the wca (2014a) report 'Summary of the derivation of predicted no effect concentrations (PNECs) for precious metal cyanide substances' (draft) it was proposed that a limited partitioning study following the OECD 106 Batch equilibrium method was conducted in order to provide partitioning information that can be used to derive soil and sediment PNECs based on the equilibrium partitioning approach and to use in the exposure assessment, which will be required for potassium dicyanoaurate. Before proposing this test a search of the published literature was conducted, but no suitable partitioning data was found.

The Precious Metal Cyanides Working Group agreed to conduct a limited OECD 106 study with potassium dicyanoaurate and this study is currently ongoing at Fraunhofer. Only the preliminary stages of the test are being performed, with three soils used to determine the partition coefficient. This approach should be sufficient for determination of a K_D value which will be adequate for the required purposes.

2.4 Ecotoxicological endpoints

Precious metal cyanides are pure inorganic substances which are composed of components which are better understood than the substances themselves. The relevant components are the precious metals silver and gold, and cyanide. For this reason it was proposed in the 2012 ITS report that, as an alternative to undertaking ecotoxicity testing on the substances themselves, it may be possible to predict the toxicity of a precious metal cyanide substance from information on the toxicities of the precious metal and cyanide, and information about the chemical speciation of the precious metal cyanide substance in the test medium.

Mixture toxicity modelling was therefore conducted in order to determine the toxicity of precious metal cyanide substances based on their components. Limited testing was also conducted at Brixham Environmental Laboratory (acute *Daphnia* and activated sludge respiration inhibition tests with potassium dicyanoargentate and potassium dicyanoaurate) in order to validate the modelling approach. The full results of the modelling approach are detailed in the wca environment (2012) report 'Mixture toxicity assessment for precious metal cyanide substances' (Revision following receipt of ecotoxicity results). For potassium dicyanoargentate and silver cyanide, silver is likely to provide the dominant contribution to the overall toxicity, but cyanide may also contribute to a lesser extent. Cyanide is expected to be the only significant contributor to the ecotoxicity of potassium dicyanoaurate, based on the limited, currently available information on gold toxicity.

Following the mixture toxicity modelling, and comparison of the calculated values with the test values, it was concluded that the modelling approach is suitable for silver cyanide substances. There was good agreement between the predicted and measured results for potassium dicyanoargentate. It was therefore considered that the approach for predicting toxicity is reliable for the silver cyanide substances potassium dicyanoargentate and silver cyanide.

For potassium dicyanoaurate, however, the mixture toxicity modelling approach was considered to be unreliable. There are several possible reasons for the poor prediction of the toxicity of gold cyanide compounds, including the oxidation state of gold following dissolution of this substance, and the ability of the VisualMINTEQ model to accurately predict the speciation of gold cyanide complexes in aqueous solution. Further consideration of the ability to accurately predict the speciation of potassium dicyanoaurate solutions would be necessary in order to refine the predictions and with the currently available information it may not be possible to conduct accurate predictions for this substance. Due to the uncertainties with the speciation predictions it was recommended to conduct direct testing to complete the remaining ecotoxicity endpoints for potassium dicyanoaurate (acute fish and toxicity to algae). Testing was conducted in 2013 at Brixham Environmental Laboratory.

Following the test programme at Brixham Environmental Laboratory and the mixture toxicity modelling assessment, the following results will be taken forward and included in the REACH dossiers.

Table 3.3 Ecotoxicity values recommended for inclusion in the REACH dossiers following the mixture toxicity assessment

Substance	Fish EC50 (mg l^{-1})	*Daphnia* EC50 (mg l^{-1})	Algae EC50 (mg L^{-1})	Microorganisms NOEC (mg l^{-1})
Potassium dicyanoargentate	3.3 (predicted)	0.022 (measured)	>100 (predicted)	0.64 (measured)
Silver cyanide	3.0 (predicted)	0.00056 (predicted)	80 (predicted)	0.0094 (predicted)
Potassium dicyanoaurate	5.7 (measured)	0.2 (measured)	30 (measured)	60 (measured)

2.5 Toxicological endpoints

Limited existing data were available for precious metal cyanide substances.

Dustiness testing and respiratory tract deposition modelling were conducted for all of the precious metal cyanide substances. The results of this are outlined in the wca (2012b) Addendum to the integrated testing strategy for precious metal cyanides – dustiness and respiratory tract deposition modelling report.

