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: SODIUM DIHYDROGENORTHOPHOSPHATE
EC Number (omit if confidential): 231-449-2
CAS Number (omit if confidential): 7558-80-7

Date of considerations: 20 July 2016

- **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

No available GLP studies on the substances for the endpoint 'reproductive toxicity'.

  - available non-GLP studies

No reliable non-GLP studies are avaialable for the endpoint ' reproductive toxicity'.

Developmental toxicity / teratogenicity studies similar to OECD 414 have been conducted on the following substances on behalf of the United States Food and Drug Administration:
- monosodium orthophosphate[1]
- monopotassium orthophosphate[2]

These studies do not provide data on reproductive parameters but do provide supporting data which suggests a lack of potential systemic toxicity for sodium and potassium orthophosphates.

  - historical human data

No human data suggesting reproductive toxicity are available for this substance. Sodium and potassium orthophosphates are approved for use as food additives (the EU food reference / INS number for monosodium phosphate / sodium dihydrogenorthophosphate is

[1] Bailey DE & Morgareidge K (1975) Teratological evaluation of FDA 73-2, monosodium phosphate in mice and rats. FDA. NTIS PB245527.
[2] Bailey DE & Morgareidge K (1975) Teratological evaluation of FDA 73-65, monopotassium phosphate in mice and rats. FDA. NTIS PB245521.

E339. No evidence exists to show that sodium or potassium orthophosphates are likely to pose a risk of reproductive or developmental toxicity. When discussing a Tolerable Upper Intake Level for Phosphorus, EFSA[3] summarised the available data relating to reproductive toxicity of inorganic phosphates. No reprotoxic effects were noted. The available data indicate that normal healthy individuals can tolerate phosphorus intakes up to at least 3000 mg phosphorus per day without adverse systemic effects. A further review conducted by EFSA in 2015[4] determined Adequate Intakes (AI) for various polpulations. These were as follows:

Infants (7-11 months): 160 mg/day
Children (1-17 years): 250-640 mg/day
Adults, including pregnant and lactating women: 550 mg/day
It is stated that these values are considerably lower than the estimated phosphorus intakes in Western countries.
This review bases it's conclusions not only on phosphorus toxicity but also on the calcium to phosphate ratio. It is not expected that a regulatory EOGRTS will take into account this ratio.
The World Health Organisation, reports that the maximum tolerable daily intake (MTDI) of phosphates for all individuals is 70 mg P/kg bw, this value is considered to be well below that observed for developmental toxicity and as such human exposure is likely to be considerably less that the level required for reprotoxicity testing. No effects on development were observed at the highest dose tested in animal studies[5].

The main toxicological finding in feeding studies with high levels of phosphates is nephrocalcinosis (the rat, particularly the Sprague-Dawley, is known to be more susceptible to these effects than humans). Moreover, these renal effects are not considered to be relevant to reproductive toxicity.

In addition, both the Na+ and the K+ cation have similar and essential biological functions and excess of these ions results in well documented toxicity; this does not include toxicity to reproduction or developmental toxicity.

- (Q)SAR

No validated (Q)SAR's exist for this endpoint in inorganic substances. There is no know mode of action for inorganic phosphates causing reprotoxic effects.

- *in vitro* methods

In accordance with ECHA's guidance on the information requirements and chemical safety assessment , chapter R7a. With regards to in vitro studies for reproductive toxicity, the regulatory acceptance of these studies and approaches to replace the animal testing for reproductive toxicity has not been achieved as they do not provide equivalent information and thus, cannot be used alone for classification and labelling and/or risk assessment.

- weight of evidence

[3] Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Phosphorus (adopted on 1 July 2005 by written procedure). The EFSA Journal (2005) 233, 1-19
[4] Scientific Opinion on Dietary Reference Values for phosphorus. EFSA Journal 2015;13(7):4185
[5] Evaluation of certain food additives and contaminants. Twenty-sixth report of the joint FAO/WHO expert committee of food additives. World Health Organisation. Technical Report Series 683. 1982. ISBN92 4 120683 7

Insufficient reliable data are available to complete the IUCLID requirements sa a weight of evidence approach. However, it could be argued that the 'weight of evidence' based on use patterns, human exposure suggests that the substance is not reprotoxic.

- grouping and read-across

An OECD 422 study exists for an analogous substance (dipotassium orthophosphate). This study does not meet the Annex IV and X REACH requirements. The OECD 422 study results are as follows: The test material was administered orally to rats throughout this period of reproduction (approximately 40 - 50 days) at dose levels up to 1000 mg/kg bw per day. There was no evidence to suggest an effect upon reproduction or offspring development and the NOAEL was determined to be >1000 mg/kg bw, considered to be a "limit dose" in the OECD.
One literature paper exists.[6] This study was performed on analogous substances and has been disregarded for the following reasons:
- Limited information on substance tested (thought to be a mixture of monopotassium orthophosphate and disodium orthophosphate).
- Age of animals is not given.
- The number of animals per group (10) is too small for a reproduction study and chronic toxicity study. This deficiency compromises the validity of the results.
- Mating is assumed to be 2 females:1 male based on the text but the length of the mating period are not included.
- Duration of exposure is not clearly articulated. There is a 9 wk to 12 wk study and a 1-10 week study which goes to 30 weeks. Days of lifespan are provided.
- Duration of exposure is not completely clear and results are not presented for all time periods and generations.
- Observations and clinical signs were not evaluated.
- No food consumption was included so that compound ingestion cannot be estimated.
- Water consumption was not included.
- Oestrus cycle is not evaluated.
- Sperm parameters are not evaluated.
- Haematology was not conducted on many required parameters.
- Clinical chemistry was not conducted.
- Organ weights are not evaluated in the reproduction/chronic toxicity study but are included in the subchronic study.
- Histopathology was not conducted on most organs. Pathology on the kidneys is discussed but there are no data on other organs and tissues. Histopathology of offspring: Not evaluated.
- Incomplete statistics.
- No individual animal data, no means and standard deviations could be calculated.

No further data exists on analogous substances. It is the intention to use test data from SODIUM DIHYDROGENORTHOPHOSPHATE for further read-across to similar substances thus avoiding the need to perform further testing.

- substance-tailored exposure driven testing [if applicable]

Not applicable – substance is used in wide-dispersive uses.

- [approaches in addition to above [if applicable]

Not applicable

- other reasons [if applicable]

[6] Van Esch GJ et al (1957) The physiological effects of phosphates. Arzneimittel Forsch 7, 172-175

Not applicable

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

Adaptation options as defined in Annexes VI to X were not applicable for this substance and this endpoint.

However, since the substance is widely used as a food additive reproductive toxicity is unlikely and a test could be avoided by allowing an adaptation on this basis and outside of Annexes VI to X.