CONSIDERATIONS OF ALTERNATIVE METHODS ON TESTING PROPOSALS IN YOUR REGISTRATION

Public substance name: Methylene-bis-4,1-(N-phenylene-N'-butylurea)
EC Number (omit if confidential): 416-600-4
CAS Number (omit if confidential): 77703-56-1

Date of considerations: 9 March 2016

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

  Bioaccumulation aquatic / sediment 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
    No GLP studies are available.

  - available non-GLP studies
    No non-GLP studies are available.

  - historical human data
    Human data are not applicable for this endpoint.

  - (Q)SAR
    The bioaccumulation potential of the registered substance was estimated using the US EPA Epiwin (v3.12) software, with an estimated log Kow of 5.50. The bioaccumulation factor (BCF) was calculated to be 3428 or log BCF = 3.535. Based on the calculated BCF the B criterion (over 2000) by not the cirtium for vB is fulfilled. Based on this result, the substance is considered critical for the B/vB assessment. The BCF was calculated on an estimated (also calculated) log Kow as a measurement of the Log Kow was technically not feasible. Taken together, the registrant came to the conclusion, that a prediction of the bioaccumulation potential based on the calculated BCF is not reliable and an in vivo test as proposed should be conducted.

  - *in vitro* methods
    Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7c: Endpoint specific guidance (page 16 ff) states that "in vitro methods have the potential to provide important data on bioaccumulation assessments, and although many require sacrifice of live animals, all may contribute to a reduction in (or refinement of) animal testing.". All the listed methods in the guidance would required sacrifice of live animals and are non-guidance and non-standard methods. The guidance comes to the conclusion that "these methods may become an important part of future test strategies, but their applicability is currently limited due to the lack of standardized protocols and limited validation based on small data sets. Further evaluation work is necessary before they can be recommended for use within an ITS.". The registrant comes to the same conculsion that reliable in vitro methods are currently not available for this endpoint.

  - weight of evidence

No data which could be used for a weight of evidence approach are available for the substance.

- grouping and read-across
  No read–across substances or a category of substances with reliable data on bioaccumulation aquatic / sediment are known to the registrant.

- substance-tailored exposure driven testing
  The substance is used in widespread professional and consumer uses and the environment may be exposed the substance based on the use profile. Nevertheless, direct or indirect exposure of the aquatic compartment is regarded as low as the substance is used in reactive one or two component adhesives or coatings and is incorporated in a polymer matix, very shorly after the use as soon as the polymeric matrix is hardened. In conclusion bioaccumulation in aquatic /sediment may be relevant and has to be investigated, based on PBT/vPvB assessment by the Frensh Competent Authority.

- approaches in addition to above
  Not applicable.

- other reasons
  Not applicable.

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

  Column 2 of REACH Annex IX, section 9.3.2 states as follows:
  "The study need not be conducted if:
  - the substance has a low potential for bioaccumulation (for instance a log Kow ≤ 3) and/or a low potential to cross biological membranes, or
  - direct and indirect exposure of the aquatic compartment is unlikely."
  The first waining argument is not applicable for the registered substance, as the substance has a log Kow over 3 (calculated to be 5.50).
  The substance is used by professional workers and consumers in widespread uses. Nevertheless, direct or indirect exposure of the aquatic compartment is regarded as low as the substance is used in reactive one or two component adhesives or coatings and is incorporated in a polymer matix, very shorly after the use as soon as the polymeric matrix is hardened.
  Even though the bioaccumulation test might not be required due to the arguments based on column 2 of Annex IX given above, the registrant proposes to conduct the study to investigate possible PBT/vBvP properties of the registered substance.