~~Confidential~~

Helsinki, 05 October 2023

Addressee(s)
Registrant(s) of JS_Cobalt_neodecanoate as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
20/09/2021

Registered substance subject to this decision ("the Substance")
Substance name: Neodecanoic acid, cobalt salt
EC/List number: 248-373-0

Decision number: Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)

DECISION ON TESTING PROPOSAL(S)

Under Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***10 January 2028***.

Information required from all the Registrants subject to Annex VIII of REACH

1. Transgenic rodent somatic and germ cell gene mutation assays (Annex I, Section 0.5.; test method: OECD TG 488 from 2022) with the analogue substance cobalt sulphate, EC number 233-334-2, in transgenic rats, inhalation route, specified as follows:
   (i) The following tissues must be analysed: lung, liver, bone marrow, and kidney; and if technically possible also adrenals and pancreas.
   (ii) The study must include measurements of cobalt concentrations in whole blood in all animals of all dose groups at 7, 14 and 28 days; the measurements must be conducted directly after the inhalation exposure period in a standardised manner.

2. In vivo mammalian alkaline comet assay (Annex I, Section 0.5.; test method: OECD TG 489) with the analogue substance cobalt sulphate, EC number 233-334-2, in F344 (Fisher) rats, inhalation route, specified as follows:
   (i) The following tissues must be analysed: adrenals, lung, liver, bone marrow, kidney, and pancreas.
   (ii) The study must have a duration of 28 days.
   (iii) The study must include measurements of cobalt concentrations whole blood in all animals of all dose groups at 7, 14 and 28 days; the measurements must be conducted directly after the inhalation exposure period in a standardised manner.
   (iv) The number of control animals per control group must be justified with a power calculation; ECHA recommends at least 15 control animals per control group.

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in

accordance with Articles 10(a) and 12(1) of REACH. The addressee(s) of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report**, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. Assessment of the read-across approach

1 You have used a read-across approach and grouped the Substance into a category and have identified the additional information which is considered necessary to produce the chemical safety report (CSR). You have proposed the following additional tests:

- Transgenic rodent somatic and germ cell gene mutation assays (Annex I, Section 0.5.)
- *In vivo* mammalian alkaline comet assay (Annex I, Section 0.5.)

2 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific testing proposals.

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used.

4 Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category.

5 Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

0.1.1. Scope of the grouping of substances (category)

6 You provide a read-across justification documents in the CSR.

7 For oral carcinogenicity and repeated dose toxicity, you have grouped cobalt substances into three groups for the oral read-across approach: 'Bioavailable Co substances', 'Inorganic poorly soluble substances' and 'Poorly soluble organic ligand' with the following members:

8 Group 1: 'Bioavailable Co substances'

- Cobalt (EC No. 231-158-0)
- Cobalt bis(2-ethylhexanoate) (EC No. 205-250-6)
- Cobalt carbonate (EC No. 208-169-4)
- Cobalt di(acetate) (EC No. 200-755-8)
- Cobalt dichloride (EC No. 231-589-4)
- Cobalt dinitrate (EC No. 233-402-1)
- Cobalt oxalate (EC No. 212-409-3)
- Cobalt oxide (EC No. 215-154-6)
- Cobalt sulfate (EC No. 233-334-2)
- Cobalt(2+)propionate (EC No. 216-333-1)
- Cobalt(II) 4-oxopent-2-en-2-olate (EC No. 237-855-6)
- Cobalt, borate 2-ethylhexanoate complexes (EC No. 295-032-7)
- Cobalt dihydroxide (EC No. 244-166-4)
- Cobalt lithium dioxide (EC No. 235-362-0)

9 Group 2: 'Inorganic poorly soluble substances'

- Cobalt hydroxide oxide (EC No. 234-614-7)
- Cobalt sulphide (EC No. 215-273-3)
- Tricobalt tetraoxide (EC No. 215-157-2)

10 Group 3: 'Poorly soluble with an organic ligand'

- Cobalt, borate neodecanoate complexes (EC No. 270-601-2)
- Naphthenic acids, cobalt salts (EC No. 263-064-0)
- Neodecanoic acid, cobalt salt (EC No. 248-373-0)
- Resin acids and Rosin acids, cobalt salts (EC No. 273-321-9)
- Stearic acid, cobalt salt (EC No. 237-016-4)

11 For mutagenicity, you have grouped all cobalt substances listed above into the same group.

12 ECHA understands that this is the applicability domain of the grouping and your predictions are assessed on this basis.

