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: 1,4-bis(2,3-epoxypropoxy)butane
EC Number (omit if confidential): 219-371-7
CAS Number (omit if confidential): 2425-79-8

Date of considerations: 29 October 2019

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

  Reproductive toxicity (pre-natal developmental toxicity) with the registered substance 1,4-butanediol, reaction product with 1-chloro-2,3-epoxypropane (Reaction products of butane-1,4-diol with 2-(chloromethyl)oxirane);

- **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
    Currently, no data on reproductive toxicity (pre-natal developmental toxicity) of the reference substance is available.

  - available non-GLP studies
    Currently, no data on reproductive toxicity (pre-natal developmental toxicity) of the reference substance is available.

  - historical human data
    the literature search revealed no information being available addressing developmental toxicity of *Reaction products of butane-1,4-diol with 2-(chloromethyl)oxirane* in humans and also no SIEF member could offer any documented human effect data.

  - (Q)SAR
    No reliable QSAR methods to address developmental toxicity are known to the registrant.

  - *in vitro* methods
    No reliable in vitro method to address developmental toxicity is known to the registrant.

  - weight of evidence
    Currently, there is no results from other studies available, that could be used in a weight of evidence approach to address the endpoint for pre-natal developmental toxicity.

- grouping and read-across
  No data on developmental toxicity from sufficiently similar substance are available that would allow a scientifically robust grouping or read-across approach. However, just recently an OECD 414 compliant developmental toxicity study using rats became available, performed with "Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane (1:2)" (EC-No. 618-939-5; CAS# 9339999-84-9) in which a NOAEL of 300 mg/kg bw/d was determined for parental animals and no treatment-related changes were detected in the offspring parameters measured or on embryofetal development. The 'No Observed Effect Level' (NOEL) for developmental toxicity was therefore considered to be 300 mg/kg bw/day too. Thus, to further assess possibilities for read-across to the similar substance, more time will be needed.

- substance-tailored exposure driven testing [if applicable]
  As the substance is also used by professionals in widespread uses (indoors and outdoors) as component in coatings, bondings and concrete, exposure based waiving or exposure driven testing is not considered approariate.

- approaches in addition to above [if applicable]
  None

- 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):
  According to REACH, Annex IX, 8.7.2. column 2 "The study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data." and more general in section 8.7 other adaptation criteria are provided. Furthermore, also in REACH, Annex X, same section, adaptation criteria can be found.
  As based on currently available data the substance is not considered being mutagenic, reproductive toxic or carcinogenic and the substance is not of low toxicological activity, the generic waiving/adaptation criteria are not applicable. In lack of any data on fertility or developmental data, also the other more specific adaptation criteria are not applicable, and considering the potential exposure of workers, the data gap on developmental toxicity is to be closed by in vivo testing by a pre-natal developmental toxicity study according to OECD 414.

  In conclusion, in order to make best use of available data and to minimize animal testing to an extent absolutely required, we want to ask to await the assessment of the suitability of the OECD 414 developmental toxicity study using rats with the similar substance "Reaction products of hexane-1,6-diol with 2-(chloromethyl)oxirane (1:2)" (EC-No. 618-939-5; CAS# 9339999-84-9). Thus, we would kindly ask to put further decisions on this testing proposal on hold for the time being.