EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000003367-71-04/F Helsinki, 4 November 2013

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For Tricobalt tetraoxide, CAS No 1308-06-1 (EC No 215-157-2), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12 (1)(e) thereof for Tricobalt tetraoxide, CAS No 1308-06-1 (EC No 215-157-2), by [redacted] (Registrant).

- Sub-chronic toxicity study (90-days, OECD 408) in rats, oral route.
- Pre-natal developmental study (OECD 414) in rats, oral route.
- Two-generation reproductive toxicity study (OECD 416) in rats, oral route.

The present decision relates solely to the examination of the testing proposals for sub-chronic toxicity (90-days) and pre-natal developmental studies. The testing proposal for the two-generation reproductive toxicity study is addressed in a separate decision although the testing proposals were initially addressed together in the same draft decision.

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 8 March 2012, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

On 29 June 2011, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 2 September 2011 until 17 October 2011. ECHA did receive information from third parties (see section III below).

On 27 April 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. In that draft decision, the testing proposal for oral sub-chronic toxicity study (90-days) with cobalt chloride was rejected.

On 28 May 2012 ECHA received comments from the Registrant agreeing to ECHA's draft decision. In his comment the Registrant did not agree with ECHAs rejection of the testing proposal for an oral sub-chronic toxicity study (90-days).

On 28 November 2012 the Registrant updated his registration dossier. In the updated dossier, the Registrant proposes testing, which is based on grouping and read-across, in the context of which two substances (*i.e.* cobalt dichloride and tricobalt tetraoxide) would be tested for sub-chronic toxicity (90-days), pre-natal developmental toxicity and two-generation reproductive toxicity. The results of the proposed studies are proposed to be used to cover all substances within the 'cobalt category', including the substance concerned by the present decision, by means of read-across.

ECHA considered the Registrant's comments received and the updated registration dossier. On that basis, Section II was amended and the Statement of Reasons (Section III) was changed accordingly. In that draft decision, the testing proposals for oral sub-chronic toxicity study (90-days) with cobalt chloride and with tricobalt tetraoxide were accepted.

On 8 March 2013 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 11 April 2013 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received for all substances within the 'cobalt category' and decided to amend the draft decision accordingly.

On 22 April 2013 ECHA referred the draft decision to the Member State Committee.

The Registrant did not provide any comments on the proposed amendments.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a two-generation reproductive toxicity study and one relating to the testing proposals for an oral sub-chronic toxicity study (90-days) and a pre-natal developmental toxicity study.

After discussion in the Member State Committee meeting on 11-14 June 2013, a unanimous agreement of the Member State Committee on the draft decision relating to the testing proposals for an oral sub-chronic toxicity study (90-days)and a pre-natal developmental toxicity study as modified at the meeting was reached on 14 June 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

The Registrant has requested to carry out the required tests using the registered substance as part of a read-across and grouping approach, in accordance with Annex XI, 1.5.

The Registrant shall carry out the following tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-days) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408); and
2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome and considering the possibilities for adaptations of the standard information requirements according to the column 2 provisions of the respective Annex and those contained in Annex XI of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **4 November 2015** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

In relation to the testing proposals subject to the present decision, the Registrant has requested to carry out the required tests using the registered substance as part of a read-across and grouping approach, in accordance with Annex XI, 1.5.

The Registrants have submitted testing proposals, based on a read-across approach, intended to fulfil information requirements for oral sub-chronic toxicity (90-days; Annex IX 7.5.2.), pre-natal developmental toxicity (Annexes IX and X, 7.8.2.), and toxicity to reproduction (Annex X, 7.8.3.). It is noteworthy that under the evaluation of the testing proposals, ECHA has not performed a compliance check on other endpoints such as mutagenicity, carcinogenicity and sub-chronic toxicity via inhalation and may do so at any time at its own discretion.