13 You justify the grouping of substances by the fact that all substances liberate the same toxic entity, i.e. the cobalt cation, upon dissolution in aqueous biological media. You consider that the toxicity resulting from the cobalt ion will be the same in qualitative terms while there may be differences in quantitative terms due to differences in dissolution rates between the groups.

14 The assessment of the proposed predictions of toxicological properties are assessed in the endpoint specific sections below.

Reasons for the decision(s) related to the information under Annex VIII of REACH

1. Transgenic rodent somatic and germ cell gene mutation assays; and

2. *In vivo* mammalian alkaline comet assay

15 Under Annex I, Section 0.5. to REACH, additional tests listed in Annex IX or X to may be proposed if the information obtained from these tests are considered necessary to produce the Chemical Safety Report (CSR).

16 In such cases, a testing strategy explaining why the additional information is necessary shall be submitted.

2.1. Further in vivo mutagenicity testing

17 You have provided a testing strategy which aims to further explore the potential for *in vivo* mutagenicity following inhalation exposure.

18 As part of this testing strategy, you have submitted testing proposals for:

(i) Transgenic rodent somatic and germ cell gene mutation assays (OECD TG 488) by inhalation route with cobalt sulphate; and

(ii) *In vivo* mammalian alkaline comet assay (OECD TG 489) by inhalation route with cobalt sulphate.

19 In addition, the following information is relevant for the testing proposal examination:

(i) Toxicology and carcinogenesis studies of cobalt sulphate heptahydrate in F344/N rats and B6C3F1 mice (inhalation studies; EC No. 233-334-2; [redacted], 1998).

(ii) Toxicology studies of cobalt metal in F344/N rats and B6C3F1/N mice and toxicology and carcinogenesis studies of cobalt metal in F344/NTac rats and B6C3F1/N mice (inhalation studies; EC No. 213-158-0; [redacted], 2014);

(iii) Oral Sub-chronic toxicity study on the Substance [redacted], 2015);

(iv) Oral Sub-acute toxicity study on the Substance ([redacted], 2015);

(v) Toxicological Profile for Cobalt (ASTDR, 2004); and

(vi) RAC Opinion on cobalt metal (CLH-O-0000001412-86-172/F; ECHA, 2017)

20 ECHA understands that you have proposed a testing strategy which intends to provide further information in support of your hypothesis that the cobalt-related cancers are not caused by a genotoxic mode of action but a secondary (indirect) consequence of a non-genotoxic mode of action, i.e. persistent inflammation resulting in meta-, hyper- and ultimately neoplasia in the respiratory tract.

21 In the sections below, ECHA has assessed the testing proposals in relation to the aims of the testing strategy.

22 Cobalt metal, cobalt sulphate, cobalt dichloride, cobalt dinitrate, cobalt carbonate and cobalt di(acetate) have harmonised classifications which include Muta. 2:H341 'Suspected to cause genetic defects'; Index No. 027-001-00-9. 027-005-00-0, 027-004-00-5, 027-009-00-2, 027-010-00-8, and 027-006-00-6, respectively.

23 The genotoxicity of cobalt metal has been reviewed in detail by RAC and can be summarised as follows: "Cobalt metal and cobalt salts can cause DNA damage measured by Comet assay and chromosomal aberrations and micronuclei in vitro, although they do not cause direct

mutagenic effects."; and "Overall, the critical issue is whether the available in vivo data gathered via physiological exposure routes can provide enough evidence to conclude that genotoxicity in vivo is not relevant via these routes. If not, classification as Muta. 2 is warranted based on i.p. [intraperitoneal] data and in vitro data. At present, although the recent studies using oral or inhalation routes suggest that genotoxicity may be below the detection limit of these test assays, it is difficult to exclude relevant systemic genotoxicity, especially when there are additionally some indications from earlier – although less reliable - studies on the genotoxic effects via physiological routes." (RAC Opinion on cobalt metal, 2017).

