EUROPEAN CHEMICALS AGENCY

Helsinki, 05 May 2021

Addressees
Registrants of JS_Potassium_Iodide as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
03/04/2013

Registered substance subject to this decision ("the Substance")
Substance name: Potassium iodide
EC number: 231-659-4
CAS number: 7681-11-0

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***10 August 2023***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. / OECD TG 471)
2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: [EU C.3./OECD TG 201 // EU C.26./OECD TG 221])

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

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)
2. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490)
3. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested below (Annex VIII, Section 8.6.1.)
4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats
5. Activated sludge respiration inhibition testing (Annex VIII, Section 9.1.4.; test method: EU C.11/ OECD TG 209)

C. Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)
3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)
4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to IX of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

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

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

How to comply with your information requirements

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

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

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

Failure to comply

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

Authorised[1] under the authority of Christel Schilliger-Musset, Director of 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 on Reasons common to several requests

1. Assessment of your read-across approach under Annex XI, Section 1.5.

In your dossier you seek to adapt the following standard information requirements by applying read-across approaches in accordance with Annex XI, Section 1.5:

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.) Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)
- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

In your comments to the draft decision, you seek to adapt the following standard information requirement by applying read-across approaches in accordance with Annex XI, Section 1.5:

- Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1)
- Activated sludge respiration inhibition testing (Annex VIII, Section 9.1.4.)

Furthermore, in your comments to the draft decision, you also provide sources of information relating to analogue substances in support of a weight-of-evidence adaptation in accordance with Annex XI, Section 1.2 for the following information requirements:

- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your read-across approaches in general before assessing the specific standard information requirements in the following appendices.

According to Annex XI, Section 1.5., two conditions must be necessarily fulfilled to apply grouping and read-across. 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).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the substances. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

For the above-mentioned information requirements, you have provided studies conducted

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

with another substance than your Substance in order to comply with the REACH information requirements.

More specifically in your dossier for the repeated dose toxicity endpoint you have provided a series of literature references reporting studies which tested hydrogen iodide (EC number 233-109-9), and relying on the [redacted] from WHO ([redacted] 2009) on iodine and inorganic iodides.

You did not provide any documentation in your dossier as to why this information is relevant for your Substance.

In your comments on the draft decision, you propose a grouping and read-across approach for a grouping of "iodine and its compounds (including iodide and iodate)" for the following information requirements:

- Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1)
- Activated sludge respiration inhibition testing (Annex VIII, Section 9.1.4.)
- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

Note that the above source substances for the sub-chronic toxicity study (90-day) fall within the applicability domain of this grouping.

You provide the following reasoning for the grouping the substances: *"Iodine and its compounds (including iodide and iodate) have broadly been studied, resulting in numerous scientific publications. All Authorities reports (for example: BPR CAR, EFSA opinions, ANSES opinions) use those data regardless of the studied iodine form. These reports are validated [...] and that is the reason why these are considered to be compliant with regulatory requirements"*.

You have not provided as part of your comments:

- a well-founded hypothesis to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the category members;
- a read-across justification document in your comments on the draft decision or in an update to your registration;
- a summary of the information which you consider are to fulfil your information requirements.

In the absence of documentation of your hypothesis, ECHA is deprived from the possibility to verify that the properties of your Substance can be predicted from the data on the source substances.

Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

In spite of this critical deficiency, ECHA has nevertheless assessed the adequacy and reliability of the source studies under section C below.

2. Assessment of the weight of evidence adaptations under the requirements of Annex XI, section 1.2

In your comments on the draft decision, you have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You have not submitted any explanation why the sources of information provide sufficient weight of evidence for each of the relevant information requirement leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation. The specific ones are set out under the information requirement concerned in the Appendices below.

Reliability of the read-across adaptation

You provide sources of information relating to analogue substances in support of a weight-of-evidence adaptation for the following information requirements:

- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

However, the reliability of these sources of information is significantly affected by the deficiencies identified in section 1 above.

