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: Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene
EC Number: 270-128-1
CAS Number: 68411-46-1

Date of considerations: 21 August 2017

- **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

    Available GLP studies are part of the registration dossiers. None of them fulfil the requirements of an extended one-generation study.

  - available non-GLP studies

    Available Non-GLP studies are part of the registration dossiers. None of them fulfil the requirements of an extended one-generation study.

  - historical human data

    Databases containing potential information reproductive toxicity of the substance in published and internal data on the substance were searched and no contributing information was found.

  - (Q)SAR

    There are no reliable QSAR models addressing the endpoint of reproductive toxicity to the extent that is assessed in the extended one-generation study.

  - *in vitro* methods

    There are no reliable in-vitro methods addressing the endpoint of reproductive toxicity to the extent that is tested in the extended one-generation study.

- weight of evidence: Considering the lack of in-vitro methods, QSAR models and multigeneration studies on the substance itself and potential analogues, a weight-of-evidence assessment is not possible.

- grouping and read-across: Potential candidates for grouping and read-across can be found in the OECD IATA case study document on the endpoint of repeated-dose toxicity. Also a list of potential candidates can be found in the Canadian draft screening risk assessment on the category of substituted alkylated diphenylamines. Since none of the potential candidates has been tested for reproductive toxicity in the extended one-generation study, read-across is not possible. For details it is refered to the table below.

- 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** (instruction: free text): Based on the existing data and hazard and use profile of the substance in question, it is not possible to apply specific adaptation possibilities listed in Annexes IX and X.

Table: Supporting information regarding the testing proposal of an extended one-generation study

	Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene CAS 68411-46-1 UVCB	Reaction products of Benzeneamine, N-phenyl- with nonene (branched) CAS 36878-20-3 UVCB	Benzeneamine, 4-octyl-N-(4-octyl-phenyl)- CAS 101-67-7 Branched side chains according to Canadian Draft Screening Risk Assessment. The structural formula in the summary for the OECD 422 study (MHW 2007) suggests that the material had unbranched side-chains.	Benzeneamine, ar-nonyl-N-phenyl CAS 27177-41-9	Bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine CAS 15721-78-5	Benzenamine, N-phenyl-, reaction products with isobutylene and 4,4-trimethyl-pentene CAS 184378-08-3 UVCB
	REACH > 1000 tpa	REACH > 1000 tpa	No REACH substance; relevant information from Canadian draft screening risk assessment and OECD IATA case study	No REACH substance; relevant information from Canadian draft screening risk assessment and OECD IATA case study	REACH 100 – 1000 tpa Relevant information from disseminated REACH dossier,	No REACH substance; relevant information from Canadian draft screening risk assessment, OECD IATA case study and

					accessed Aug 2017	US HPV program
Toxikokinetic information	Dose-dependent liver effects observed in subacute gavage study with rats Full grown rats are more sensitive to liver effects than young animals No information on reversibility	Dose-dependent liver effects observed in 90-day study with rats up to 1000 mg/kg bw.		Spleenic pigment accumulation observed at 500 mg/kg bw in female rats in the 28-day study not reversible within recovery period. Liver effects partly reversible	NOEL of 1000 mg/kg bw in the subchronic toxicity study with rats is interpreted by registrant as lack of systemic uptake after ingestion	Dose-dependent liver effects observed in subacute gavage study with rats
Information on 2-generation study in rats						
Teratogenicity in rats (OECD 414, GLP)	Not teratogenic in rats (assessed by read-across)	Not teratogenic at the highest tested dose of 500 mg/kg bw			Not teratogenic at highest tested dose of 1000 mg/kg bw	
Teratogenicity in other species		Testing ongoing in rabbits (OECD 414, GLP)				
Screening for fertility/toxicity to reproduction (OECD 422 adopted in 1996, GLP)	No adverse effects on fertility at highest dose of 225 mg/kg bw NOEL (general toxicity) = 25 mg/kg		No adverse effects at the highest tested dose of 250 mg/kg bw (MHW 2007)			NOEL (reproduction /developmental): 25 mg/kg bw/day (actual dose received) (Treatment-related

This guideline version does not include the endocrine disruptor parameters introduced with the update of 28 July 2015	bw Pups showed no clinical signs, normal body weights and no macroscopic findings. Increase in postnatal pup mortality at 225 mg/kg bw, mostly in one animal.					effects on reproduction were observed at 125 mg/kg/day, consisting of shorter gestation lengths and a higher incidence of offspring deaths.) NOEL (general toxicity) = 5 mg/kg bw
Experimental data on genotoxicity	Ames negative Assessed as non-genotoxic by read-across	"non genotoxic" by read-across, all three in-vitro studies ongoing	Not genotoxic in vitro. Dominant Lethal test in rat positive	Ames negative and in-vitro CA negative	Ames negative, HPRT negative, in-vitro micronucleus assay negative	
Effects on glands in repeated-dose toxicity studies	No effects on organ weight or histopathology in OECD 422. Thyroid stimulating hormone (TSH) was much higher than controls for all groups (both sexes, not always statistically significant). These data showed high	No absolute changes in weight up to the limit dose of 1000 mg/kg bw in 90-day study Relative changes in thyroid and adrenal gland weights in males.	None reported in OECD 422 (MHW 2007)	None mentioned in Canadian screening assessment. (28-day study with 15, 150 and 500 mg/kg bw mentioned in Canadian Screening Assessment)	No adverse effects reported in 90-day study.	

	variability with one or more individuals in each treated group showing extremely high values (Group 2, male no. 11, Group 3 male nos. 22, 25, and female no. 62 and Group 4 male no. 33). When recalculated excluding the outliers, group means remained higher than controls (males Group 2: 0.518, Group 3: 0.548, Group 4: 0.475; females Group 3: 0.386), though no dose-dependent distribution was apparent. In the absence of a clear relationship with total T3 or T4, and in the absence of adverse findings seen in the thyroids during the microscopic examination, no toxicological relevance was					

	attributed to higher TSH values.					
Metabolome (study day 28)	No endocrine-related pattern detected. Increase in testosterone and androstenedione at 300 mg/kg bw considered incidental, since no further related changes	No changes in endocrine-related patterns detected				
Identification of structural analogues	Last performed as part of the Canadian Draft Screening Risk Assessment on the category of alkylated diphenylamines, published December 2016; IATA case study on repeated-dose toxicity. Potential structural analogues without data: CAS 4175-37-5, 24925-59-5, 26603-23-6, 68608-77-5, 68608-79-9					