## 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: N,N-bis(2-ethylhexyl)-5-methyl-1H-benzotriazole-1-methylamine, N,N-bis(2-ethylhexyl)-4-methyl-1H-benzotriazole-1-methylamine, 2H-Benzotriazole-2-methanamine, N,N-bis(2-ethylhexyl)-4-methyl-, 2H-Benzotriazole-2-methanamine, N,N-bis(2-ethylhexyl)-5-methyl-, 1H-Benzotriazole-1-methanamine, N,N-bis(2-ethylhexyl)-6-methyl-(Mixture)
EC Number (omit if confidential): 939-700-4
CAS Number (omit if confidential): NS

Date of considerations: 27 August 2019

- **Hazard endpoint for which vertebrate testing was proposed: subchronic repeated dose toxicity**

  **Sub-chronic toxicity (90-day): oral 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
    *A GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) is available. This study revealed parental toxicity at 150 mg/kg bw (clinical signs, reduced body weight gains with lower food consumption, slightly reduced thymus organ weight, and microscopic findings in the thymus and spleen). The NOAEL was considered to be 45 mg/kg body weight per day. This study, is, however, not sufficient to address subchronic repeated dose toxicity as required for substance registered at a tonnage level of above 100t.*

  - available non-GLP studies
    *No non-GLP-compliant repeated-dose toxicity studies are available*

  - historical human data
    *No historical human data that could address the remaining concern are available*

  - (Q)SAR
    *(Q)SAR tools sufficiently addressing repeated dose toxicity are not available*

  - *in vitro* methods
    *In vitro methods sufficiently addressing repeated dose toxicity are not available*

- weight of evidence
  *No data to be used in a weight of evidence approach addressing the remaining concern are available*

- grouping and read-across
  *No data from structurally related comnpounds are available to address repeated dose toxicity*

- substance-tailored exposure driven testing [if applicable]

- [approaches in addition to above [if applicable]

- other reasons [if applicable]

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

  Column 2 of Annex IX states that the sub-chronic toxicity study does not need to be performed 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.*

  None of these conditions are met by the test substance:

  1) The test article was not classified based on the results of the available OECD 422 study. This study was performed in male and female Wistar Han rats at dose levels of 15, 45 and 150 mg/kg bw/day by oral gavage. Toxicity was noted at 150 mg/kg bw/day. For females, it was characterized by clinical signs, reduced body weight gains with lower food consumption, and slightly reduced thymus organ weight. The slightly lower thymus organ weights were in line with the observation of lymphoid atrophy (involution) present in 4 out of the 7 examined females in this high dose group (2 minimal, 1 slight, 1 moderate). Further microscopic findings consisted of lower mean grade of hematopoietic foci in the spleen of females at 150 mg/kg bw/day. Slightly lower body weight gains were also observed for males at 150 mg/kg bw/day. No toxicologically significant changes were noted in any of the remaining parental parameters investigated in this study (i.e. mortality, functional observations, haematology, clinical biochemistry, macroscopic abnormalities). The findings described above are not considered to reflect severe organ damage, therefore no classification was warranted.
  2) No reliable chronic study is available.

3) Although the test item was shown to by hydrolytically unstable, the data available for the individual potential hydrolysis products (Diethylhexylamine, Tolyltriazole and Formaldehyde) are not consistent with the findings observed in the OECD 422 study described above. Diethylhexylamine was investigated in a OECD 422 study which showed increased liver and kidney weights in females at 25 and 75 mg/kg bw/day without hints for an impaired function of these organs by clinical chemistry and histopathology (Source: Disseminated Dossier). Tolyltriazole was tested in an OECD 407 study where no adverse effects were observed at doses of up to 150 mg/kg bw. A dose of 450 mg/ kg bw/day lead to apathy after gavage, to a changed blood count and raised plasma activity of transaminases GOT and GPT (Source: Disseminated Dossier). The main effects in chronic drinking water studies with Formaldehyde with rats are local lesions in the forestomach and the glandular stomach at a concentration of 0.10% in the drinking water corresponding to 50 mg/kg bw/day (Tobe et al., 1989) or 0.19% corresponding to 82 mg/kg bw/day in males and 109 mg/kg bw/day in females (Til et al., 1989). In both studies the NOAEC for local effects is very similar: 0.026% formaldehyde in the drinking water corresponding to 15 mg/kg bw/day in males and 21 mg/kg bw/day in females (Til et al. 1989) or in the study of Tobe (1989) 0.02% corresponding to 10 mg/kg bw/day (Source: Disseminated Dossier).
4) The test item was shown to be systemically available as demonstrated by findings reported in OECD 422 study.

Therefore, the above listed column 2 adaptions cannot be applied.