24 Currently local (direct) genotoxicity at the port-of-entry cannot be excluded due to lack of data.

25 Therefore, further information is needed to produce the CSR.

2.2. Information provided

26 You have submitted testing proposals for a Transgenic rodent somatic and germ cell gene mutation assays (OECD TG 488); and an *in vivo* mammalian alkaline comet assay (OECD TG 489) both studies are proposed to be conducted with the analogue substance cobalt sulphate, EC No. 233-334-2.

27 ECHA requested your considerations for alternative methods to fulfil the information requirement for *in vivo* mutagenicity. You provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

28 ECHA agrees that the proposed studies are necessary to produce the chemical safety report for the Substance.

2.3. Grouping of substances and read-across approach

29 You have provided a read-across justification document in the CSR and IUCLID.

30 As explained in Section 0.1. above you have grouped all cobalt substances into the same group.

31 To generate additional information needed for the CSR, you propose to test cobalt sulphate (EC No. 233-334-2) for *in vivo* mutagenicity. The selection of the test material is based on a 'worst-case' approach.

32 ECHA understands that you read-across hypothesis assumes that different compounds have the same type of effects. The properties of the Substance are predicted based on a worst-case approach.

33 Cobalt sulphate belongs to the 'Bioavailable Co substances' and is soluble and fully dissociated in water (and biological media). Following oral or inhalation administration, at toxicologically relevant dose levels, the cobalt sulphate can be assumed to be fully dissociated based on the water solubility of the substance, toxicokinetic information and available repeated dose toxicity studies.

34 Furthermore, the toxicity profile of the counter-ion is already known and does not require further investigation.

35 Therefore, cobalt sulphate can be considered as a worst-case in terms of exposure to the cobalt ion for all groups of cobalt substances.

36 As explained above, you have established that the properties of the Substance can be predicted from data on the analogue substance.

37 ECHA agrees with your read-across hypothesis.

38 However, ECHA emphasises that any final determination on the validity of your read-across adaptation will only be possible when the information on requested studies will be available in the dossier and after assessing whether it confirms or undermines the read-across hypothesis.

2.4. Test selection

39 You have proposed to conduct a Transgenic rodent somatic and germ cell gene mutation assays (OECD TG 488); and an *in vivo* mammalian alkaline comet assay (OECD TG 489).

40 The proposed tests explore different aspects of mutagenicity, i.e. gene mutations and chromosomal aberrations. According to the OECD TG 489, the comet assay "can detect single and double stranded breaks, resulting, for example, from direct interactions with DNA, alkali labile sites or as a consequence of transient DNA strand breaks resulting from DNA excision repair. These strand breaks may be repaired, resulting in no persistent effect, may be lethal to the cell, or may be fixed into a mutation resulting in a permanent viable change".

41 Therefore, the in vivo comet assay is regarded as indicator assay for general DNA damage, but not as an assay to detect specific mutations.

42 In contrast, the transgenic rodent will evaluate gene mutations only.

43 Therefore, to be able to differentiate between gene mutations and chromosomal aberrations following inhalation exposure both tests are needed.

44 In addition, the tests may provide support for a non-genotoxic mode of action for the cancers observed following inhalation exposure.

45 Therefore, ECHA considers that both tests will provide important information needed to further explore genotoxicity following inhalation exposure.

46 However, a significant amount of information is required to demonstrate an alternative non-genotoxic mode of action. This will require a side-by-side comparison of the key events in the different modes of action in terms of time and dose concordance for both for systemic and port-of-entry effects. Any conclusion with regard to potential for *in vivo* genotoxicity is dependent on the outcome of the proposed test.

47 On this basis, a transgenic rodent somatic and germ cell gene mutation assays (OECD TG 488) and an *in vivo* mammalian alkaline comet assay (OECD TG 489) are needed to develop the CSR for all cobalt substances in Groups 1-3.