The results of the investigations on the precious metal cyanide substances indicated that one substance in particular – potassium dicyanoaurate – is relatively fragile under the rotating drum conditions. The other materials were more resistant to dust formation. The dusts formed had mass median aerodynamic diameters that indicated the potential for inhalation into the respiratory tract. However, using the MPPD modelling software showed that most of the substances would be deposited in the head region (the majority of which would then be eliminated by swallowing) with very little reaching the trachea-bronchial or pulmonary regions (and in the case of trachea-bronchial, again most of the substances would be eliminated via the gastrointestinal tract). Overall, the results obtained from the investigation indicate that the oral route of administration would be appropriate for hazard assessment, and that a route-to-route extrapolation could be performed for assessment of inhalation risk.

In the 2012 ITS report it was proposed that further investigation of cyanide dissociation from each of the precious metal cyanide substances be conducted before initiating any further testing. It was anticipated that most of the toxicity from precious metal cyanide substances would most likely be due to release of free cyanide from these compounds. Therefore for those substances where high dissociation of free cyanide is expected read across from a soluble cyanide substance would, most likely, be a suitable way of filling the endpoints under REACH, without having to conduct new testing.

This concept was investigated and a proposal for conducting dissociation experiments was obtained from Intertek. In addition, stability constants for each of the precious metal cyanide substances were obtained and, based on these, estimations of the amount of free cyanide likely to be released were made. It was ultimately decided not to conduct any dissociation experiments but, based on the dissociation calculations, to conduct direct testing in order to complete any data gaps for potassium dicyanoaurate and silver cyanide (following a tiered testing approach). For potassium dicyanoargentate it was agreed, based on the dissociation calculations, that release of free cyanide is likely to be higher from this substance and therefore read across from a free cyanide substance was likely to be suitable for potassium dicyanoargentate.

Consequently, the following tests were commissioned for silver cyanide and potassium dicyanoaurate:

- Skin irritation (EPISKIN) (OECD 439) at Harlan Laboratories,
- Skin corrosion(EPISKIN) (OECD 431) at Harlan Laboratories,
- *In vitro* eye irritation / corrosion (BCOP) (OECD 437) at Harlan Laboratories,
- *In vivo* eye irritation (OECD 405) at Harlan Laboratories (Silver cyanide only),
- Skin sensitisation (Local lymph node assay) (OECD 429) at Harlan Laboratories,
- Ames screen and main test (OECD 471) at Covance,
- *In vitro* mammalian cell micronucleus test (OECD 487) at Harlan Laboratories,
- *In vitro* mammalian cell gene mutation assay (OECD 476) at Covance (silver cyanide only),

- Acute oral toxicity (OECD 423) at LPT (silver cyanide only),
- Acute dermal toxicity (OECD 402) at LPT,
- Repeat dose / reproductive toxicity (OECD 422) at LPT.

The results obtained from these studies to date are presented in Table 3.4.

Table 3.4 Results from toxicology tests conducted as part of the REACH test programme for precious metal cyanides

Test	Result	
	Potassium dicyanoaurate	**Silver cyanide**
Skin irritation (EPISKIN) (OECD 439	Irritant (classified skin irritant category 2).	Irritant (classified skin irritant category 2).
Skin corrosion(EPISKIN) (OECD 431)	Non-corrosive	Non-corrosive
Eye irritation / corrosion (BCOP)	Corrosive	No irritant
In vivo eye irritation (OECD 405)	Corrosive (classified eye damage category 1)	Corrosive (classified eye damage category 1)
Skis sensitisation (Local lymph node assay) (OECD 429)	Sensitising (classified skin sensitiser category 1)	Not sensitising
Ames screen and main test (OECD 471)	Negative	Negative
In vitro mammalian cell micronucleus test (OECD 487)	Positive	Negative
In vitro mammalian cell gene mutation assay (OECD 476)	Not required – positive result in OECD 487	In progress
In vivo micronucleus test (OECD 474)	To be conducted – testing proposal required	Not required – negative result in OECD 487
Acute oral toxicity (OECD 423)	Not required – existing data available	LD50: 125 mg/kg
Acute dermal toxicity (OECD 402)	LD50: >2000 mg/kg bw	LD50: >2000 mg/kg bw

Test	Result	
	Potassium dicyanoaurate	Silver cyanide
Repeat dose / reproductive toxicity (OECD 422)	In progress	In progress

Following the positive result for potassium dicyanoaurate in the LLNA study, it was agreed to conduct an adapted LLNA study for this substance at MBR (USA) in order to determine whether the result was a false positive based on the irritancy potential of the substance. The adapted LLNA was conducted and strongly indicated that potassium dicyanoaurate is a sensitiser. The substance is therefore assigned a skin sensitisation classification, category 1.