According to the Registrant, the read-across hypothesis is based on cobalt (Co) ion toxicity and applies without restriction to all cobalt substances capable of releasing cobalt ions. More specifically, the Registrant concludes that cobalt metal and cobalt containing substances are subject to "corrosion" processes or dissociate in aquatic media containing oxygen, liberating cobalt ions; the dissolution process is pH dependent. In addition the hypothesis is based on the fact that *in vitro* bioaccessibility in artificial gastric fluid is a better estimate for bioavailability than water solubility. The low pH in the stomach will cause dissolution of the substances, facilitate gastrointestinal absorption, and thereby determine systemic exposure.

To support the proposed read-across hypothesis, the Registrant has provided experimental data on water solubility, cobalt speciation in the environment, *in vitro* bioaccessibility studies (of all cobalt substances in the proposed category) in various artificial physiological fluids, and four sub-acute toxicity studies (28-days). The results from the *in vitro* bioaccessibility studies demonstrate that the predicted bioaccessibility (gastric release) is high for most substances within the category regardless of water solubility. Furthermore, the bioaccessibility studies show that cobalt substances are likely to be absorbed through the inhalation route.

To further support the proposed read-across hypothesis, the Registrant has provided four oral sub-acute repeated dose toxicity studies (28-days, all four conducted with cobalt "carboxylates"): cobalt stearate, CAS No 13586-84-0 (EC No 237-016-4); cobalt borate neodecanoate complexes, CAS No 68457-13-6 (EC No 270-601-2); cobalt (II) 4-oxopent-2-en-2-olate, CAS No 14024-48-7 (EC No 237-855-6); and resin acids and rosin acids, cobalt salts CAS No 68956-82-1 (EC No 273-321-9). Furthermore, three additional oral sub-acute repeated dose toxicity studies on cobalt metal powder CAS No 7440-48-4 (EC No 231-158-0); cobalt sulphide CAS No 1317-42-6 (EC No 215-273-3); and tricobalt tetraoxide CAS No 1308-06-1 (EC No 215-157-2) that are reported as ongoing. In addition, the dossier contains oral non-guideline repeated dose toxicity studies from scientific literature on cobalt dichloride. The overall toxicological effects observed in the studies above support the hypothesis of cobalt ion toxicity and provide experimental support for use of the *in vitro* bioaccessibility parameter to allow prediction of cobalt ion toxicity within the category, although applicability of this information towards for reproductive toxicity endpoints needs to be established.

In the dossier update, the Registrant proposes to perform the intended tests on two substances: cobalt dichloride CAS No 76679-9 (EC No 231-589-4) and tricobalt tetraoxide CAS No 1308-06-1 (EC No 215-157-2). Based on the studies mentioned above, these substances are respectively the most bioaccessible cobalt substance and the least bioaccessible cobalt substance within the 'cobalt category'. It is ECHA's understanding that the Registrant intends to use the results from the proposed two tests per endpoint, together with available data including *in vitro* bioacessibility, to derive substance specific DNELs for each substance within the category.

1. Sub-chronic toxicity study (90-days)

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A sub-chronic toxicity study (90 days) is a standard information requirement as laid down in Annex IX, section 8.6.2 of the REACH Regulation. ECHA notes that the Registrant has submitted testing proposals for sub-chronic toxicity studies (90 days) to be performed by the oral route. The Registrant justifies the testing proposal by stating that it is needed for robust risk assessment and as a dose-finder for the proposed two-generation reproductive toxicity study.

The Registrant has submitted a 13-week inhalation toxicity study (NTP 1991) and a carcinogenicity study (also via inhalation, NTP 1998) perfomed using cobalt sulphate CAS No 10124-43-3 (EC No 233-334-2), which are in essence consistent with the respective test guidelines.

With regard to oral repeated dose toxicity, ECHA notes that the technical dossier contains four reliable oral sub-acute toxicity studies performed with other members of the proposed 'cobalt category'. Three additional sub-acute toxicity studies are reported as on-going (see read-across considerations above). In addition, the technical dossier contains a number of oral sub-acute/chronic studies from scientific literature on primarily cobalt dichloride which are considered 'not reliable' by the Registrant as they are not useful for robust risk assessment. ECHA notes that there are no sub-chronic toxicity studies (90 days) by oral route available; for the substance covered by the present decision.