2.5. Specification of the study design for the transgenic rodent somatic and germ cell gene mutation assays

48 Based on the recent update of the OECD TG 488, you are requested to follow the new 28+28d regimen, as it permits the testing of mutations in somatic tissues and as well as in tubule germ cells from the same animals.

2.5.1. Specification of test species

49 You proposed testing in transgenic rats.

50 According to the OECD TG 488, the test may be performed in transgenic mice or rats.

51 The aim of the testing strategy is to exclude local (port-of-entry) genotoxicity as a mode of action for the tumours observed in the carcinogenicity studies with cobalt sulphate and cobalt metal ([redacted], 1998; [redacted]; 2014). An additional aim is to identify threshold values for both secondary (indirect) genotoxic effects and inflammation at the site of contact.

52 The [redacted] studies were conducted in F344 (Fisher) rats.

53 Ideally, the test should be performed in F344 (Fisher) rats because this was the strain in which the concern was identified.

54 However, this is a transgenic model and changing the genetic background of the model would require a significant number of animals to back-cross the transgenic rats onto the preferred genetic background.

55 Therefore, ECHA agrees with your proposal.

2.5.2. Specification of the route of exposure

56 You proposed testing by the inhalation route.

57 According to the OECD TG 488, the test substance is usually administered orally.

58 However, having considered the aim of the testing strategy (investigate site-of-contact mutagenicity following inhalation exposure), the anticipated routes of human exposure, and adequate exposure of the target tissue(s), performance of the test by the inhalation route is appropriate.

59 You propose to use dust as the form of dispersion.

60 According to the OECD TG 488, test chemicals can be administered as gas, vapour, or a solid/liquid aerosol, depending on their physicochemical properties.

61 In the previous inhalation studies with the cobalt sulphate ([redacted] 1998), "cobalt sulphate heptahydrate in deionized water (approx. 400 g/L) was siphoned from the bulk reservoir to the nebulizer reservoir and then aspirated into the nebulizer chamber and expelled as a stream through the larger orifice. Shear forces broke the stream into droplets that were evaporated to leave dry particles of cobalt sulphate heptahydrate."

62 This dispersion method is demonstrated to be technically feasible and using a similar method of dispersion will facilitate result comparison.

63 Therefore, cobalt sulphate must be dispersed as previously described by [redacted].

2.5.3. Specification of target tissues

64 You proposed to analyse tissues from bone marrow and kidney in addition to liver and lung.

65 According to the OECD TG 488 "the selection of tissues to be collected should be based upon the reason for conducting the study and any existing mutagenicity, carcinogenicity or toxicity data for the test chemical under investigation".

66 The aim of the testing strategy is to determine local (port-of-entry) genotoxicity as a mode of action for the tumours observed in the carcinogenicity studies with cobalt sulphate and cobalt metal ([redacted] 1998; [redacted]; 2014).

67 Based on measured cobalt tissue organs content/concentration from available toxicity studies ([redacted], 2014; ASTDR, 2004), the following tissues/organs may be target organs for cobalt ion: adrenals, bone marrow, brain, heart, kidney, liver, lung, pancreas and testis.

68 ECHA agrees that analysis of bone marrow and kidney should be included in the study because they are cobalt target organs.

69 However, in the inhalation carcinogenicity studies ([redacted], 1998; [redacted]; 2014) systemic tumours were also observed in the adrenals, pancreas and liver.

70 To confirm or exclude the hypothesis of the testing strategy, tissues where tumours have been observed must be investigated in the study. This is because you have not demonstrated the representativeness of the target organs of bone marrow and kidneys, taking into account the fact that the mechanism of tumour formation is unknown.

71 In your comments on the draft decision, you agree to analyse tissues in the TGR animals that are technically feasible (i.e. of sufficient size/weight) and qualified (i.e. historical control database, positive control data). You state that based upon discussions with the testing laboratory, that both the adrenal glands and pancreas are not qualified tissues and the adrenals may not be technically feasible to analyse in the TGR study and that further discussion with the laboratory is needed.