The *in vitro* mammalian cell micronucleus test also returned a positive result for potassium dicyanoaurate. The next step for this substance would therefore be to conduct an *in vivo* micronucleus test. However, ECHA guidance on genotoxicity testing has recently been updated (ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R7a: Endpoint specific guidance Version 3.0, August 2014) and now clarifies that this test should always be considered an Annex IX test. As such, a testing proposal needs to be submitted to ECHA before any testing, and specifically the OECD 474 *in vivo* micronucleus test, can commence. A testing proposal will therefore be prepared for this test to be included in the REACH dossier for potassium dicyanoaurate.

For potassium dicyanoargentate it was originally considered that read across from a soluble cyanide substance would be suitable, as discussed in earlier paragraphs. However, following the testing conducted with the other precious metal cyanide substances, this conclusion has been re-evaluated. The difference in the results for two specific endpoints (skin sensitisation and mammalian cell chromosome damage endpoints) between potassium dicyanoaurate and silver cyanide indicate that toxicity is likely not be solely due to the free cyanide being released, and that the metal ion also has a major influence. This would mean that reading across solely from free cyanide is unlikely to be appropriate. Instead, the metal ion must also be considered. Potassium dicyanoargentate and silver cyanide are both precious metal cyanide substances, but are structurally different and have different stability constants. Therefore they may not behave in the same way in toxicological studies and reading across from silver cyanide to potassium dicyanoargentate is not considered to be appropriate. As the metal ion is likely to influence toxicity, reading across from potassium dicyanoaurate is also not appropriate. Therefore, direct testing of potassium dicyanoargentate is now recommended.

Testing for the following endpoints has been proposed and provisionally agreed by the Precious Metal Cyanides Working Group, for potassium dicyanoargentate. Testing for skin and eye irritation studies has been initiated. It is likely that testing for other endpoints will be delayed until 2016. Testing will be conducted in a tiered manner, as with the previous precious metal cyanide test programme.

- Skin irritation (EPISKIN) (OECD 439),
- Skin corrosion(EPISKIN) (OECD 431),
- *In vitro* eye irritation / corrosion (BCOP) (OECD 437), and possibly OECD 438 ICE study,
- Skin sensitisation (Local lymph node assay) (OECD 429),
- Ames screen and main test (OECD 471),
- *In vitro* mammalian cell micronucleus test (OECD 487),
- *In vitro* mammalian cell gene mutation assay (OECD 476),
- Acute oral toxicity (OECD 423),
- Acute dermal toxicity (OECD 402),
- Repeat dose / reproductive toxicity (OECD 422).

3 SUMMARY OF UPDATES SINCE 2012 ITS REPORT

The following updates have been agreed since the ITS report was finalised in 2012:

- Remaining physico-chemical tests have been conducted at Harlan Laboratories. All physico-chemical endpoints are now complete.
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- Testing has been conducted for potassium dicyanoaurate and silver cyanide to complete all toxicological endpoints for which existing data was not available, and data waivers could not be used.
- The toxicological testing with potassium dicyanoaurate and silver cyanide showed differences in behaviour between the two substances, particularly with the positive results for potassium dicyanoaurate in the LLNA and *in vitro* micronucleus assay, suggesting that the metal ion contributes to toxicity, in addition to the free cyanide.
- Due to the differences observed in the testing with the other precious metal cyanide substances, read across from free cyanide is no longer considered to be appropriate for potassium dicyanoargentate. Testing has therefore been proposed for this substance, instead of read across.

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APPENDIX 1

Current registration intentions are as follows: potassium dicyanoargentate as a 10 – 100 tpa substance, potassium dicyanoaurate as a 10 – 100 tpa substance and silver cyanide as a 10 – 100 tpa substance.

A1.1 Physico-chemical properties

A1.1.1 Appearance/ physical state/ colour

Data are available from peer-reviewed handbooks indicating that the potassium dicyanoargentate is a white, crystaline solid (Lide 2008, O'Neil 2006). No further testing is proposed.

Data are available from peer-reviewed handbooks indicating that potassium dicyanoaurate is a white, crystaline solid (Lide 2008, O'Neil 2006). No further testing is proposed.

Data are available from peer-reviewed handbooks to indicate that silver cyanide exists as white-grey crystals (Lide 2008, O'Neil 2006). No further testing is proposed.

