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-Vinyloxyethoxy)ethyl acrylate
EC Number (omit if confidential): 451-690-9
CAS Number (omit if confidential): NS

Date of considerations: 2 February 2016

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

  Reproductive toxicity (pre-natal developmental toxicity) with the registered substance substance 2-(2-Vinyloxyethoxy)ethyl acrylate

- **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

    An inquiry dossier alerting ECHA that we intended to increase supply to the Annex IX tonnage band was submitted back in 2014. In the response to this inquiry dossier, ECHA indicated no data was available for this particular endpoint. Also please note that a literature search was conducted, the results of the literature search showed that no study data was available.

  - available non-GLP studies
    The results of a literature search confirmed there was no study data available.

  - historical human data
    No data available.

  - (Q)SAR
    The Annex IX submission was made on the 19/02/2016. It was unclear whether a QSAR assessment was done prior to the initial Annex IX submission. In order to respond to this inquiry the following QSAR assessments were undertaken:
    TOPKAT
    VEGA
    TEST
    QSAR toolbox

    The results of these assessments seemed contradictory and not conclusive, the results indicated that the OECD 414 pre-natal developmental toxicity study will be required.

- *in vitro* methods
  No acceptable In Vitro methods are currently available for this endpoint.

- weight of evidence:
  A weight of evidence approach would not be possible as no study data is available and no reliable QSAR data was found. Combining the results of several QSAR assessments is not believed to provide a sufficient assessment of this particular endpoint, due to the conflicting information that is available.

- grouping and read-across
  An acceptable surrogate was not identified at the time of submitting testing proposals. Before responding to this inquiry we double checked the data within the QSAR toolbox. We were unable to find a suitable analogue in order to use read across. The analogues identified looked to only have OECD 422 data available and no additional study data required for the Anenx IX tonnage band.

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

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

- other reasons [if applicable]
  None

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

Prior to our submission on the 19/02/2017, we looked into the posisbilities of waiving this particular endpoint in accordance with a column 2 adaptation of Annex IX of the REACH regulations. The conclusion to this was as follows:

Developmental toxicity data is available from the OECD 422 screening study. However, this study does not fully investigate developmental toxicity, so a pre-natal developmental toxicity (OECD 414) is proposed.

The sub-chronic OECD 414 study (REACH Annex IX, 8.7.2) should not be waived based on the column 2 adaptations (8.7) as:
- the substance is not a known to be a genotoxic carcinogen
- the substance is not a germ cell mutagen but a positive result was produced in a second in-vitro Chromosome Aberration which may potentially have an influence on developmental toxicity as a worst case scenario.
- the substance has shown evidence of toxicity in available studies and there is evidence that systemic absorption may occur.

Worker exposure to the substance during the formulation of final products and during certain industrial/professional end use activities will be limited by appropriate engineering controls and risk management measures, but limited exposure may still occur as not all substance will be handled in using closed systems. Waiving the OECD 414 study soley on exposure grounds is therefore not considered appropriate.

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

  Sub-chronic toxicity (90-day): oral with the registered substance 2-(2-Vinyloxyethoxy)ethyl acrylate

- **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

  An inquiry dossier alerting ECHA that we intended to increase supply to the Annex IX tonnage band was submitted back in 2014. In the response to this inquiry dossier, ECHA indicated no data was available for this endpoint. Also please note that a literature search was also conducted, the results of this showed that no data was available.

  - available non-GLP studies

  The results of a literature search confirmed there was no study data available.

  - historical human data

  No data available.

  - (Q)SAR

  The Annex IX submission was made on the 19/02/2016. It was unclear whether a QSAR assessment was done prior to the initial submission. In order to respond to this inquiry TOPKAT and the QSAR toolbox were used to provide an assessment of this endpoint, however the results were inconclusive and not of sufficient quality to cover a 90 day repeat dose toxicity study.

  - *in vitro* methods

  No acceptable In Vitro methods are available to fulfil this endpoint.

  - weight of evidence

  A weight of evidence approach would not be possible as no study data is available and no reliable QSAR data was found. Combining the results of several QSAR assessments is not going to provide a sufficient assessment for this particular endpoint.

  - grouping and read-across

  An acceptable surrogate was not identified at the time of submitting testing proposals. Before responding to this inquiry we double checked the data within the QSAR toolbox. We were unable to find a suitable analogue in order to use read across. The analogues identified had available data from OECD 422 studies, however no additional Annex IX data was available.

  - substance-tailored exposure driven testing [if applicable]

  Not applicable

  - [approaches in addition to above [if applicable]

  Not applicable

  - other reasons [if applicable]

  None

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

Prior to our submission on the 19/02/2017, we looked into the posisbilities of waiving this particular endpoint in accordance with a column 2 adaptation of Annex IX of the REACH regulations. The conclusion to this was as follows:

Repeated dose toxicity data is available from a 28 -day repeat dose toxicity study and an OECD 422 study. However, a 90 -day repeat dose toxicity study (OECD 408) is proposed based on the following.

The sub-chronic 90 -day toxicity study (REACH Annex IX, 8.6.2) should not be waived based on the column 2 adaptations as:
- a reliable 28 day toxicity study is available and does show adverse effects, but not sufficient to classify as STOT-RE (R48).
-a reliable chronic toxicity study is not available.
- there is no evidence that the substance will undergo immediate disintegration.
- there is evidence of absorption and toxicity in the 28 -day study.

In addition, the OECD 422 study, whilst having a longer exposure period than the 28 -day study, failed to identify a NOAEL and hence the long-term systemic DNEL's have been based on the 28 -day study.

Worker exposure to the substance during the formulation of final products and during certain industrial/professional end use activities will be limited by appropriate engineering controls and risk management measures, but limited exposure may still occur as not all substance will be handled in using closed systems. Waiving the 90 -day study soley on exposure grounds is therefore not considered appropriate.