72 ECHA considers that it is important to investigate adrenals and pancreas because these tissues are identified target organs in the [redacted] carcinogenicity studies. You must investigate these tissues if technically feasible.

73 Based on the above, the following tissues should be analysed in the study: lung, liver, bone marrow and kidney; and if technically feasible adrenals and pancreas.

2.5.4. Germ cells

74 You should collect the male germ cells (from the seminiferous tubules) at the same time as the other tissues, to limit additional animal testing. According to the OECD 488, the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years (at or below −70 ºC). This duration is sufficient to allow you or ECHA to decide on the need for assessment of mutation frequency in the collected germ cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

2.5.5. Measurements of cobalt levels in the blood

75 Where a test method offers flexibility in the study design, the chosen test design must ensure that the data generated are adequate for hazard identification and risk assessment (by analogy, REACH Annexes VII-X, introductory paragraphs).

76 In this case, the objective of testing is to generate adequate information for hazard identification, to confirm or invalidate the hypothesis of your testing strategy, and risk assessment, in particular to assess which route(s) of human exposure may require or not specific risk management measures.

77 According to the OECD TG 488, blood measurement may be considered to demonstrate tissue exposure. The OECD TG 488 does not prohibit, and therefore leaves flexibility, to consider such measurement in light of the testing objective.

78 In this case, the objective for testing is to confirm or exclude a hypothesis based on existing data as well as with other data to be generated for the same purpose.

79 The measurements are required to demonstrate tissue exposure as well as to be able to compare the effects observed in these studies with the previously conducted carcinogenicity studies via inhalation route.

80 The fact that blood measurement has been done in the past in the [redacted] studies confirms that this is technically feasible.

81 Therefore, you must include measurements of cobalt concentrations in whole blood in the study design after 7 days, 14 days and at 28 days of exposure. The cobalt blood measurements can be done in either as part of the main study or in a satellite group with identical exposure conditions.

82 In your comments on the draft decision, you propose to measure cobalt levels in the TGR animal tissues if technically feasible. ECHA considers that you may include tissue measurements in the study at your own discretion as long as it does not interfere with the objectives of the study.

83 In addition, this is an inhalation study. Therefore, measurements of cobalt levels in the blood must be conducted immediately after the inhalation exposure in a standardised manner.

2.6. Specification of the study design for the In vivo mammalian alkaline comet assay

2.6.1. Specification of rat strain

84 You proposed testing in the rat.

85 According to the OECD TG 489, rats are the preferred species.

86 The aim of the testing strategy is to exclude local (port-of-entry) genotoxicity as a mode of action for the tumours observed in the carcinogenicity studies with cobalt sulphate and cobalt metal ([redacted], 1998[redacted]; 2014). These studies were conducted in F344 (Fisher) rats.

87 Therefore, the study must be conducted using F344 (Fisher) rats.

88 In your comments on the draft decision, you agree to conduct the study in F344 (Fisher) rats.

89 However, you raise the issue that there may be problems with having an adequate historical control as many laboratories stopped using Fisher rats 10 years ago. To accommodate this and the variation in the Comet assay you propose to add more concurrent control animals in the study.

90 Normally, there are 5 animals in each control group of the OECD TG 489. However, the lack of adequate historical controls must be compensated by a higher number to ensure the reliability of the study. In this situation, the study results must be interpreted solely based on the concurrent controls. A reliable method to determine such number is the power calculation. Based on a preliminary assessment, considering the results of other comet assays, ECHA recommends using at least 15 control animals per control group must be included to facilitate the interpretation of the results. A higher number may be required under the power calculation on the basis of more detailed information that are available to a laboratory.

2.6.2. Specification of the route of exposure

91 You proposed testing by the inhalation route.

92 According to the OECD TG 489, test substance is usually administered orally.

93 For the same reasons as explained in Section 2.5.2., the study must be performed with dispersion of cobalt sulphate as previously described by [redacted].

2.6.3. Specification of the study duration

94 According to the OECD TG 489, animals should be given daily treatments over 2 or more days and extended dose regimens, e.g. 28-day daily dosing are acceptable.