The Registrant has provided several arguments on why an oral sub-chronictoxicity study (90-days) is necessary.

Firstly, according to the Registrant: "*The repeated dose toxicity studies via inhalation with cobalt sulphate are not suitable for use in the hazard assessment of systemic effects (via route to route extrapolation). The respiratory tract of test animals is more susceptible to adverse effects by inhaled cobalt, showing an inflammatory response at concentrations at which systemic effects cannot be observed*". ECHA agrees with the Registrant in that, due to the reason given above, local respiratory effects may have prevented accurate identification of systemic effects and would not provide a basis for derivation of the DNEL for systemic toxicity (oral route) for the cobalt category. Consequently, oral sub-chronic toxicitystudy (90 days) is considered valuable in addressing the systemic effects of cobalt.

Secondly, concerning the need to cover both inhalation and oral route of exposure by sub-chronic studies, the Registrant has demonstrated that the *in vitro* bioaccessibility (and likely also gastrointestinal absorbtion) of the substances within the 'cobalt category' differs depending on the route of exposure, *i.e.* the absorption by oral route is clearly higher than via the inhalation route. ECHA considers that this supports the proposal of the Registrant to test representative cobalt substances by using the oral route as it will provide a more robust assessment of systemic effects.

Finally, all of the oral repeated dose toxicity studies in the dossier, with the exception of the recent sub-acute studies, have not been made according to current test guidelines. Although, the NTP studies observed some aspects of systemic toxicity, ECHA considers that a new oral sub-chronic toxicity study (90-days) is necessary in order to fully characterise the systemic effects of cobalt substances. It is noteworthy that according to Annex I of REACH Regulation and according to the ECHA Guidance on information requirements and chemical safety assessment (Chapter R.8.), DNELs for both local and systemic effects may need to be derived depending on the substance in the *'cobalt category'*.

According to Column 2, Annex IX, Section 8.6.2, the study is to be performed using the most appropriate route of administration considering the likely route of human exposure. Based on information submitted on uses and exposure, ECHA notes that in the present case the most likely route of human exposure could be oral and/or inhalation depending on the substance within the proposed 'cobalt category'. In the dossier update, the Registrant has further justified the route of administration and considers that overall within the 'cobalt category' the oral route of administration is the most appropriate. For the purpose of testing proposal evaluation, both oral and inhalation exposures are therefore considered as appropriate routes of human exposure.

The hypothesis of the proposed read-across relies on the testing of cobalt dichloride and tricobalt tetraoxide. ECHA has noted that the studies which formed the basis for the classification, although, sufficient for hazard identification, is not considered by the Registrant as sufficient to support robust risk assessment across the category. No information on sub-chronic toxicity (90-days) is available for tricobalt tetraoxide. For cobalt dichloride, no guideline compliant oral sub-chronic toxicity study (90-days) is available. In order for the Registrants to make full use of the proposed read-across approach for interpolation across the category, it is important to have equal quality data at the boundaries of the category. Therefore, ECHA accepts the testing proposals on both cobalt dichloride and tricobalt tetraoxide with respect to oral sub-chronic toxicity.

ECHA would like to point out some additional considerations with regard to the proposed sub-chronic toxicity study (90-days). There is already an identified hazard with regard to male reproduction for cobalt dichloride. For female reproduction there is no information available. At least one of the substances proposed to be tested is highly likely to produce adverse effects on reproductive organs sufficient for classification as *Repro. 1B:H360* as a result of the proposed tests. Some additional examinations on reproductive parameters that are normally performed in the two-generation toxicity to reproduction study (test method: EU B.35/OECD 416) can be included into the proposed oral sub-chronic toxicity study (90-days). If these additional examinations are included in the proposed oral sub-chronic toxicity study (90-days), and both substances tested produce adverse effects that are sufficient for classification as *Repro. 1B:H360* the proposed two-generation toxicity to reproduction study may not be necessary (see Section II.3 and Section III.3). ECHA therefore recommends the Registrant to include additional examinations of male and female reproductive parameters (oestrous cycle, sperm parameter, and reproductive and other certain organs and tissues) that produce respective information as outlined for P parental animals in EU test method B.35, sections 1.5.3, 1.5.4 and 1.5.6 to 1.5.8.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the public consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information 9:

