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'''-propane-1,3-diylbis(1-octadecylurea)
EC Number (omit if confidential): 252-667-4
CAS Number (omit if confidential): 35674-65-8

Date of considerations: December 2015

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

  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: none available
  - available non-GLP studies: none available
  - historical human data: none available
  - (Q)SAR: none available, cf. considerations below
  - *in vitro* methods: none available, cf. considerations below
  - weight of evidence: not applicable, no supporting data available
  - grouping and read-across: not applicable, no group/category definition possible
  - substance-tailored exposure driven testing [if applicable]: not applicable
  - [approaches in addition to above [if applicable]: none
  - other reasons [if applicable]: not applicable
- **Considerations that the specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were not applicable** (instruction: free text):

None of the the adaption possibilities, especially those mentioned under number 8.6.2 in column 2 of Annex IX are applicable to the substance.

Moreover, a search for appropriate and reliable alternative methods to substitute the

proposed oral sub-chronic toxicity (90-day) study did not yield any applicable method. Instead, the summary of the Scientific Committee on Consumer Safety (SCCS) on repeated-dose toxicity testing as published in the THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION (9th revision, 2015) was found to be true:

"For repeated-dose toxicity testing, currently no validated or generally accepted alternative method is available for replacing animal testing. There have been efforts in the domains of e.g. hepatotoxicity, neurotoxicity and nephrotoxicity, but to date, no method or screening battery has been formally pre-validated (Adler et al., 2011; JRC 2014)."
(ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf)

This result was further confirmed by the most current status report of EURL ECVAM (JRC 2015, Report EUR 27474) summarizing the development, validation and regulatory acceptance of alternative methods and approaches. The report states that currently no validated in vitro or in silico methods to substitute the study proposed are available.
(ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/eurl-ecvam-status-report-development-validation-and-regulatory-acceptance-alternative-0?search)

Furthermore, in its state-of-the art review on alternative methods for regulatory toxicology (2014, Report EUR 26797), the JRC draws the conclusion that no alternative methods for the study proposed are expected to evolve in the near future.
(ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/alternative-methods-regulatory-toxicology-state-art-review?search)

In summary, the registrant concludes that neither general adaptation possibilities of Annex XI of the REACH Regulation were adequate nor specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were applicable nor any other reliable alternative methods exist to substitute the study propsed.

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Public substance name: N',N'''-propane-1,3-diylbis(1-octadecylurea)
EC Number (omit if confidential): 252-667-4
CAS Number (omit if confidential): 35674-65-8

Date of considerations: December 2015

- **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** (instruction: please address all points below):
  - available GLP studies: none available
  - available non-GLP studies: none available
  - historical human data: none available
  - (Q)SAR: none available, cf. considerations below
  - *in vitro* methods: none available, cf. considerations below
  - weight of evidence: not applicable, no supporting data available
  - grouping and read-across: not applicable, no group/category definition possible
  - substance-tailored exposure driven testing [if applicable]: not applicable
  - [approaches in addition to above [if applicable]: none
  - other reasons [if applicable]: not applicable
- **Considerations that the specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were not applicable** (instruction: free text):

None of the the adaption possibilities, especially those mentioned under number 8.7 in column 2 of Annex IX are applicable to the substance.

Moreover, a search for appropriate and reliable alternative methods to substitute the proposed pre-natal developmental toxicity did not yield any applicable method. Instead, the summary of the Scientific Committee on Consumer Safety (SCCS) on repeated-dose toxicity testing as published in the THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION (9th revision, 2015) was found to be true:

"For reproductive toxicity testing, currently no validated or generally accepted alternative method is available for replacing animal testing (Adler et al., 2011; JRC 2014a)."
(ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf)

This result was further confirmed by the most current status report of EURL ECVAM (JRC 2015, Report EUR 27474) summarizing the development, validation and regulatory acceptance of alternative methods and approaches. The report states that currently no validated in vitro or in silico methods to substitute the study proposed are available.
(ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/eurl-ecvam-status-report-development-validation-and-regulatory-acceptance-alternative-0?search)

Furthermore, in its state-of-the art review on alternative methods for regulatory toxicology (2014, Report EUR 26797), the JRC draws the conclusion that no alternative methods for the study proposed are expected to evolve in the near future.
(ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/alternative-methods-regulatory-toxicology-state-art-review?search)

In summary, the registrant concludes that neither general adaptation possibilities of Annex XI of the REACH Regulation were adequate nor specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were applicable nor any other reliable alternative methods exist to substitute the study propsed.