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: MELAMINE
EC Number (omit if confidential): 203-615-4
CAS Number (omit if confidential): 108-78-1

Date of considerations: 26 April 2016

- Hazard endpoint for which vertebrate testing was proposed:

  Reproductive toxicity (extended one-generation reproductive toxicity study) with the registered substance, as required by Annex X, 8.7.3 of REACH.

- 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
    No one- or two- or multi-generation GLP-study on reproduction toxicity is available.
    A few GLP-studies on single aspects of reproductive toxicity are available, such as lesions to the reproductive organs or teratogenicity. But these studies are not covering the key parameters foreseen to be investigated in the prescribed test method (EOGRT-test methd B.56 of the Commission Regulation on test methods or OECD 443). Reports or publications are by Early 2013, Stine 2011, and Hellwig 1996; see Sections 7.5.1 and 7.8.2 of IUCLID.

  - available non-GLP studies
    No one- or two- or multi-generation non-GLP-study on reproduction toxicity is available.
    Some studies on single aspects of reproductive toxicity are available, such as lesions to the reproductive organs; on functional parameters of the spermatozoa; on effects to testes and spermatogenesis; or on toxicokinetic parameters. Reports or publications are e.g. by NTP 1983, El Rabey 2014, Ubaydullayev 1993, Kim 2011, Yin 2013, Stine 2014, Zhang 2011, Jingbin 2010, Wang 2013, Chang 2014. See Sections 7.1.1, 7.5.1, 7.8.1, 7.8.2 and 7.8.3 of IUCLID.
    The quality of the studies ranges from acceptable to non-acceptable. Results obtained are conflicting and do not allow a conclusion on the possible reproductive toxicity, and not even on the single investigated aspects of reproductive toxicity.

According to Annex XI, 1.1.2 the "Data shall be considered to be equivalent to data generated by the corresponding test methods referred to in Article 13(3) if the following conditions are met:
(1) adequacy for the purpose of classification and labelling and/or risk assessment;
(2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided."

These criteria are not met because inter alia the key parameters foreseen to be investigated in the prescribed test method (B.56 or OECD 443) are not covered and because adequate and reliable documentation is partly missing.

- historical human data
  Data are not available on the effects on reproduction.
- (Q)SAR
  (Q)SAR investigations are not available and not considered to be an acceptable alternative to the one-generation reproduction toxicity study (EOGRTS). Especially if thinking of solving the conflicting results obtained in non-GLP investigations on individual features of reproduction.
  See also the recent Practical Guide 5 of ECHA on How to use and report (Q)SARs, where it is stated on page 10: "(Q)SAR models able to fully cover the complexity of higher-tier endpoints do not exist yet (e.g. repeated dose toxicity or reproductive toxicity)".
- *in vitro* methods
  In vitro methods are not available and not considered to be an acceptable alternative to the one-generation reproduction toxicity study, if thinking of solving the conflicting results obtained in the non-GLP investigations on individual features of reproduction.
  The European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM) reports validated alternative methods for different toxicological endpoints on its website. Although the website for reproduction toxicity is (still) under construction (20 April 2016), it is clear from the reports of ECVAM and JRC that no in vitro method exists that could replace the EOGRT animal experiment at present.
  Reports of EURL ECVAM and of JRC that were screened for statements on reproduction toxicity are:
  - EURL ECVAM strategy for achieving 3Rs impact in the assessment of toxicokinetics and systemic toxicity (2015),
  - EURL ECVAM Status Report on the Development, Validation and Regulatory Acceptance of Alternative Methods and Approaches (2015), and
  - Alternative methods for regulatory toxicology – a state-of-the-art review (2014).
  The last report states, inter alia: "Given the diversity of physiological processes associated with the mammalian reproductive cycle, and the complexity of the underlying regulatory networks, it is not possible to model chemical effects on the whole cycle with a single or limited number of non-animal approaches."
- weight of evidence
  Wreight of evidence approaches are not available and not considered to be an acceptable alternative to the one-generation reproduction toxicity study.

Especially the conflicting results obtained in the non-GLP investigations on individual effects of reproductive toxicity render it unlikely to succeed in a weight of evidence approach.

- grouping and read-across
  No substances with available reproduction toxicity characteristics are known (to the applicant) whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity, so that a group or a category of substances may be considered (Annex XI 1.5)
- substance-tailored exposure driven testing [if applicable]
  Although the main use of melamine is when incorporated in articles, an exposure of workers during manufacturing of melamine or of the articles can not be excluded in the identified scenario (Annex XI 3.2).
- [approaches in addition to above [if applicable]
  Not available.
- other reasons [if applicable]
  Not available.

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

  The amended REACH regulation (EU) 2015/282 explicitly requires an animal experiment, because the standard information under 8.7.3 of Annex X reads: "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, ...". Methods B.56 and OECD 443 are animal experiments.
  No adaptation is foreseen in column 2 of 8.7.3 in Annex X to waive the study or replace the animal experiment by an alternative method, except for presenting an old two-generation reproduction toxicity study instead of.