Public substance name: Reaction products of a polyol of pentaerythritol and propylene oxide, epichlorohydrin and hydrogen sulfide

EC Number: 615-735-8

CAS Number: 72244-98-5

Date of considerations: 07 November 2016

- **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: there are no GLP studies available for the endpoint toxicity to reproduction

  - available non-GLP studies: there are no non-GLP studies available for the endpoint toxicity to reproduction

  - historical human data: there are no historical human data that can be considered acceptable for this higher tier toxicity endpoint.

  - (Q)SAR: Although (Q)SAR programmes include several endpoints that are related to toxicity to reproduction, these (Q)SAR endpoints do not cover all endpoints that need to be investigated for the endpoint reproductive toxicity. In some cases (Q)SAR for this endpoint can be useful as a first indication for possible reproductive toxicity; however absence of structural alerts is considered not acceptable to replace further studies for this toxicity endpoint, neither for registration nor for classification purposes. According to ECHA Practical Guide on alternatives to animal testing (July 2016) ECHA's experience of using adaptations to address standard information requirements reveals that there are no simple (Q)SAR solutions for complex health endpoints such as reproductive toxicity.

  - *in vitro* methods: there are no reliable *in vitro* tests available that can be considered for the endpoint reproductive toxicity that sufficiently cover the endpoint for risk assessment and classification purposes

  - weight of evidence: there is no relevant information available that can be used in a WoE to cover the endpoint reproductive toxicity for registration and classification purposes.

  - grouping and read-across: there are currently no structures known (and that also have reliable data on reproductive toxicity) that can be used for grouping or read-across, and which is acceptable for registration and classification purposes.

  - **Considerations that the specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were not applicable**: The specific rules for adaptation from column 1 as given in column 2 are not met, as

the available data do not demonstrate that the substance is a genotoxic carcinogen or germ cell mutagen. The available data are indicative for systemic absorption, whereas data demonstrating adverse effect on fertility meeting the criteria for classification as Repr Cat 1 or 2 (with adequate data to support risk assessment). According to Column 1 and Column 2 of Regulation (EC) No 1907/2006 concerning REACH an extended one-generation toxicity study (OECD 443), basic test design (cohorts 1A and 1B without extension to include a F2 generation) needs to be performed in case the available repeated dose toxicity studies (e. g. 90-day study) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. No treatment-related effects were observed on all sexual organ weights, estrous cycle length and number, and sperm motility, count and percentage of abnormal sperms in a reliable 90-day repeated dose toxicity study in rat. The weight of the thyroid gland was increased in females and slight/minimal follicular hypertrophy/hyperplasia was seen in males and females at 1000 mg/kg bw/day and in males at 250 mg/kg bw/day also follicular hypertrophy/hyperplasia was seen. Hormones made in the thyroid gland are involved in the regulation of T-lymphocyte development and growth. The extended one generation study is proposed to contain the developmental immunotoxicity cohort (DIT) due to the thyroid effects observed in the 90-day study. The reproduction-developmental screening study is waived, based on testing proposals for an extended one-generation toxicity study (OECD 443) and a developmental toxicity study (OECD 414) for ANNEX IX registration.

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

  Reproductive toxicity (pre-natal developmental toxicity) 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**:

  - available GLP studies: there are no GLP studies available for the endpoint developmental toxicity/teratogenicity

  - available non-GLP studies: there are no non-GLP studies available for the endpoint developmental toxicity/teratogenicity

  - historical human data: there are no historical human data that can be considered acceptable for this higher tier toxicity endpoint.

  - (Q)SAR: Although (Q)SAR programmes include several endpoints that are related to developmental toxicity/teratogenicity, these (Q)SAR endpoints do not cover all endpoints that need to be investigated for this toxicity endpoint. In some cases (Q)SAR for this endpoint can be useful as a first indication for possible developmental toxicity/teratogenicity; however absence of structural alerts is considered not acceptable to replace further studies for this toxicity endpoint, neither for registration nor for classification purposes. According to ECHA Practical Guide on alternatives to animal testing (July 2016) ECHA's experience of using adaptations to address standard informational requirements reveals that there are no simple (Q)SAR solutions for complex health endpoints such as developmental toxicity/teratogenicity.

  - *in vitro* methods: there are no reliable *in vitro* tests available that can be considered for the endpoint developmental toxicity/teratogenicity that sufficiently cover the endpoint for risk assessment and classification purposes

  - weight of evidence: there is no relevant information available that can be used in a WoE to cover the endpoint developmental toxicity/teratogenicity for registration and classification purposes.

  - grouping and read-across: there are currently no structures known (that also have reliable data on developmental toxicity/teratogenicity) that can be used for grouping or read-across, and which is acceptable for registration and classification purposes.

- **Considerations that the specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were not applicable**: The specific rules for adaptation from column 1 as given in column 2 are not met, as the available data do not demonstrate that the substance is a known genotoxic carcinogen or germ cell mutagen. The available data are indicative for systemic absorption, and there are no data available indicative for developmental toxicity meeting the criteria for classification as Repr Cat 1 or 2 with adequate data available to support a robust risk assessment. According to Column 1 (standard information required) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), a pre-natal developmental

toxicity study in one species is required for substances manufactured or imported in quantities of 100 tonnes or more (ANNEX IX). To fulfill these data requirements, an oral pre-natal developmental toxicity study in rat (OECD 414) is proposed.