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: 2-(2-Ethoxyethoxy)-2-methylpropan
EC Number (omit if confidential): 257-196-8
CAS Number (omit if confidential): 51422-54-9

Date of considerations: 18 January 2016

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

  - **Sub-chronic toxicity (90 day): inhalation**
  - **Reproductive toxicity (pre-natal developmental toxicity)**

  using the registered substance

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

  - available GLP studies
    A GLP-compliant Combined Repeated Dose Toxicity Study With a Reproduction/Developmental Toxicity Screening Test performed with the registered substance is available.

    In this study, the registered substance did not adversely impact the reproduction of rats, nor did treatment impact delivery and pup viability. However, an OECD 422 study, which is only meant to fulfil the requirements of Annex VIII, cannot be regarded as the equivalent of a pre-natal developmental toxicity (OECD 414) and therefore cannot fulfil the requirements of Annex IX, 8.7.2. of the REACH Regulation. For this reasons, a PNDT study according to OECD 414 was proposed.

    Concerning systemic toxicity, treatment with the substance caused normochromic normocytic anemia as well as extramedullary hematopoiesis in the spleen. Based on the current data available, a final assessment on classification and labeling of the substance is up to now not possible under Regulation (EC) No 1272/2008. Moreover, a sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, section 8.6.2. of the REACH Regulation. Therefore, a 90 day repeated dose toxicity study according to OECD 413 was proposed.

  - available non-GLP studies
    No non-GLP-compliant studies on the endpoints repeated dose toxicity and developmental toxicity/teratogenicity are currently available.

- historical human data
  No historical human data that could address the current data gaps are available.

- (Q)SAR
  (Q)SAR tools sufficiently addressing the endpoints repeated dose toxicity and developmental toxicity/teratogenicity are currently not available.

- *in vitro* methods
  In vitro methods sufficiently addressing the endpoints repeated dose toxicity and developmental toxicity/teratogenicity are currently not available.

- weight of evidence
  No data available which could be used in a weight of evidence approach.

- grouping and read-across
  A lot of read-across structures could be imaginable. However, either the toxicological properties of those structures are not comparable and therefore not suitable to allow predicting the toxicological properties from each other. On the other hand, data on read-across substances, if it even exists, are not sufficient to address the data gaps concerning repeated dose toxicity and developmental toxicity/teratogenicity.

- substance-tailored exposure driven testing [if applicable]
  Not applicable.

- [approaches in addition to above [if applicable]
  Not applicable.

- other reasons [if applicable]
  Not 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 **repeated dose toxicity** studies do not need to be performed if:
  - *a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL- 90 days for the same route of exposure, or*
  - *a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used, or*
  - *a substance undergoes immediate disintegration and there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake), or*
  - *the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure.*

  None of these conditions are met by the registered substance. The test article is not classified as R48 (Directive No. 67/548/EEC) or to cause a specific target organ

toxicity (Regulation (EC) No 1272/2008), there are no results of a chronic study available, and the substance has not be shown to undergo immediate disintegration. Furthermore, the test item was shown to be systemically available as demonstrated by findings reported in the Combined Repeated Dose Toxicity Study With a Reproduction/Developmental Toxicity Screening Test. Therefore, the above listed column 2 adaptions cannot be applied and a sub-chronic repeated dose toxicity study was proposed.

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 the registered substance. 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 Combined Repeated Dose Toxicity Study With a Reproduction/Developmental Toxicity Screening Test. 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 revealed no reproductive effect. Moreover, since the available data are not considered sufficient to fulfil the requirements of Annex IX, 8.7.2 a final assessment on classification and labeling of the substance is not possible under Regulation (EC) No 1272/2008 at this point. Therefore, the above listed adaptions cannot be applied and a pre-natal developmental toxicity study was proposed.