A1.1.2 Melting point/ freezing point

Proprietary data are available to indicate that potassium dicyanoargentate decomposes with melting from approximately 368°C (Harlan 2011a). No further testing is proposed.

Proprietary data are available to indicate that potassium dicyanoaurate decomposes from approximately 383°C, therefore no value for melting point could be determined (Harlan 2011c). No further testing is proposed.

Data are available from peer-reviewed handbooks to indicate that silver cyanide decomposes at 320°C (Lide 2008, O'Neil 2006). No further testing is proposed.

A1.1.3 Boiling point

A boiling point study does not need to be carried out for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide, in accordance with column 2 of REACH Annex VII as these substances are solids which melt above 300°C. No further testing is proposed.

A1.1.4 Density

Published data are available to indicate that the density of potassium dicyanoargentate is 2.36 (Lide 1990 cited in US Department of Health and Human Services 2006), however this value comes from a secondary source and is not sufficient to fulfil this endpoint. Testing was conducted at Harlan Laboratories as part of the REACH test programme. The test results determined that the relative density of potassium dicyanoargentate is 2.43 at 20 ± 0.5°C (Harlan 2012a).

Handbook data indicate that the relative density of potassium dicyanoaurate is 3.45 (Lide 2008). As data are only available from one handbook another source is required. Testing was conducted at Harlan Laboratories as part of the REACH test programme. The test results determined that the relative density of potassium dicyanoaurate is 3.6 at 20 ± 0.5°C (Harlan 2012b).

Data are available from peer-reviewed handbooks for silver cyanide to indicate that the relative density of the substance is 3.95 (Lide 2008, O'Neil 2006). No further testing is proposed.

A1.1.5 Particle size distribution (granulometry)

Proprietary data are available to indicate that the proportion of potassium dicyanoargentate <100 µm was 16.8% (Harlan 2011a).

Proprietary data are available to indicate that the proportion of potassium dicyanoaurate <100 µm was 17.6% (Harlan 2011c).

Proprietary data are available to indicate that the proportion of silver cyanide <100 µm was 46.4% (Harlan 2011b).

A1.1.6 Vapour pressure

A vapour pressure study does not need to be conducted for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide in accordance with Column 2 of Annex VII, as the substances have a melting point above 300°C. No further testing is proposed.

A1.1.7 Partition coefficient

The partition coefficient does not need to be determined for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide, in accordance with Column 2 of Annex VII, as the substances are inorganic. No further testing is proposed.

A1.1.8 Water solubility

Published data indicates that the water solubility of potassium dicyanoargentate is 250 g l^{-1} at 20°C (EPA 1985 cited in US Department of Health and Human Services 2006), however this value comes from a secondary source and is not sufficient to fulfil this endpoint. Testing was conducted at Harlan Laboratories as part of the REACH testing programme. The results determined that the water solubility of potassium dicyanoargentate is in the range 20.0 to 21.9% w/w of solution at 20 ± 0.5°C (Harlan 2012a).

Data are available for potassium dicyanoaurate from peer-reviewed handbooks indicating that the substance is very soluble (>10,000 mg l^{-1}) (Lide 2008, O'Neil 2006). No further testing is proposed.

Data are available for silver cyanide from peer-reviewed handbooks to indicate that the water solubility is <0.1 mg l^{-1} (insoluble) (Lide 2008, O'Neil 2006). No further testing is proposed.

A1.1.9 Surface tension

The surface tension does not need to be determined for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide, in accordance with Column 2 of Annex VII, as surface activity is not expected or predicted and surface activity is not a desired property of the materials. No further testing is proposed.

A1.1.10 Flash point

The flash point study does not need to be determined for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide, in accordance with Column 2 of Annex VII, as the substances are inorganic. No further testing is proposed.

A1.1.11 Autoflammability

Proprietary data are available for potassium dicyanoargentate indicating that no signs of self-ignition or self-heating were observed when the substance was held at 140°C for 24 hours. However, when the test item was heated from 140 – 400°C the sample temperature exceeded the oven temperature by greater than 60°C at an oven temperature of approximately 400°C (Harlan 2011a). No further testing is proposed.

Proprietary data are available for potassium dicyanoaurate to indicate that the substance showed no sign of self-ignition or self-heating when the test item was held at 140°C for 24 hours and when the test item was heated from 140°C to 400°C the temperature did not exceed the oven temperature by greater than 60°C (Harlan 2011c). No further testing is proposed.