Appendix A: Reasons to request information required under Annex VII of REACH

1. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

Your dossier does not contain any *in vitro* study in bacteria. Instead you have provided an adaptation stating that "*chapter R.7a, the bacterial reverse mutation test is just the screening test to genotoxicity. At the tonnage band of 100-1000 tones per year, the genotoxicity assessment for the substance should be based on* in vitro *and* in vivo *mutagenicity test on mammalian. Existing both of the* in vitro *and* in vivo *mutagenicity tests on mammalian gave negative results. Thus this screening test is unnecessary.*"

ECHA understands from your statement that you argue that the *in vitro* gene mutation study in bacteria required under Annex VII is not necessary because other tests are available under other Annexes of REACH to identify the same property.

However, Article 12 of REACH requires explicitly registrants to fulfil cumulatively the information requirements set out in all the applicable Annexes of the Regulation. Therefore, fulfilling requirements at a higher Annex is not *per se* a justification to omit data required under a lower Annex, unless specified as such in column 2 of the respective Annex.

Therefore, the information requirement is not fulfilled.

In your comments on the draft decision you agreed to conduct this study.

Note also that ECHA discusses below the compliance of *"the in vitro and in vivo mutagenicity tests on mammalian [giving] negative results."*

2. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided one study for this endpoint in your dossier: a 7-day cell multiplication inhibition test in *Scenedesmus quadricauda* (green algae) on a source substance, sodium iodide (EC number 231-679-3): [redacted] 1980, [redacted]

Although you do not explicitly claim an adaptation, ECHA understands that the study was submitted in order to meet the required information by way of adaptation according to Annex XI, Section 1.1.2. This adaptation rule enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods.

We have assessed this information and identified the following issues:

A. For the reason explained in section 1 of the Appendix on reasons common to several requests), your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

B. In addition to the above reason, we have assessed the adequacy and reliability of the source study.

The adaptation rule in Annex XI, Section 1.1.2 imposes a number of cumulative conditions for an adaptation to be valid, in particular:

- Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), in this case OECD TG 201;
- Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3);
- Adequacy for the purpose of classification and labelling and/or risk assessment.

OECD TG 201 requires that the following conditions are met (among others):

- Suitable species of green algae specified in OECD TG are *Pseudokirchneriella subcapitata*, (formerly known as *Selenastrum capricornutum*), ATCC 22662, CCAP 278/4, 61.81 SAG and *Desmodesmus subspicatus* (formerly known as *Scenedesmus subspicatus*) 86.81 SAG. If other species are used, you must first confirm that exponential growth of the selected test alga can be maintained throughout the test period under the prevailing conditions.
- At least five concentrations, arranged in a geometric series with a factor not exceeding 3.2, should be tested, preferably covering the range causing 5 to 75% inhibition of algal growth rate.
- The test design should include three replicates at each test concentration with at least three control replicates.
- The performance criteria as set up in the test guideline must be met:
  (a) the biomass in the control cultures should have increased exponentially by a factor of at least 16 within the test period,
  (b) the mean coefficient of variation for section by section specific growth rates in the control cultures must not exceed 35% and
  (c) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures must not exceed 10%.
- The test solutions should be analysed to verify the initial concentrations and maintenance of the exposure concentrations during the test.

The provided study was not performed based on OECD TG 201. In particular the study is not acceptable for the following reasons:

- The study was conducted in the green algae species *Scenedesmus quadricauda,* not one of the suitable species specified in OECD TG 201; and you have not confirmed that exponential growth can be maintained throughout the test period.
- The concentrations tested are not reported.
- The number of replicates are not reported.
- Information to establish the performance criteria are met is not reported.
- There was no solution analysis.

Therefore, the information you provided does not fulfil the information requirement.

In your comments on the draft decision you agreed to conduct this study.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have provided in your dossier:

i. A key study published in 2004: "[redacted]";

ii. A supporting study: [redacted] (1976)

For the reason explained in section 1 of the Appendix on reasons common to several requests), your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected. In addition to this reason, we have assessed the adequacy and reliability of the source study i. and we identified the following issue:

To fulfil the information requirement, the study has to be an *in vitro* chromosomal aberration test or an *in vitro* micronucleus test, conducted in mammalian cells in accordance with OECD TG 473 or OECD TG 487, respectively[5]. The key parameters of these test guidelines include that, among others:

- Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation.
- At least 3 concentrations must be evaluated, in each test condition.
- The response for the concurrent negative control must be inside the historical control range of the laboratory.
- Data on the cytotoxicity and the frequency of micronuclei for the treated and control cultures must be reported.