A third party acting on behalf of the Registrants has communicated to ECHA that the Registrants intend to update the testing strategy and test cobalt dichloride, CAS No 7646-79-9 (EC No 231-589-4) rather than cobalt sulphate, CAS No 10124-43-3 (EC No 233-334-2). ECHA considered the corresponding information provided by the Registrants in the updated technical dossier.

Third party information 10:

A third party has proposed a read-across approach for ECHA to take into account before further tests on vertebrate animals are required. As part of this approach, the third party provided results from the US National Toxicology Program (NTP). The third party has noted that the registration dossier contain results from NTP 105-week carcinogenicity studies in mice and rats, which were performed with the read-across substance cobalt sulphate heptahydrate (CAS No 10026-24-1) using inhalation exposure. The third party has noted that the results from 16 day and 13 week range-finding studies are available as a separate report but are not included in the registration dossier. The third party proposes that the information from the range-finding studies may be sufficient to fully address the data requirement, with the consequence that the proposed 90-day oral toxicity study is not scientifically justified.
ECHA has taken the information provided into account and concludes that the information provided by the third party is provided by the Registrant. The information has been considered in relation to the endpoint (see Section III.1a). ECHA concludes that the information provided is sufficient to fulfil the information requirements for Annex IX, Section 8.6.2. for the inhalation route for 'highly soluble' category members. However, in light of the overall, read-across approach, testing strategy and the available information by the oral route, ECHA considers that testing for sub-chronic toxicity is required also by the oral route in order to support robust risk assessment of the 'cobalt category'.

Third party information 11:

A third Party points out that cobalt sulphate and several other cobalt containing compounds already are classified as *Carc. 1B* and *Repro.1B* and listed in the Candidate List as a Substance of Very High Concern, as the first part of the Authorisation process. The third party argues that no testing is necessary for cobalt sulphate because a carcinogenic compound will subject to very rigorous exposure controls and Authorisation (once completed) will prohibit some uses and only allow those uses where the exposure can be demonstrated to be safe (or because of adequate socio-economic justification). The third party further argues that the risk management measures required to control the risks from carcinogenicity, which is non-threshold effect, will be much more restrictive than those which would result from the additional tests and the resulting DNELs. Furthermore, the third party argues that, because of the read-across and category approach proposed by the Registrant, all cobalt should be considered to have the same carcinogenicity hazard as cobalt sulphate and therefore no additional testing is required. On this basis, the third party considers the additional toxicity testing on vertebrates is unnecessary, and proposes rejection of them in the interests of animal welfare.

Third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy or for waiving as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement. ECHA also points out that not all substances in the 'cobalt category' are classified for carcinogenicity.

Third party information 12:

A third party has submitted two studies by Grice *et al.* and Domingo *et al.* in which rat were exposed sub-chronically to cobalt (sulphate and chloride, respectively). In these studies, increased heart weight and degenerative heart lesions were observed. A third party also referred to an international assessment report (CICAD 69, Cobalt and inorganic cobalt compounds) published by the World Health Organization.

