ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 25 June 2019

Addressee: [redacted]

Decision number: CCH-D-2114471126-52-01/F
Substance name: Dipotassium hexafluorotitanate
EC number: 240-969-9
CAS number: 16919-27-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17/05/2013
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14./OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**

3. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

4. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

5. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance ;**

6. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance ;**

You have to submit the requested information in an updated registration dossier by **3 January 2022**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by **Claudio Carlon**, Head of Unit, Hazard Assessment

[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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA in the following provides the reasons for rejecting the read-across on a general basis before it provides its reasons for the above requests for information on the individual endpoints in the sequence of numbering of above requests (the ones concerned by your adaptation based on read-across are those in sections 2, 3, 4, 6 and 7 below).

Grouping of substances and read-across approach

You have sought to adapt the information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5 for the endpoints:

- sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.);
- screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.);
- long term aquatic toxicity test to aquatic invertebrates (Annex IX, Section 9.1.5.);

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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. 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 (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological and ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Thus physicochemical properties influence the human health and environmental properties of a substance and should be considered in read-across

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

assessments. However, the information on physicochemical properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s) - the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s) - the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties or follow a regular pattern (trend) as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance (target) Dipotassium hexafluorotitanate (EC No 240-969-9) by using data from the simple fluoride salts Potassium fluoride (CAS No 7789-23-3), Sodium fluoride (EC no 231-667-8) and Hydrogen fluoride (EC no 231-634-8). These substances are the source of data for your read across adaptation.

You have provided read-across documentation in the CSR and in the endpoint summary in the IUCLID dossier for environmental fate and ecotoxicology as well as under human health endpoints.

You use the following arguments to support the prediction of the properties of the registered substance from data for the source substances: on the basis of structural similarity, and similarity in toxicokinetics, physico-chemical, toxicological and ecotoxicological properties, it is possible to predict the human health and environmental properties of the registered substance. More specifically, you expect that the target and source substances will dissolve and dissociate to form fluoride ions and that the fluoride ions will drive the toxicological and ecotoxicological properties of the selected substances as specified underneath.

For the human health endpoints in the CSR (p. 35) you stated:

"Read-across between sodium fluoride and potassium fluoride can be considered as justified (cfr. CSR for potassium fluoride) assuming (i) similar dissociation behaviour under physiological conditions and (ii) similar absorption and distribution/elimination kinetics once becoming systemically available as "fluoride" anions. The substance K2TiF6 is characterised by a moderate to high water solubility of 12.8 g/L, which is very similar to that of sodium fluoride (ca. 40 g/L), and is assumed to dissociate in a similar way upon uptake via ingestion or inhalation. Based on (i) the similarities in water solubility as a surrogate for bioavailability, (ii) the fact that the majority of "fluoride" toxicity and toxicokinetic studies were in fact generated for sodium fluoride, and (iii) the titanium moiety of the substance will hydrolyse to a poorly soluble precipitate (i. e. titanium oxides or -hydroxides), it is assumed that the toxic potential is driven by the fluoride content. Thus, unrestricted read-across between K2TiF6 and sodium/potassium fluoride is considered justified."

In respect of predicting enviromental toxicity you further explain that:

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

"Dipotassium hexafluorotitanate is an inorganic substance which will rapidly dissociate into fluoride, potassium and titanium ions upon dissolution in the environment. However, potassium and titanium ions do not remain as such in solution, only fluoride ions do. [...] Thus, regarding the environmental fate and toxicity of dipotassium hexafluorotitanate, it can be assumed that toxicity (if any) will be driven by the fluoride anion. Therefore, full read-across to potassium fluoride (CAS #7789-23-3) and other fluorides based upon a molecular weight conversion is justified."
You further explained that as regards the source substance Potassium fluoride:
"KF is a simple inorganic substance which will rapidly ionise in the environment and will not be subject to biodegradation.
However, the fate and behaviour of fluorides in the environment is discussed below. The information is primarily taken from the EU RAR for HF and the Dutch ICD fluorides document (Sloof et al,1989).
Sources of environmental fluoride are anthropogenic (industrial, application of phosphate fertiliser) and natural [...]. The environmental behaviour of fluoride is essentially independent of source."
You further explain that the following information is taken into account for any environmental exposure assessment:
"[...] full read-across to potassium fluoride (CAS #7789-23-3) and other fluorides based upon a molecular weight conversion is justified. Relevant information are reported for fluoride in the EHC (2002). Fluoride strongly adsorbs to soil and is essentially immobile with very low levels of leaching. A similar conclusion can be made for dipotassium hexafluorotitanate."

ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument for the read-across is that the similarity in chemical structure and in some of the physico-chemical, toxicological and ecotoxicological properties between the source and registered substances is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical, toxicological and environmental properties does not necessarily lead to predictable or similar human health or ecotoxicological properties in other endpoints.

On the read across from data on the fluoride salts that you have included in the registration i.e. Potassium fluoride (CAS No 7789-23-3), Sodium fluoride (EC no 231-667-8) and Hydrogen fluoride (EC no 231-634-8), ECHA agrees that formation of fluoride following uptake by inhalation/ingestion or after release to the environment may be toxicologically relevant. In this context ECHA considers the use of read across from data on simple fluoride salts as specified above to account for the toxicological properties of fluoride ions as acceptable. However, ECHA notes that your hypothesis relies on the assumption that the dissociation behaviour of the registered substance is similar to simple fluoride salts giving rise to fluoride species in solution while titanium is anticipated to precipitate out as an oxide or hydroxide. This implies a complete and rapid dissociation of the hexafluorotitanate complex which is not demonstrated in the registration dossier. In fact, there is available data in the literature which suggests that hexafluorotitanate is resistant to hydrolysis and expected to hydrolyse only partially releasing some coordinated fluoride as F- ions while various hydroxo species with F coordinated to Ti would remain depending on the pH (Schmitt et al. 1960, J. Am. Chem. Soc., 82, 5292; Bayoumi F. & Ateya B. 2006,

Electro.Comm. 8, 1, 38-44). Dissociation is a critical part of your hypothesis which you have not addressed in your registration dossier.

Given that hexafluorotitanate may be resistant to hydrolysis and may not completely and rapidly dissociate, it is necessary to take account of the potential contribution that fluorotitanate species may have on the prediction. ECHA notes that data has not been provided on the hexafluorotitante species which would support the predicition that the toxicity is driven by fluoride ions. Therefore, your hypothesis cannot be confirmed and therefore is rejected.

In your comments on the draft decision, you acknowledge that the justification for the read-across between the registered substance and simple fluoride salts needs to be improved.

On the read-across for environmental fate and ecotoxicological properties:

You consider that the results of the analytical monitoring of exposure concentrations in the short-term aquatic toxicity studies support your hypothesis that TiF_6^{2-} is rapidly dissociated into Ti^{4+} and F^-. In this context, you state that "*the analyses of dissolved titanium levels in aquatic toxicity test solutions for algae, daphnia and fish* [...] *with dipotassium hexafluorotitanate indicate that up to a loading of 100 mg/L dipotassium hexafluorotitanate, very low levels of titanium (< 10% or even < 5%) remain in solution at environmentally relevant pH while nearly all of the fluoride (> 65 % in algae medium and > 95% in fish and daphnia media) was recovered at test end*". You also postulate that any dissolved Ti^{4+} would be rapidly transformed to insoluble hydroxides.

ECHA agrees that the fact that (most) fluoride stays in solution while dissolved titanium concentrations decrease to low levels may be regarded as supporting the hypothesis that (i) the TiF_6^{2-} coordination complex dissociates and (ii) the released Ti^{4+} are rapidly transformed to an insoluble species. However, the data you provided do not constitute direct proof of your hypothesis but only act as indirect evidence that may be subject to a number of methodological biases. In particular for the acute aquatic toxicity studies conducted on dipotassium haxafluorotitanate (EC no 240-969-9):