The reported data for the key study you have provided does not include:

- two separate test conditions as it was only conducted in the absence of metabolic activation;
- the evaluation of at least 3 concentrations in the presence of metabolic activation.
- a true negative control;
- A report of data on the cytotoxicity and/or the frequency of micronuclei for the treated and control cultures.

The information provided does not cover some of the key parameters required by the OECD TG 487 or by the OECD TG 473.

Therefore, the information you provided do not fulfil the information requirement.

In your comments on the draft decision you agreed to conduct this study.

Information on the study design

To fulfil the information requirement for the Substance, both *in vitro* cytogenicity study in mammalian cells (OECD TG 473) and *in vitro* micronucleus study (OECD TG 487) are considered suitable.

[5] ECHA Guidance R.7a, Table R.7.7-2, p.557

2. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

For Annex VIII, Section 8.4.3., you have provided two studies in your dossier:

i. a study published in 2004, [redacted];

ii. a study published in 1980, [redacted]

For the reason explained in section 1 of the Appendix on reasons common to several requests), your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected. In addition to this reason, we have assessed the adequacy and reliability of the source studies and we identified the following issue:

To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490. The key parameter(s) of these test guidelines include:

- Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation (see eg. paragraph 38 of OECD TG 476).
- At least 4 concentrations must be evaluated, in each test condition.
- The response for the concurrent negative control must be inside the historical control range of the laboratory.
- Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

However, the reported data for the studies you have provided do not include:

- two separate test conditions, as both studies i. and ii were only conducted in the absence of metabolic activation ;
- the evaluation of at least 4 concentrations in the presence of metabolic activation for both studies i. and ii;
- a negative control with a response inside the historical control range of the laboratory;
- data on the cytotoxicity and the mutation frequency for the treated and control cultures.

The information provided does not cover key parameter(s) required by the OECD TG 476 or by the OECD TG 490. Therefore, the information you provided do not fulfil the information requirement.

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or the *in vitro* micronucleus study provide a negative result.

Information on the study design

To fulfil the information requirement for the Substance, both the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) and the thymidine kinase gene (OECD TG 490) are considered suitable.

3. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

Because you have not provided any study for a 28-day repeated dose toxicity study, either in the form of a robust study summary nor an adaptation, according to Column 2 of Annex VIII, Section 8.6.1. or according to Annex XI, the absence of information does not fulfil the information requirement.

Column 2 of Annex VIII, Section 8.6.1. provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

In your comments on the draft decision you proposed to address this endpoints "*through a read-across strategy on iodine (EC number 231-442-4)*" according to the Annex XI, section 1.5. Your adaptation is rejected for the reasons described in section 1 of the Appendix on Reasons common to several requests.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Section C.1). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted.

Because you must still comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

4. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

Because you have not provided any information for a screening for reproductive/developmental toxicity study, either in the form of a robust study summary nor in the form of an adaptation, according to Column 2 of Annex VIII, Section 8.6.1. or Annex XI, the absence of information does not fulfil the information requirement.

In your comments on the draft decision you proposed to address this endpoints "*through a read-across strategy on iodine (EC number 231-442-4)*" according to the Annex XI, section 1.5. Your adaptation is rejected as described in the Appendix on Reasons common to several requests.

Information on study design

According to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422, the study must be performed in rats with oral[6] administration of the Substance.

[6] ECHA Guidance R.7a, Section R.7.6.2.3.2.

5. Activated sludge respiration inhibition testing

Activated sludge respiration inhibition testing is a standard information requirement in Annex VIII to REACH.

You provide the following justification for waiving this study: '*Testing for this endpoint is not considered to be necessary as the CSR does not indicate a risk to aquatic organisms when considering the environmental risk mitigation measures. Furthermore, iodine is a natural ubiquitously present essential trace element. It is highly mobile and cycles through all environmental compartments via a range of mechanisms including disproportionation to different oxidation states by abiotic and biotic mechanisms coupled with binding to organic matrices and biological organisms. These act to significantly mediate the aquatic toxicity when compared to laboratory conditions.*'

Although you do not explicitly claim an adaptation, ECHA understands that the information provided was submitted by analogy to the specific rule for adaptation of column 2 of Annex IX, section 9.1 regarding long-term aquatic toxicity studies to be proposed by the registrant if the outcome of the CSR indicats the need to investigate further the effects on aquatic organisms.

