## CONSIDERATIONS OF ALTERNATIVE METHODS ON TESTING PROPOSAL

Public substance name: 2,2-dimethylpropane-1,3-diyl dibenzoate
EC Number (omit if confidential): 224-081-9
CAS Number (omit if confidential): 4196-89-8

Date of considerations: 8 February 2016

- **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:**

  Based on the below discussed compound specific information provided in the dossier of the registered substance the registrant considers testing of 2,2-dimethylpropane-1,3-diyldibenzoate for potential developmental toxicity should have low priority.

  A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Experimental information on this endpoint is not available for the registered substance, but needs to be present in the technical dossier to meet the formal information requirements.

  - available GLP studies

    There are no experimental animal studies with the registered substance or an analogue substance available for the endpoint pre-natal developmental toxicity.

  - available non-GLP studies

    There are no experimental animal studies with the registered substance or an analogue substance available for the endpoint pre-natal developmental toxicity.

  - historical human data

    No historical human data available.

  - (Q)SAR

    Profiling based on the most recent OECD Toolbox (version 3.3.5.17) indicate that the registered substance is of low toxicological concern. Concerning developmental and reproductive toxicity the toolbox highlights: “not known precendent reproductive and development toxicity potential” (DART scheme v 1.0).

- *in vitro* methods

  There are no in vitro studies with the registered substance or an analogue substance available with relevant information on the endpoint pre-natal developmental toxicity.

- weight of evidence

  For detailed information please refer to the dossier of the registered substance. Based on the available physikochemical data it can be assumed that the absorption potential of 2,2-dimethylpropane-1,3-diyldibenzoate is low in particular taking into account the experimental animal data which demonstrate no systemic toxicicity even at high, limit, doses.

  2,2-dimethylpropane-1,3-diyldibenzoate is a white to yellowish solid with mild odor. Its molecular weight is 312 g/mol. Its melting point is about 46.5 °C at 1017 hPa and the boiling point is >300°C at 1004 hPa. The vapor pressure of 2,2-dimethylpropane-1,3-diyldibenzoate is estimated to be < 0.0001 hPa at 25°C. The water solubility of the substance is 1.16 mg/L at 20 °C. The n-octanol/water partition coefficient (log Pow) of 2,2-dimethylpropane-1,3-diyldibenzoate was determined to be 4.7 at 25°C and pH 7.

  In an acute oral study 5000 mg 2,2-dimethylpropane-1,3-diyldibenzoate/kg bw was applied to rats. Animals revealed only unspecific findings and no animal died. Furthermore in a repeated dose oral gavage study in rats according to OECD TG 407 over a period of 28 days the resulting NOAEL accounts for 1000 mg/kg bw/day (limit dose), because the test substance was well tolerated without relevant clinical signs and mortality. Gross and histopathological examinations did not reveal relevant alterations.

  Referring to dermal absorption the low water solubility of 1.16 mg/L and the log Pow of 4.7 of 2,2-dimethylpropane-1,3-diyldibenzoate and the molecular weight >100 g/mol indicate that the rate of transfer between the stratum corneum and epidermis is limited and therefore also dermal absorption into the body. The available acute dermal toxicity study in rabbits yielded no mortality, no clinical signs and animals gained weight during the post application period. In acute skin and eye irritation studies in rabbits no systemic intolerance reactions have been reported and no sensitizing effect has been identified in the Local Lymph Node assay.

  Based on the negative results of the in vitro genotoxicity tests with 2,2-dimethylpropane-1,3-diyldibenzoate it is concluded that DNA reactive metabolites of the substance will most probably not to be generated in mammals in the course of hepatic biotransformation.

  No hazard is identified for 2,2-dimethylpropane-1,3-diyldibenzoate for any toxicological endpoint and, consequently, the hazard assessment conclusion for all toxicological endpoints is "no hazard identified" and the substance is not classified according to DSD or GHS.

  Overall, no compound related adverse effects are reported in any toxicity study conducted with 2,2-dimethylpropane-1,3-diyldibenzoate up to the limit doses. Taking into account the physicochemical properties it is unlikely that 2,2-dimethylpropane-1,3-diyldibenzoate is substantially absorbed in animals

or humans, consequently, the registrant considers the testing for the endpoint developmental toxicity should have low priority for the registered substance.

- grouping and read-across

  No analogue substances for grouping and/or read-across are identified taking into account expert judgement and the most recent OECD Toolbox (version 3.3.5.17).

- substance-tailored exposure driven testing

  Not applicable.

- 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:**

  No specific rules for adaptation are given in Annex IX, Section 8.7.2. of the REACH Regulation.