- neither the fluoride electrode nor the ICP-MS method (used to monitor fluoride and titanium, respectively) provide a selective quantification of dissolved ions. The fluoride selective electrode involves the use of TISAB buffer which contains a chelating agent (i.e. CDTA) that preferentially binds various metals ions that form complexes with fluoride. Therefore, it permits only a measurement of <u>total</u> fluoride. Similarly, ICP-MS does not allow quantification of specific titanium species unless a separation method such as ion chromatography is used. As non-selective analytical methods were used, the preparation of samples for analysis must be described in detail and the interpretation of results carefully explained as part of your hypothesis.
- in the acute fish study, there was a lack of repeatability with the analytical monitoring results for titanium which adds to the uncertainty in the interpretation.
- different results were obtained depending on the test medium used in the acute studies and no information is available on the rate of decrease of titanium concentrations.
- the results of the analytical monitoring in the selected studies suggest that there is a pH dependency on the removal of titanium from the water phase. Therefore, in addition to the above methodological uncertainties/deficiencies, it remains unclear if your hypothesis would be valid under the full range of environmentally relevant pH (i.e. from 5.5 to 8.5).

On the read-across for human health properties:

You state that "*the hexafluorotitanate ion is considered as rather stable thermodynamically, the assumption is that it will continuously dissociate to release fluoride ions when entering the human body or that of an experimental animal*" and that "*the released fluoride ion is the toxicologically relevant species, and any remaining titanium-containing species are of negligible relevance. Therefore, read-across from studies with non-complexated "fluoride", such as sodium fluoride, to the registered substance is considered feasible*".

To justify the read-across hypothesis you propose to update the dossier and include the following:

- recently conducted comparative toxicokinetic and mass-balance studies, in which rats have been dosed orally with either K_2TiF_6 or KF at equivalent doses of "fluoride". In these studies, similar concentrations of fluoride in the blood serum of test animals were observed (measured using a fluoride selective electrode after TISAB addition);
- a yet to be conducted *in-vitro* experiment on the hydrolysis of hexafluorotitanate at different pH values;
- a yet to be conducted 28-day repeated dose toxicity study conducted with K_2TiF_6, for use as a bridging study in the read-across justification.

ECHA understands that you intend to further justify the read-across by generating additional data and considers that the proposed approach may provide relevant additional information. This information is currently not available in the registration dossier and therefore will be evaluated at the follow-up of the decision making process. However, based on the provided information, ECHA has the following comments:

- the quantification method used in the toxicokinetics study is not specific (as already explained above). Therefore, the fact that similar fluoride concentrations were determined in blood serum does not prove that dissociation of the TiF_6^{2-} coordination complex occurs under physiological conditions;
- as already explained above you need to take into account the pH dependency of the dissociation of the TiF_6^{2-} coordination complex in your read-across justification;

if complete dissociation of the coordination complex does occur under relevant conditions, you need to provide information on the rate at which this would occur in order to prove that the test animals are not significantly exposed to fluorotitanate species.

Based on the significant remaining uncertainties discussed above, your justification based on the similarity in chemical structure and in some of the physico-chemical, toxicological and ecotoxicological properties between simple fluoride salts and the registered substance has not yet established why the prediction is reliable for the human health and environmental endpoints for which the read across is claimed.

Therefore, ECHA considers that this read-across approach does not provide a reliable basis whereby the human health and environmental effects of the registered substance may be predicted from data for simple fluoride salts. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between simple fluoride salts and the registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health and environmental properties.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) Adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: *S. typhimurium* TA1535; TA1537 or TA97a or TA97; TA98; TA100; *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). This includes four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by *E.coli* WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.

You have provided a test from the year 1997 according to OECD TG 471 and GLP with an assigned reliability score of 2. The test used five different strains of *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and it did not include tests with strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with *S. typhimurium* TA102 or *E. coli WP2* uvrA or *E. coli* WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

In your comments on the draft decision, you specify that the study was conducted shortly before the update of the OECD TG 471 was published. You also point out that no induction of bacterial mutation was observed in any of the tested strains. However, as already explained in the decision, adaptations according to Annex XI, Section 1.1.2. require that the selected study provides an adequate and reliable coverage of the key parameters of the

corresponding recommended guideline. As already discussed above, the study did not include strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101), therefore the requirements of Annex XI, Section 1.1.2. are not fulfilled.