Although ECHA recognises that the information as provided by the third party might be scientifically relevant, it does not fulfil as such the Annex IX, Section 8.6.2 requirements, because these studies have been classified as "not reliable" by the Registrant and they have not been made and reported according to respective test guidelines. Therefore, the studies are not sufficient to allow ECHA to reject the testing proposal solely on the basis of these studies.

c) Outcome

ECHA has examined the testing proposal considering all the relevant and available data in the context of the proposed read-across approach and the information submitted by third parties during the public consultation. The available information is not considered as sufficient to permit a robust conclusion on sub-chronic toxicity (90-days), to serve as a starting point for robust risk assessment across the proposed 'cobalt category', including the substance concerned by the present decision. It is thus necessary to generate additional data for this endpoint, in accordance with the provisions of Annex IX, section 8.6.2., column 2.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-days) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408), using the indicated test method using the indicated test method and the registered substance concerned by the present decision.

As indicated in Section IV, below, the selection of the sample of substance tested shall take particular consideration of the particle size of the substance subject to the present decision.

2. Pre-natal developmental toxicity study

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA notes that the Registrant has submitted four relevant studies (published scientific journals) in relation to this information requirement. Three studies were performed in rats and one in mice using cobalt dichloride or cobalt sulphate. Each of these studies covers some aspects of the pre-natal developmental toxicity. In addition, the Registrant has also submitted testing proposals for a pre-natal developmental toxicity study (test method: EU B.31/OECD 414) to be performed by the oral route.

While ECHA notes that some relevant data is available in the dossier on pre-natal developmental toxicity, these studies are not considered sufficient to fulfil the information requirement. More specifically, ECHA considers that the studies submitted do not cover all the parameters and observations according to the current test guideline (EU B.31, OECD 414). In addition, the size of animal groups used in the studies is smaller than stipulated within the test guidelines and therefore, the statistical sensitivity of these studies is compromised.

ECHA also notes that this information originates from published literature, where the adherence to standard test guidelines and the robustness of reported study results may not be as stringent as in study reports specifically designed for regulatory purposes. ECHA acknowledges that the studies provided do not enabled the Registrant to prepare appropriate robust study summaries, in accordance with REACH Regulation requirements, since the relevant information on the methods applied and detailed results are not always given in the scientific publications.

Annex IX 8.7, Column 2 of the REACH Regulation stipulates:

> "*if a substance is known to have an adverse effect on fertility, meeting the criteria for classification as Repro. 1A or 1B: H360, and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for development toxicity must be considered*" (emphasis added).

Testing for pre-natal developmental toxicity is therefore proposed by the Registrant as he considers that, due to the limited data available, a test using the appropriate guideline is necessary. As previously explained, the information on pre-natal developmental toxicity is currently insufficient to cover the 'cobalt category'. ECHA acknowledges that the Registrant legitimately considered that pre-natal developmental toxicity data performed according to the accepted test guideline was necessary to support a robust risk assessment. Furthermore, the tests proposed will provide a more adequate basis for derivation of the DNEL for the 'cobalt category'.

The Registrant did not specify the species and route to be used for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

For the sake of clarity, ECHA highlights that only the information requirement concerning the testing with "first" species has been considered at this stage.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. At the time of the consultation the testing proposal indicated cobalt sulphate as the substance to be tested. Later the Registrant updated the dossier and proposed cobalt chloride to be tested. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information 1:

For this information requirement, a third party have submitted information that is identical to that addressed in Third party information 9 for the pre-natal developmental toxicity study above (see Section III.1.b).

Third party information 2:

A third Party highlights that cobalt sulphate and several other cobalt containing compounds are currently classified as *Carc. 1B* and *Repro. 1B* and listed in the Candidate List as Substances of Very High Concern, as the first part of the Authorisation process. The third party argues that no testing is necessary for cobalt sulphate because a carcinogenic compound will be subject to very rigorous exposure controls and Authorisation (once completed) will prohibit some uses and only allow those uses where the exposure can be demonstrated to be safe (or because of adequate socio-economic justification). The third party further argues that the risk management measures required to control the risks from carcinogenicity (a non-threshold effect) will be much more restrictive than those which would result from the additional tests and the resulting DNELs. Furthermore, the third party argues that, because of the read-across and category approach proposed by the Registrant, all cobalt compounds should be considered to have the same carcinogenicity hazard as cobalt sulphate and therefore no additional testing is required. On this basis, the third party considers that the additional toxicity testing on vertebrates is unnecessary, and proposes rejection of them in the interest of animal welfare.