Proprietary data are available for silver cyanide to indicate that no sign of self-ignition or self-heating was observed when the test item was held at 140°C for 24 hours. However, when the test item was heated from 140 to 400°C the sample temperature exceeded the oven temperature by greater than 60°C at an oven temperature of approximately 355°C (Harlan 2011b). No further testing is proposed.

A1.1.12 Flammability

Proprietary data indicate that potassium dicyanoargentate is not classified as a readily combustible solid under Division 4.1 (Harlan 2011a). No further testing is proposed.

Proprietary data are available to indicate that potassium dicyanoaurate is not classified as a readily combustible solid under Division 4.1 (Harlan 2011c). No further testing is proposed.

Proprietary data indicate that silver cyanide is not classified as a readily combustible solid under Division 4.1 (Harlan 2011b). No further testing is proposed.

A1.1.13 Explosiveness

The explosive properties study does not need to be conducted for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide, in accordance with column 2 of REACH Annex VII, as there are no chemical groups associated with explosive properties present in the molecule. No further testing is proposed.

A1.1.14 Oxidising properties

The oxidising properties study does not need to be conducted for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide, in accordance with Column 2 of Annex VII, as the substance is incapable of reacting exothermically with combustible materials on the basis of its chemical structure. No further testing is proposed.

A1.2 Environmental fate

A1.2.1 Hydrolysis

There are currently no data available to fulfil this endpoint for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide. Hydrolysis is defined as the decomposition or degradation of a chemical by reaction with water. We therefore propose that this test is waived using the following REACH adaptation:

In accordance with REACH Annex XI Section 1: testing does not appear to be scientifically necessary because this method is used on organic substances to measure the decomposition or degradation of a chemical reacting with water. For inorganics this type of method is not appropriate.

A1.2.2 Biodegradation

This study is not required for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide, in accordance with Column 2 of Annex VII, as the substances are inorganic. No additional testing is proposed.

A1.2.3 Adsorption / desorption

There are currently no data available to fulfil this endpoint for potassium dicyanoargentate, potassium dicyanoaurate or silver cyanide. The standard test guideline (OECD 121) may not work for inorganic compounds; the method has not been validated for any inorganic compounds and none of the recommended reference substances are inorganic compounds.

For potassium dicyanoargentate and silver cyanide partitioning information from silver and cyanide, taking into account the likely speciation of each of the cyanide substances, can be used to determine the likely behaviour of each substance in the environment.

For potassium dicyanoaurate no existing data are available, therefore a modified OECD 106 study is currently underway at Fraunhofer to provide information to complete this endpoint.

A1.3 Ecotoxicology

A1.3.1 Short-term toxicity to fish

Predicted values based data for silver and cyanide and mixture toxicity assumptions will be used to complete this endpoint for potassium dicyanoargentate and silver cyanide. Predicted EC50 values determined in this way are 3.3 and 3.0 mg L^{-1}, respectively

Testing has been conducted at Brixham Environmental Laboratory for potassium dicyanoaurate. The EC50 determined from this testing is 5.7 mg L^{-1} (Brixham Environmental Laboratory 2013a).

A1.3.2 Short-term toxicity to aquatic invertebrates

Testing has been conducted at Brixham Environmental Laboratory for potassium dicyanargentate. The EC50 determined from this testing is 0.002 mg L^{-1} (Brixham Environmental Laboratory 2012a).

Predicted values based data for silver and cyanide and mixture toxicity assumptions will be used to complete this endpoint for silver cyanide. The predicted EC50 value determined in this way is 0.00056 mg L^{-1}.

Testing has been conducted at Brixham Environmental Laboratory for potassium dicyanoaurate. The EC50 determined from this testing is 0.2 mg L^{-1} (Brixham Environmental Laboratory 2012b).

A1.3.3 Toxicity to aquatic algae and cyanobacteria

Predicted values based data for silver and cyanide and mixture toxicity assumptions will be used to complete this endpoint for potassium dicyanoargentate and silver cyanide. Predicted EC50 values determined in this way are >100 mg L^{-1} and 80 mg L^{-1} respectively.

Testing has been conducted at Brixham Environmental Laboratory for potassium dicyanoaurate. The EC50 determined from this testing is 30 mg L^{-1} (Brixham Environmental Laboratory 2013b).

A1.3.4 Toxicity to microorganisms

Testing has been conducted at Brixham Environmental Laboratory for potassium dicyanargentate. The EC50 determined from this testing is 0.64 mg L^{-1} (Brixham Environmental Laboratory 2012c).

Predicted values based data for silver and cyanide and mixture toxicity assumptions will be used to complete this endpoint for silver cyanide. The predicted EC50 value determined in this way is 0.0094 mg L^{-1}.

