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: COBALT DICHLORIDE
EC Number (omit if confidential): 231-589-4
CAS Number (omit if confidential): 7646-79-9

Date of considerations: 12 April 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

  There are no GLP and Guideline-compliant studies available that may be used to avoid animal testing.

  - available non-GLP studies

  There is a substantial data base on the effects of soluble cobalt compounds to organs of male reproduction. However, the studies in themselves do not show a clear dose-response relationship and beyond that suffer from several shortcomings in experimental design and reporting. Furthermore, none of the available studies represent state-of-the-art, guideline-compliant, extended one-generation reproduction toxicity studies or other relevant study designs, from which robust no-effect levels for human risk assessment could be derived as specifically required under the REACH regulation. For this reason DNELs for reproductive toxicity cannot be established with adequate reliability. Moreover, the above mentioned studies have a primary focus on effects in males, whereas there are no adequate data which would allow a hazard or risk assessment for effects on female reproduction.

  Existing studies show a hazard for male reproductive organs at high doses of cobalt dichloride. These findings have led to an existing harmonised classification as Cat 1 B for the substance cobalt dichloride and 4 additional (assumed) highly water soluble cobalt substances. However, the database having led to the hazard conclusion is not suitable for the derivation of a DNEL, nor is it suitable to assess any effect on female reproductive organs or on developmental effects. The proposed testing would represent a major element in a weight of evidence approach needed to address the endpoint reproductive toxicity.

- historical human data

There are no human data for reproductive or developmental toxicity that may be used to avoid animals testing.

- (Q)SAR

QSAR methods are not applicable to inorganic metal substances.

- *in vitro* methods

In vitro methods, replacing such a complex test design of an extended one-generation reproductive toxicity study are not available (see http://alttox.org/mapp/toxicity-endpoints-tests/reproductive-developmental-toxicity/ and http://eurl-ecvam.jrc.ec.europa.eu/eurl-ecvam-recommendations).

- weight of evidence

Please see above statement given under "available non-GLP studies"

- grouping and read-across

No reliable data available (Please see above statement given under "available non-GLP studies"). The substance cobalt dichloride is the source substance for a grouping and read-across strategy for the oral route. Read across of the results from the proposed study is foreseen.

- substance-tailored exposure driven testing [if applicable]

Not applicable

- [approaches in addition to above [if applicable]

Not 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):

Criteria given in Annex IX and X, Column 2, Section 8.7 Reproductive toxicity:

— the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or

Cobalt dichloride is a known inhalation carcinogen with a clear local and threshold mediated adverse outcome pathway, showing test item induced neoplastic lesions in the respiratoy tract only. A non-threshold genotoxic mediated mode of action can safely be excluded.

— the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or

Cobalt dichloride is not a germ cell mutagen. There is no convincing evidence that cobalt dichloride shows somatic or germ cell mutagenicity with relevance for humans.

— the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs

via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.

There is convincing evidence that following oral administration, cobalt dichloride shows adverse effects in the haematopoietic system. After 90-day oral repeated exposure in rats, increased haematocrit values was considered the leading adverse effect based upon which the NOAEL for cobalt dichloride was derived and used in the risk assessment. Based on this, a "low toxicological activity" statement is not warranted.

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CAS Number (omit if confidential): 7646-79-9

Date of considerations: 12 April 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** (instruction: please address all points below):

  - available GLP studies

  There are no GLP and Guideline-compliant studies available that may be used to avoid animal testing.

  - available non-GLP studies

  There is a very limited database on developmental toxicity in some species (including rats and rabbits) for soluble bivalent cobalt compounds (largely cobalt (II) dichloride and cobalt (II) sulfate). The available studies show several experimental and reporting deficiencies or are contradictory in nature, are therefore considered unsuitable for a human health hazard and risk assessment purposes.

  Existing studies show a hazard for male reproductive organs at high doses of cobalt dichloride. These findings have led to an existing harmonised classification as Cat 1 B for the substance cobalt dichloride and 4 additional (assumed) highly water soluble cobalt substances. However, the database having led to the hazard conclusion is not suitable for the derivation of a DNEL, nor is it suitable to assess any effect on female reproductive organs or on developmental effects.

  - historical human data

  There are no human data for reproductive or developmental toxicity that may be used to avoid animals testing.

  - (Q)SAR

  QSAR methods are not applicable to inorganic metal substances.

- *in vitro* methods

In vitro methods, replacing such a complex test design of a pre-natal developmental toxicity study are not available (see http://alttox.org/mapp/toxicity-endpoints-tests/reproductive-developmental-toxicity/ and http://eurl-ecvam.jrc.ec.europa.eu/eurl-ecvam-recommendations).

- weight of evidence

Please see above statement given under "available non-GLP studies"

- grouping and read-across

No reliable data available (Please see above statement given under "available non-GLP studies"). The substance cobalt dichloride is the source substance for a grouping and read-across strategy for the oral route. Read across of the results from the proposed study is foreseen.

- substance-tailored exposure driven testing [if applicable]

Not applicable

- [approaches in addition to above [if applicable]

Not applicable

- other reasons [if applicable]

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— the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or

Cobalt dichloride is not a germ cell mutagen. There is no convincing evidence that cobalt dichloride shows somatic or germ cell mutagenicity with relevance for humans.

— the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.

There is convincing evidence that following oral administration, cobalt dichloride shows adverse effects in the haematopoietic system. After 90-day oral repeated exposure in rats, increased haematocrit values was considered the leading adverse effect based upon which the NOAEL for cobalt dichloride was derived and used in the risk assessment. Based on this, a "low toxicological activity" statement is not warranted.