Third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy or for waiving as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement. However, ECHA has considered the arguments provided by the third party. Testing proposal examination under REACH is a process that is formally independent of the Authorisation process. The Authorisation process is ongoing and ECHA can not predict the outcome of this process. Therefore risk management measures and the levels of exposure cannot be assessed at present.

In addition, the third party suggests that additional testing for reproductive toxicity is not necessary as the substance proposed to be tested is classified as *Carc. 1B*, the associated hazard phrase is *H350i "May cause cancer by inhalation"*. ECHA agrees with the third party that appropriate risk management measures should be in place with regard to inhalation exposure. However, some of the cobalt substances included within the proposed category also have oral exposure as a route of human exposure and therefore, ECHA considers the testing to be necessary.

Third party information 3:

A third party suggests that additional testing for reproductive toxicity is not necessary as the proposed test substance is classified as *Carc. 1B, H350i "May cause cancer by inhalation"*; Muta. 2, H341 *"Suspected of causing genetic defects"* and therefore testing should only be necessary if appropriate risk management measures are not in place. ECHA agrees with the third party in that according to Annex IX, 8.7 reproductive toxicity studies would not be required if the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented. However, the Registrant did not clarify whether the risk management measures (RMMs) are implemented and therefore ECHA cannot assess the implementation of the RMMs in the context of the testing proposal examination. Furthermore, some cobalt compounds are listed in the Candidate List as Substances of Very High Concern, as the first part of the Authorisation process, and their RMM will depend on this process. Appropriate risk management measures should be in place with regard to inhalation exposure. However, some of the cobalt substances included in the proposed category also have oral exposure as route of human exposure, therefore, ECHA considers the testing to be necessary (see also Section III.1.b.11).

Third party information 4:

A third party has submitted one study (Szakmary *et al.*) on the effects of cobalt sulphate on prenatal development of mice, rats, and rabbits, and on early postnatal development of rats; and an international assessment report (CICAD 69, Cobalt and inorganic cobalt compounds) published by the World Health Organization. The study provided by the third party is already considered by the Registrant. Although the study investigates pre-natal developmental effects following oral exposure to cobalt sulphate in three species, there are several methodological and reporting deficiencies in the study. In particular, multiple study designs are used and the total number of animals used in each study design is too low for regulatory purposes. The CICAD report confirms the Registrant's claim that there is a limited database on pre-natal developmental toxicity of cobalt and that the results are somewhat contradictory. Therefore, ECHA concludes that the information provided by the third party is not sufficient to fulfil the standard information requirements as laid down in Annexes IX and X, section 8.7.2 of the REACH Regulation.

c) Outcome

ECHA has examined the testing proposal considering all the relevant and available data in the context of the proposed read-across approach and the information submitted by third parties during the public consultation. The available information is not considered as sufficient to permit a robust conclusion on the pre-natal developmental toxicity potential of the substances within the 'cobalt category' including the substance concerned by the present decision. Thus, it is necessary to generate additional data for this endpoint, in accordance with the provisions of Annex IX, section 8.7.2., column 2.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the indicated test method using the indicated test method using the indicated test method and the registered substance concerned by the present decision.

As indicated in Section IV, below, the selection of the sample of substance tested shall take particular consideration of the particle size of the substance subject to the present decision.

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

3. Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a reproductive toxicity study according to the standard information requirement of Annex X, 8.7.3. of the REACH Regulation. As the testing proposal for this information requirement is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies are appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

More specifically in the present case, ECHA notes that the substance concerned by the present decision is a cobalt salt. The total surface area of the particles (*i.e.* particle size) is an important factor that needs to be considered as it will affect the rate of solubilisation. As a result, the particle size of the sample of substance tested should be selected in such a way that it does not underestimate the potential hazard of the substance concerned by the present decision.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]

Jukka Malm
Director of Regulatory Affairs