CONSIDERATIONS OF ALTERNATIVE METHODS ON TESTING PROPOSAL(S) IN YOUR REGISTRATION

Please complete this form and provide information for each of the points below.

If you have more than one testing proposal, please copy and paste the three bullet points within the same document and complete the details as appropriate for each testing proposal.

This document will be published on ECHA website along with the third party consultation on the testing proposal(s).

Public substance name: triethoxy(3-isocyanatopropyl)silane
EC Number (omit if confidential): confidential
CAS Number (omit if confidential): confidential

Date of considerations: 26 January 2016

- **Hazard endpoint for which vertebrate testing was proposed:**

  Genetic toxicity in vivo with the analogue substance 3-(trimethoxysilyl)propyl isocyanate (CAS 15396-00-6)

- **Considerations that the general adaptation possibilities of Annex XI of the REACH Regulation were not adequate to generate the necessary information**:

  - available GLP studies

    The following GLP-compliant *in vitro* and *in vivo* studies have been considered prior to making the test proposal which is being addressed by this document:

    Gene mutation (Bacterial reverse mutation assay / Ames test): negative with and without activation in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and *E.coli* WP2 *uvrA* (similar to OECD 471) (BioReliance, 1999).

    Mutagenicity in mammalian cells: read-across from 3-(trimethoxysilyl)propyl isocyanate (CAS 15396-00-6): positive with and without metabolic activation in mouse lymphoma L5178Y cells (OECD 476) (BSL BioService, 2012).

    Micronucleus assay in mouse (oral administration): read-across from 3-(trimethoxysilyl)propyl isocyante (CAS 15396-00-6): negative at doses up to the maximum tolerated dose (MTD) of 1000 mg/kg bw (OECD 474) (Harlan, 2011).

    Micronucleus assay in mouse (intraperitoneal administration): read-across from the intermediate hydrolysis product of the registered substance, 3-aminopropyltriethoxysilane (CAS No. 919-30-2): negative at doses up to high dose of 90 mg/kg bw, (toxicity evident at >112 mg/kg bw) (similar to OECD 474) (BRRC, 1998)).

  - available non-GLP studies

    No non-GLP studies were available.

  - historical human data

No historical human data were available.

- (Q)SAR

  QSAR is not considered to be appropriate because there is no existing QSAR method which can discriminate between *in vivo* cytogenicity and mutagenicity, which is the remaining uncertainty of the data set. The approach to assessing genotoxicity of the registration substance is based on read-across from the analogous substance 3-(trimethoxysilyl)propyl isocyanate (CAS 15396-00-6).

- *in vitro* methods

  The following *in vitro* methods have been considered prior to making test proposal which is being addressed by this document:

  - OECD 471 – data available for registered substance and analogue substance (CAS 15396-00-6)
  - OECD 473 – not required because *in vivo* micronucleus study available for analogue substances (CAS 15396-00-6 and CAS 919-30-2)
  - OECD 476/490 – read-across data available for analogue substance (CAS 15396-00-6), indicating potential for mutagenicity.

  The available *in vitro* methods have therefore been considered as a part of the tiered approach.

- weight of evidence

  The available *in vitro* data suggest there is potential for *in vivo* mutagenicity, however there are no available data to fill this data gap via a weight of evidence approach.

- grouping and read-across

  The current approach uses read-across. *In vitro* results for the read-across substance, 3-(trimethoxysilyl)propyl isocyanate, indicate that the substance has potential for mutagenicity. The results of an *in vivo* micronucleus assay on 3-(trimethoxysilyl)propyl isocyanate indicate that the substance is not clastogenic. Further information is required on the potential for mutagenicity of the analogue substance, so an *in vivo* Comet assay proposal for the 3-(trimethoxysilyl)propyl isocyanate is read-across to triethoxy(3-isocyanatopropyl)silane.

- substance-tailored exposure driven testing

  Not applicable.

- approaches in addition to above

  Not applicable.

- other reasons

  Not applicable.

- **Considerations that the specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were not applicable**

  Appropriate *in vivo* mutagenicity studies shall be considered in the case of a positive result in any of the genotoxicity studies in Annex VII or VIII. Since a positive result for mutagenicity in mammalian cells (OECD 476) is reported, it needs to be established whether the effect is evident *in vivo.* The currently available *in vivo* studies only establish the lack of cytogenicity. It needs to be determined whether the observed *in vitro* mutagenicity is due to DNA damage, and if the effect occurs *in vivo.* The Comet Assay is able to determine this effect.