Testing has been conducted at Brixham Environmental Laboratory for potassium dicyanoaurate. The EC50 determined from this testing is 60 mg L^{-1} (Brixham Environmental Laboratory 2012d).

A1.4 Mammalian toxicology

A1.4.1 Skin irritation

Proprietary data indicate that potassium dicyanoaurate is severely irritating to the skin of the rabbit (Berthold 1992). An EPISKIN result for the same substance indicates that it is irritating, but not corrosive to skin (Harlan 2014a,b).

EPISKIN results for silver cyanide indicate that the substance is irritating, but not corrosive to kin (Harlan 2014c,d).

Testing is proposed for this endpoint for potassium dicyanoargentate.

A1.4.2 Eye irritation

Proprietary data indicate that potassium dicyanoaurate is corrosive to the eye of the rabbit (Berthold 1992). An *in vitro* result also indicates that the substance is corrosive (Harlan 2014e).

An *in vitro* eye irritation study (BCOP) with silver cyanide indicated that it is not irritant (Harlan 2014f), however an *in vivo* study with the same substance showed that it was corrosive (Harlan 2014g).

Testing is proposed for this endpoint for potassium dicyanoargentate.

A1.4.3 Skin sensitization

Potassium dicyanoaurate was shown to be sensitising in an LLNA assay (Harlan 2014h). An adapted LLNA assay conducted at MBR confirmed that the substance is a sensitiser, and the final report for this study is currently being prepared.

Silver cyanide was shown to be non-sensitising in an LLNA assay (Harlan 2014i).

Testing is proposed for this endpoint for potassium dicyanoargentate.

A1.4.4 Genotoxicity

A1.4.4.1 *In vitro* mutagenicity study in bacteria

Both potassium dicyanoaurate and silver cyanide produced negative results in an Ames screen and main study (Covance 2013a, Covance 2014a, Covance 2013b, Covance 2014b).

Testing is proposed for this endpoint for potassium dicyanoargentate.

A1.4.4.2 *In vitro* cytogenicity in mammalian cells

A positive result was seen for potassium dicyanoaurate in an *in vitro* micronucleus assay conducted at Harlan. The final test report is currently being prepared.

A negative result was seen for silver cyanide in an *in vitro* micronucleus assay conducted at Harlan. The final test report is currently being prepared.

Testing is proposed for this endpoint for potassium dicyanoargentate, following a tiered testing approach.

A1.4.4.3 *In vitro* gene mutation study in mammalian cells

An OECD 476 study is in progress at Covance for silver cyanide.

This study will not be conducted for potassium dicyanoaurate due to the positive result in the *in vitro* micronucleus assay.

Testing is proposed for this endpoint for potassium dicyanoargentate, following a tiered testing approach.

A1.4.4.4 *In vivo* micronucleus assay

A testing proposal will be submitted for potassium dicyanoaurate for an *in vivo* micronucleus assay, following a positive result in the *in vitro* micronucleus assay.

This study is not required for silver cyanide due to the negative results in the other genotoxcity assays.

The requirement for conducting this study with potassium dicyanoargentate will be evaluated following completion of the other genotoxicity studies.

A1.4.5 Acute toxicity, oral route

Based on existing data the oral LD50 for potassium dicyanoaurate was found to be 29.2 mg kg^{-1} (Berthold 1992).

An LD50 of 175 mg/kg/bw was determined for silver cyanide (LPT 2014a).

Testing is proposed for this endpoint for potassium dicyanoargentate.

A1.4.6 Acute toxicity, inhalation

Testing is not required for this endpoint for any of the precious metal cyanide substances following the conduct of dustiness testing and respiratory tract deposition modelling.

A1.4.7 Acute toxicity, dermal

LD50 values of >2000 mg/kg/bw were determined for both potassium dicyanoaurate and silver cyanide (LPT 2014b,c).

Testing is proposed for this endpoint for potassium dicyanoargentate.

A1.4.8 Short term repeated dose toxicity study (28 days)

Testing is in progress at LPT for potassium dicyanoaurate and silver cyanide, following the OECD 422 method (LPT 2014d).

Testing is proposed for this endpoint for potassium dicyanoargentate.

A1.4.9 Screening for reproductive / developmental toxicity

Testing is in progress at LPT for potassium dicyanoaurate and silver cyanide, following the OECD 422 method (LPT 2014d).

Testing is proposed for this endpoint for potassium dicyanoargentate.

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