You also specify (i) that no genotoxicity was observed in an *in vitro* mammalian cell gene mutation (OECD TG 476) conducted with the registered substance, and (ii) that while the registered substance was found to induce micronuclei in cultured human peripheral blood lymphocytes (OECD TG 487), this effect was not confirmed in an *in vivo* micronucleus test (OECD TG 474). However, ECHA notes that (i) a negative *in vitro* mammalian cell gene mutation and (ii) *in vitro* or *in vivo* cytogenicity studies in mammalian cells cannot be used to adapt the information requirement for an *in vitro* gene mutation study in bacteria.

Finally, you point out that ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a, section R.7.7.6 (version 6.0, July 2017) which states that "*bacterial mutagenesis assays of inorganic metal compounds are frequently negative due to limited capacity for uptake of metal ions and/or the induction of large DNA deletions by metals in bacteria potentially leading to an increased death rate in mutants. The high prevalence of false negatives for metal compounds might suggest that mutagenesis assays with mammalian cells, as opposed to bacterial cells, would be the preferred starting point for testing for this class of Annex VII substances*". However, the cited ECHA Guidance does not specify that an *in vitro* gene mutation study in bacteria does not need to be conducted for metals.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the following read across information on the source substances:

1. A study record for an oral sub-acute repeated dose toxicity study (28-day) in rat with the source substance sodium fluoride (EC no 231-667-8). The test was conducted in 1990, performed similar to OECD 407, GLP compliant and assigned a reliability score of 1;
2. A study record for an oral combined repeated dose and carcinogenicity study in rat

with the source substance sodium fluoride (EC no 231-667-8). The study was conducted in 1990, was performed similar to EPA OPP 83-5, GLP compliant and assigned a reliability score of 1;

3. A study record for an oral (drinking water) 6 months NTP-study in rat with the source substance sodium fluoride (EC no 231-667-8). The study was conducted in 1990, non-guideline, GLP compliant and was assigned a reliability score of 2;
4. A study record for an oral (drinking water) combined repeated dose and carcinogenicity study (2 year NTP study) in rat, with the source substance sodium fluoride (EC no 231-667-8). The study was conducted in 1990, non-guideline, GLP compliant and was assigned a reliability score of 2;
5. A study record for an oral (drinking water) 6-months NTP study in mouse with the source substance sodium fluoride (EC no 231-667-8). The study was conducted in 1990, non-guideline, GLP compliant and was assigned a reliability score of 2;
6. A study record for an oral (drinking water) combined repeated dose and carcinogenicity study (2 year NTP study) in mouse with the source substance sodium fluoride (EC no 231-667-8). The study was conducted in 1990, non-guideline, GLP compliant and was assigned a reliability score of 2;

However, for the reasons given above in Appendix 1, section Grouping of substances and read-across approach of this decision, your adaptation of the information requirement is rejected. You have not provided a subchronic toxicity study (90-day) conducted on the registered substance or an adaptation which would address the information requirement for a repeated dose 90-day oral toxicity study.

In your comments on the draft decision, you state that the provided studies with sodium fluoride are fully reliable in accordance with current OECD guidelines. You specify that you intend to update the read-across justification and consider that the studies on sodium fluoride are thus adequate to fulfil the information requirement.

As explained in Appendix 1, section Grouping of substances and read-across approach of this decision, there are significant remaining uncertainties regarding your read-across hypothesis and therefore the read-across approach does not yet provide a reliable basis whereby the human health properties of the registered substance can be predicted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically,

- according to the Chemical Safety Report, risk management measures are in place to prevent exposure of humans via inhalation.
- the registered substance is a dust but no significant proportion (>1% on weight basis) of particles of inhalable size (MMAD < 50 µm).

Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method OECD TG 408, the rat is the preferred species. ECHA considers

this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: OECD TG 408) in rats.

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a three-generation reproductive toxicity study (no test guideline) with the source substance sodium fluoride (EC no 231-667-8). However, for the reasons given above in Appendix 1, section Grouping of substances and read-across approach of this decision, your adaptation of the information is rejected.

In your comments on the draft decision, you state that "*there are studies available generated with sodium fluoride that are fully reliable in accordance with current OECD guidelines*". You specify that you intend to update the read-across justification and consider that the studies on sodium fluoride are thus adequate to fulfil the information requirement. You also acknowledge that "*It is further anticipated that the new 28-days repeated dose study ("the bridging study", see above), will also include endpoints to address reproductive and developmental toxicity*".