To be compliant under REACH, a column 2 adaptation must apply to the relevant column 1 standard information requirement.

Your statement is not a valid column 2 adaptation under either the specific rules of column 2, Annex VIII, section 9.1.4..

Therefore, the information you provided do not fulfil the information requirement.

In your comments on the draft decision you proposed to address this endpoints "*through a read-across strategy on iodine (EC number 231-442-4)*" according to the Annex XI, section 1.5. Your adaptation is rejected for the reasons described in section 1 of the Appendix on Reasons common to several requests.

Appendix C: Reasons to request information required under Annex IX of REACH

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

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided a key study and supporting information for this endpoint in your dossier:

i. A key study assessing the developmental toxicity and psychotoxicity of potassium iodide in rats ([redacted], 1984, no test guideline and non-GLP).
ii. A supporting study (reliability 3) from the [redacted] (WHO, 2009, [redacted]) on iodine and inorganic iodides.
iii. A summary of human data and estimation of TDI, for the analogue substance EC number 233-109-9 (hydrogen iodide), and relying on several sources of handbook or secondary literature papers (from 1988 to 2009), including the supporting study under i. below on rats.

Although you do not explicitly claim an adaptation, ECHA understands that the information submitted was submitted in order to meet the required information by way of adaptation under Annex XI, Section 1.1.2. This adaptation rule enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods.

In addition, in your comments on the draft decision you provided an adaptation under Annex XI, Section 1.2. of REACH (weight of evidence) with the following additional supporting information:

iv. further references to publications from ANSES (opinion from 2018), from EFSA (2009, 7(9): 1214), from SCF (2002), regarding some effects of iodine.

We have assessed this information and identified the following issues:

a) Adaptation according to Annex XI, Section 1.1.2 in the dossier.

For the reason explained in section 1 of the Appendix on reasons common to several requests), your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected. In addition to this reason, we have assessed the adequacy and reliability of the source studies and we identified the following issues:

A. Adequacy and reliability of the key study i.
To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The key parameter(s) of this test guideline include, among others:
- at least 10 female and 10 male animals should be used at each dose level (including control group);
- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study;
- clinical observations, ophthalmological examination, sensory reactivity to various stimuli and functional observations of the animals, recording of body weight, hematology, clinical biochemistry, and pathology of sexual (male and female) organs, Full detailed gross necropsy and subsequent histopathology of both types tissues/ other.

- The study i. you have provided does not contain the required information regarding the number of animals per sex per test dose group. The study does not fulfil the criterion set in OECD TG 408.
- The study does not have the required exposure duration of 90 days of the parent animals, as required in OECD TG 408, because you indicated an exposure duration of 71 days for the pregnant females, and an exposure duration of 28 days for the males.
- The study you have provided was not performed according to the criteria of the OECD TG 408, since no key parameters are reported, e.g. the examination of the animals for gross necropsy of organs and tissues, including thyroid, sexual organs and observations of alterations (variations and malformations) were not performed or reported.

B. Adequacy and reliability of the summary of human data iii.
The adaptation rule in Annex XI, Section 1.1.2 imposes a number of cumulative conditions for an adaptation to be valid, in particular:
1. Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
2. Adequate and reliable documentation of the study is provided;
3. Adequacy for the purpose of classification and labelling and/or risk assessment.

However, the provided publications do not cover the conditions described above.
1. None of the pieces of information address, alone or together, the key conditions of the OECD TG 408 discussed above: no doses were described, no examinations were reported to cover the key parameters to be assessing during such repeated dose toxicity study.
2. You have not reported the study details in a form of a robust study summary, as required by Article 10(a)(vii) and Article 3(28), and merely listed the titles of each secondary source publication. This is depriving ECHA from being able to make an independent assessment and to conclude on the results of the study.
3. Based on the above, the provided information cannot be considered to be adequate for classification and labelling and/or risk assessment.

b) Adaptation according to Annex XI, Section 1.2 (weight-of-evidence) in your comments

To fulfil the information requirement, normally a study performed according to OECD TG 408 must be provided. OECD TG 408 requires the study to investigate systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system.

