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 (extended one-generation reproductive toxicity study) and sub-chronic toxicity (90 day) oral 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 of the reference substance is available, neither addressing developmental toxicity, nor addressing fertility. Also, there is no long-term repeated dose toxicity study (sub-chronic) available, but only a short-term repeated dose toxicity study (sub-acute) by oral route, GLP-compliant.

  - available non-GLP studies
    Despite the GLP study mentioned above, currently no data on reproductive toxicity or repeated dose toxicity of the reference substance is available as non-GLP study.

  - historical human data
    the literature search revealed no information being available addressing reproductive toxicity or sub-chronic 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 reproductive toxicity or sub-chronic toxicity are known to the registrant.

  - *in vitro* methods
    No reliable in vitro method to address reproductive toxicity or sub-chronic 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 reproductive toxicity or sub-chronic 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 a sub-chronic oral toxicity study 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 and in result of an approved testing proposal on the substance, an EOGRTS study according to OECD 443 has just been commissioned. First draft results are expected in the year 2020 and this substance may be useful for read-across to substance 1,4-butanediol, reaction product with 1-chloro-2,3-epoxypropane. 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 appropriate.

- 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, 8.6.2. column 2 a sub-chronic toxicity study (90 days) does not need to be conducted 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.

  As none of the criteria above does apply to the substance and the available sub-acute toxicity study by oral route to the substance did not show effects of severity, justifying a Repeat Exposure STOT classification, the performance of a 90 day (sub-chronic) toxicity study by oral route is required.

According to REACH, Annex and X, 8.7.2. column 1 an Extended One-Generation Reproductive Toxicity Study (B.56 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 443), basic test design (cohorts 1A and 1B without extension to include a F2 generation), one species, most appropriate route of administration, having regard to the likely route of human exposure, unless already provided as part of Annex IX requirements is mandatory and no waiving grounds at Annex X level are accepted.
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 reproductive toxicity and on sub-chronic toxicity is to be closed by a combined in vivo testing applying an EOGRTS study design according to OECD 443, modifying the pre-mating interval from 10 weeks to 13 weeks to also include animal exposure and analysis in line with OECD 408.
The registrants believe that the most complete and clean approach to addressing the need of both repeat dose and reproductive toxicity data, while minimising unnecessary testing and animal use, will be to incorporate the data requirements of the 90-day repeat dose study into the pre-mating interval of the EOGRTS. This represents a saving of the full number of animals required by the OECD TG 408 protocol and this approach is outlined in more detail in the original testing proposal submitted within the dossier and shall not be repeated here again.
In conclusion, at greater than or equal to 1000 tonnes/year (Annex X) a sub-chronic toxicity study (90 day) in a single rodent species and an EOGRTS, basic test design (Cohorts 1A and 1B without extension to include a F2 generation) in one species is usually required. Review of the data available does not indicate the need to extend the EOGRTS basic test design to include endocrine disruption, developmental neurotoxicity or developmental immunotoxicity Cohorts.
With the goal of minimising unnecessary testing and animal use, the registrant proposes to incorporate the data requirements of the 90-day repeat dose study into the pre-mating interval of the EOGRTS; specifically:
1) Extending the pre-mating interval from 10 weeks to 13 weeks.
2) Collecting full haematology and clinical chemistry at the end of the extended pre-mating period.
3) Conducting neurobehavioral functional testing at the end of the extended pre-mating period.
A modified EOGRTS (modified OECD TG 443) by oral route is expected to be available approximately 2 years after commencing the study.

However, 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 outcome of the currently ongoing OECD 443 (EOGRTS) study 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). Time will also be used to contact the lead registrant of the substance to more closely assess read-across options.