CONSIDERATIONS OF ALTERNATIVE METHODS ON TESTING PROPOSALS 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: O,O,O-triphenyl phosphorothioate
EC Number (omit if confidential): 209-909-9
CAS Number (omit if confidential): 597-82-0

Date of considerations: 24 November 2015

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

  Reproductive toxicity (extended one-generation reproductive toxicity study) with the registered substance

- **Considerations that the general adaptation possibilities of Annex XI of the REACH Regulation were not adequate to generate the necessary information** (instruction: please address all points below):

  - available GLP studies
    A GLP-compliant Reproduction/Developmental Toxicity Screening Test performed with a structural analogue is available. In this study, no relevant adverse effects on reproductive performance were observed. In addition, a summary of a GLP-compliant Combined Repeated Dose Toxicity Study With a Reproduction/Developmental Toxicity Screening Test performed with CAS 597-82-0 is available. In this study, reproductive effects mainly in the high dose group were recorded (reduced number of implantation sites and reduced pup viability). The test substance used in this study was characterized by a lower purity (95%). Since these two studies produced contradictory results, a concern regarding reproductive toxicity remains. To clarify this concern, an extended one-generation reproductive toxicity study is proposed in compliance with Annex IX of the REACH regulation.

  - available non-GLP studies
    No non-GLP-compliant fertility studies are available

  - historical human data
    No historical human data that could address the remaining concern are available

  - (Q)SAR
    (Q)SAR tools sufficiently addressing fertility and reproduction are not available

  - *in vitro* methods
    In vitro methods sufficiently addressing fertility and reproduction are not

available

- weight of evidence
  No data to be used in a weight of evidence approach addressing the remaining concern are available

- grouping and read-across
  A structurally related compound has been identified. However, the data available for the read-across substance are not sufficient to address the remaining concern regarding fertility and reproduction.

- substance-tailored exposure driven testing [if applicable]

- [approaches in addition to above [if applicable]

- other reasons [if applicable]

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

  Column 2 of Annex IX states that the reproductive toxicity studies do not need to be performed if:

  - *the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented; or*
  - *the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented; or*
  - *the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available) it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.*

  None of these conditions are met by CAS 597-82-0. The test article is not classified for carcinogenicity or mutagenicity. Furthermore, the test item was shown to be systemically available as demonstrated by findings reported in the repeated dose and reprotoxicity studies. Therefore, the above listed column 2 adaptions cannot be applied.

  Further column 2 adaptions are:

  - *If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as Repr Cat 1 or 2: R60, and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for development toxicity must be considered.*
  - *If a substance is known to cause developmental toxicity, meeting the criteria for classification as Repr Cat 1 or 2: R61, and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.*

  The available reproduction toxicity data partially revealed reproductive effect.

However, since the available data are contradictory, the results are not considered sufficient to classify CAS 597-82-0 for fertility or developmental toxicity at this point. Therefore, the above listed adaptions cannot be applied. However, since some concern regarding reproduction toxicity does remain, an extended one-generation reproductive toxicity study is proposed.