95 You have proposed a duration of 28 days for this study.

96 The test is proposed as part of a testing strategy. This strategy also includes a transgenic rodent somatic and germ cell gene mutation assays (OECD TG 488) to be conducted with the same substance.

97 To facilitate interpretation of the results ECHA considers that the duration of both studies should be identical.

98 According to the OECD TG 488, the study duration must be at least 28 days.

99 Therefore, the duration of this study must 28 days.

2.6.4. Specification of target tissues

100 You did not specify which tissues are to be investigated in the study.

101 To be able to achieve the goals of the testing strategy and allow a side-by-side comparison of the results. ECHA considers that the same tissues should be analysed in both the OECD TG 488 and OECD TG 489. For reasons for selection of target organs, see Section 2.5.3.

102 In your comments on the draft decision, you highlight that although technically feasible to collect the adrenals has not been measured in the past and there are no historical controls.

103 ECHA notes that to compensate for the lack of adequate historical controls for the Fisher strain you propose to increase the number of concurrent controls. ECHA considers that with an increased number of concurrent controls, there is no reason not to investigate also the adrenals.

104 Therefore, the following tissues must be analysed in the study: adrenals, lung, liver, bone marrow, kidney, and pancreas.

2.6.5. Measurements of cobalt levels in the blood

105 Measurements of cobalt levels in the blood must be included in the study as explained in Section 2.5.5.

2.6.6. Germ cells

106 You may consider collecting the male gonadal cells from the seminiferous tubules in addition to the other afore mentioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

2.6.7. Additional investigations

107 You propose additional analyses for cytotoxicity and other parameters to assess potential secondary effects foreseen (such as: 8-OH-dG lesions, hypoxia upregulation, inflammatory markers, cell infiltration, cytotoxicity, 8-oxoguanine DNA glycosylase, poly ADP ribose and gamma H2AX). Your justification is that the additional analyses are needed to correlate cytotoxicity to comet assay results, due to the sensitivity and lack of specificity of the comet assay.

108 It is at your discretion whether to include these as part of the study as long as inclusion of these additional parameters does not compromise the integrity of the OECD TG 489 study design, or the additional investigations specified in this decision.

2.7. Outcome

109 Under Article 40(3)(b) your testing proposals for a transgenic rodent somatic and germ cell gene mutation assays; and an *in vivo* mammalian alkaline comet assay are accepted under modified conditions and you are requested to conduct the test with the analogue substance cobalt sulphate, EC No. 233-334-2, as specified above.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).

All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs); ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

ECHA received your testing proposal(s) on 4 February 2020 and started the testing proposal evaluation in accordance with Article 40(1).

This decision only addresses the testing proposals submitted as part of your testing strategy to address genetic toxicity *in vivo*. The testing proposal for a pre-natal developmental toxicity study included in your dossier will be addressed in a separate decision.

ECHA held a third-party consultation for the testing proposal(s) from 21 January 2021 until 8 March 2021. ECHA did not receive information from third parties.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and amended the request(s).

In your comments on the draft decision, you requested an extension of the deadline to provide information from 60 to 72 months from the date of adoption of the decision.
You also propose that ECHA allows for the staggered conduct of the 5 testing proposal studies for the cobalt categories. You cite laboratory capacity, significant animal use and the significant resources needed for inhalation toxicity testing. You propose the following schedule:

a. Oral combined chronic/carcinogenicity study – As soon as final decision received
b. 90-day RDT inhalation study – As soon as final decision received
c. In vivo TGR and COMET studies – 1 year after start of combined chronic/carcinogenicity study
d. EOGRTS – 1.5 – 2 years after start of combined chronic/carcinogenicity study.

The initial draft decision contained one deadline for the inhalation *in vivo* TGR and comet studies (36 months). The deadline set in the initial decision already considered the fact that some tests within a given decision are interrelated. ECHA recognises that this is a testing strategy for a large group of substances and that there are interrelations also between the different decisions. The deadline has been extended to 48 months.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third-party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

[2] https://echa.europa.eu/practical-guides

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

[3] https://echa.europa.eu/manuals