As explained in Appendix 1, section Grouping of substances and read-across approach of this decision, there are significant remaining uncertainties regarding your read-across hypothesis and therefore the read-across approach does not yet provide a reliable basis whereby the human health properties of the registered substance can be predicted. ECHA also understands from your comments that you intend to conduct a study on a substance containing hexafluorotitanate that would be used to fulfil the information requirement.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats. ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:
- Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017."

4. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the following information on source substances:

1. A study record for an oral (drinking water) developmental toxicity study in rat with the source substance sodium fluoride (EC No 231-667-8). The study was conducted in 1996, similar to EPA OPPTS 870.3700 and GLP and was assigned a reliability score of 1;
2. A study record for a non-guideline oral (drinking water) developmental toxicity study in rat with the source substance sodium fluoride (EC No 231-667-8). The study was conducted in 2001, according to GLP and was assigned a reliability score of 2;
3. A study record for a non-guideline oral (drinking water) developmental toxicity study in rat with the source substance sodium fluoride (EC No 231-667-8). The study was

conducted in 1995, according to GLP and was assigned a reliability score of 2.

However, for the reasons given above in Appendix 1, section Grouping of substances and read-across approach of this decision, your adaptation of the information requirement is rejected.

In your comments on the draft decision, you state that "*there are studies available generated with sodium fluoride that are fully reliable in accordance with current OECD guidelines*". You specify that you intend to update the read-across justification and consider that the studies on sodium fluoride are thus adequate to fulfil the information requirement. You also acknowledge that "*It is further anticipated that the new 28-days repeated dose study ("the bridging study", see above), will also include endpoints to address developmental toxicity*".

As explained in Appendix 1, section Grouping of substances and read-across approach of this decision, there are significant remaining uncertainties regarding your read-across hypothesis and therefore the read-across approach does not yet provide a reliable basis whereby the human health properties of the registered substance can be predicted. ECHA also understands from your comments that you intend to conduct a 28-days repeated dose toxicity study on a substance containing hexafluorotitanate that would be used to fulfil the information requirement. However, ECHA emphasizes that a screening study for reproductive/developmental toxicity (OECD TG 421/422) does not provide equivalent information to a pre-natal developmental toxicity study (OECD TG 414) and therefore cannot be used to fulfil the information requirement for this endpoint.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

5. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for an OECD TG 201 used as Key study (Schlechtriem, 2012, GLP and reliability 2) for your registered substance. However, ECHA considers the study not reliable for the reasons set out below.

In your study summary you state that "*chemical analysis of fluoride in the fresh test medium at test start revealed a recovery of 67 - 441% of the nominal concentrations. Fluoride concentrations of the aged test medium at test end were 65 - 315% of the nominal fluoride concentrations. While the two highest concentrations remained stable and within 20% of the nominal concentrations, the remaining lower concentrations decreased from the nominal by more than 20%. Therefore the geometric mean of the measured concentrations was calculated in accordance with the OECD guidance document 23 (2000)*". In addition, you also state that the measured recovery of the lowest concentration was higher "*than the nominal value possibly due to a dilution error or error in test solution preparation*" and "*The chemical analysis of titanium in the fresh test medium at test start revealed a recovery of 90 - 101% of the nominal concentrations. Concentrations of the aged test medium at test end were 1 - 102% of the nominal titanium concentrations*". As a decrease of >20% of nominal titanium and fluoride concentrations was observed, you derived the effect values based on the geometric mean of measured concentrations (as specified in OECD GD 23).

According to the information reported by you, ECHA notes that there are significant dicrepancies between the nominal and measured exposure concentrations which have not been explained in the registration dossier.

In your comments on the draft decision, you explain that very low levels of titanium remained in solution at environmentally relevant pH while nearly all of the fluoride (> 65 % in algae medium) were recovered at test end and that this supports the hypothesis that the TiF_6^{2-} coordination complex fully dissociates. The lower recovery of fluoride in the algae study as compared to the other aquatic toxicity studies is attributed by you to the composition of the OECD algae medium, which leads to the complexation of some fluoride and its transformation to insoluble fluoride species that are lost from the test medium.

ECHA notes that you still did not justify why the mean measured fluoride concentration at 0.1 mg/L K_2TiF_6 (nominal) amounts to 373% of nominal concentrations and neither did you explain why your hypothesis as described above with loss of fluoride due to interaction with the OECD algae medium does not apply at this concentration. Also fluoride quantification is conducted after addition of TISAB buffer which contains a chelating agent and should therefore allow quantification of total fluoride in solution which contradicts your hypothesis that the low recovery of fluoride at certain concentrations results from the composition of the test medium. Consequently, ECHA concludes that you have not demonstrated that the analytical determination of exposure concentrations is reliable.

In addition to the deficiencies in the monitoring of exposure concentrations, ECHA notes that:

a. insufficient information on the study results (i.e. raw data in a tabular form) was provided to fully assess the reliability of this study and if it fulfils all validity criteria of OECD TG 201;
b. the spacing factor between test concentrations is not compliant as it is above the maximum value of 3.2. In you test study you use a factor of 10 with the nominal concentrations tested of 0.1, 1.0, 10, 100 mg/L. ECHA notes that this may have affected the precision of the effect value estimates.

Regarding point a., you state in your comments on the draft decision that the "*study report was finalised in 2014, and thus after the registration of dipotassium hexafluorotitanate*".

However, you have not provided additional information as part of your comments on the draft decision to allow ECHA to verify if the validity criteria of OECD TG 201 were fulfilled. Therefore the deficiency identified by ECHA in the draft decision remains.

Regarding point b., you specify that another focus of the study was to evaluate "*the fate of dipotassium hexafluorotitanate in the environmental medium over a range of concentrations*" which explains the wider spacing factor used in the study design. However, you consider that as "*the derived effect concentrations ErC10 and ErC50 of 1.31 and 10.82 mg/L dipotassium hexafluorotitanate are close to the tested concentrations of 1 and 10 mg/L so that a narrower spacing is not expected to make a significant difference*".

ECHA notes that in the absence of additional information on this study (i.e. raw data in a tabular form), it cannot verify to what extent this deviation from the requirement of OECD TG 201 may have impacted the determination of effect values. OECD TG 201 specifies that *"for the final definitive test at least five concentrations, arranged in a geometric series with a factor not exceeding 3.2, should be selected"*. Finally, ECHA reminds you that effect concentrations must be based on the measured values rather than nominal values unless the test concentrations are maintained within 20% of the measured initial concentrations throughout testing.

You have further sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing supporting study records for studies performed on freshwater and marine algae with the source substances Potassium fluoride or Fluoride (CAS No 7789-23-3) with data stemming from the EU RAR and ICD reports.

However, as explained above in Appendix 1, section Grouping of substances and read-across approach of this decision, your adaptation of the information cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Algae growth inhibition test, EU C.3./OECD TG 201).

6. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.
You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing as key study 2 study records for Daphnia magna reproduction test (secondary sources, no guideline followed reported and reliability 2) with the source substances Potassium Fluoride (CAS No 7789-23-3) and Sodium fluoride (EC no

231-667-8), using the EU RAR report (2001) and the ICD report from 1989 (based on Sloof *et al.,* 1988 work).

However, for the reasons given above in Appendix 1, section Grouping of substances and read-across approach of this decision, your adaptation of the information requirement cannot be accepted.

In your comments on the draft decision, you state that "*Available relevant studies of the long-term toxicity of sodium fluoride on aquatic invertebrates are in accordance with current OECD guidelines and reliable*". You specify that you intend to update the read-across justification and considers that the studies on sodium fluoride are thus adequate to fulfil the information requirement.

As explained in Appendix 1, section Grouping of substances and read-across approach of this decision, there are significant remaining uncertainties regarding your read-across hypothesis and therefore the read-across approach does not yet provide a reliable basis whereby the ecotoxicological properties of the registered substance can be predicted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

Note for your consideration for aquatic toxicity testing (sections 5. and 6.)

Due to the substance properties and as observed under Appendix 1 section 4 of the decision, you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s). You shall further consider and choose proper analytical methods and reporting when deciding on the study design and providing with the study results.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 05 April 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments. Based on the information provided in your comments and the dossier ECHA agrees that fish appears to be the least sensitive species and therefore the request for a Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.) was removed.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is 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 or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.