The sources of information ii., iii. and iv. do not provide relevant information as they do not inform on effects in non-pregnant and adult male and femal rats on the various physiological systems.

The source of information i. provides relevant information, but there are deficiencies affecting its reliability, as described above.

Consequently, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 408 study. Therefore, your adaptation

is rejected and the information requirement is not fulfilled.

2. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have provided a key study and two supporting studies for this endpoint in your dossier:

i. A key study assessing the developmental toxicity and psychotoxicity of potassium iodide in rats ([redacted], 1984.
ii. a supporting study from the [redacted] (WHO, 2009, [redacted]) on iodine and inorganic iodides.
iii. A supporting study relying on a 1965 publication from [redacted].

Although you do not explicitly claim an adaptation, ECHA understands that the information provided under ii. and iii. was submitted in order to meet the required information by way of adaptation under Annex XI, Section 1.1.2. This adaptation rule enables registrants to claim that the data from experiments not carried out according to GLP or to the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods.

In addition, in your comments on the draft decision you provided an adaptation under Annex XI, Section 1.2. of REACH (weight of evidence) with the following additional supporting information:

iv. further references to "more recently published" literature data from [redacted] (2015), from [redacted] (1995) and from [redacted] (2017), regarding some effects of iodine.

We have have assessed this information and identified the following issues:

a) Adaptation according to Annex XI, Section 1.1.2 in the dossier

A. Adequacy and reliability of the key study i.
In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the study has to meet the requirements of OECD TG 414. The key parameter(s) of this test guideline include amonth others:

- testing of at least three dose levels and a concurrent control,
- highest dose level should aim to induce some developmental and/or maternal toxicity
- 20 female rats (and 16 female rabbit) animals with implantation sites for each test and control group,
- examination of the dams for weight and histopathology of the thyroid gland, gravid uterus weight, uterine content, body weight of the dams, clinical signs of the dams,
- examination of the foetuses for sex and body weight/external, skeletal and soft tissue alterations (variations and malformations)/number of resorptions.

- You have referred to one dose level in describing the test designing while you seem to imply in the concluding summary that more doses have been tested. Because the information is not clear the study does not fulfil the criterion of at least three dose levels.
- The highest dose level in the study did not induce any developmental and/or maternal toxicity and you have not shown that the aim was to induce toxicity. Therefore, the dose level selection was too low, and the study does not fulfil the criterion.

- You have not provided the number of pregnant females for each test group. Therefore ECHA could not assess whether the statistical power of the information provided is sufficient and whether the criterion of pregnant females for each test group was fulfilled.
- In the study you not have provided any detailed information regarding the weight and histopathology, e.g. the thyroid gland, in the dams, gravid uterus weight has not been measured. In addition the uterine content has not been examined nor have the body weights or clinical signs of the dam.
- Since the pups have been also administered the test material until day 90, you have not provided any information related to the examination of the foetuses, as required in OECD TG 414 such as sex, body weight or external, skeletal and soft tissue alterations. There is also no information on number of resorptions or dead foetuses.

B. Adequacy and reliability of the supporting studies ii. and iii.

An adaptation under Annex XI, Section 1.1.2 enables registrants to claim that the data from experiments not carried out according to GLP or to the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods, provided that a number of cumulative conditions for an adaptation to be valid are met, in particular:

1. Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
2. Adequate and reliable documentation of the study is provided;
3. Adequacy for the purpose of classification and labelling and/or risk assessment.

However, the provided publications do not cover the conditions described above.

1. No examinations were reported to cover the key parameters to be assessing during such developmental toxicity study *"Embryotoxic / teratogenic effects:not examined"*.
2. You have not reported the study details in a form of a robust study summary, as required by Article 10(a)(vii) and Article 3(28). This is depriving ECHA from being able to make an independent assessment and to conclude on the results of the study.
3. Based on the above, the provided information cannot be considered to be adequate for classification and labelling and/or risk assessment.

b) Adaptation according to Annex XI, Section 1.2 (weight-of-evidence) in your comments.

To fulfil the information requirement, normally a study performed according to OECD TG 414 must be provided. OECD TG 414 requires the study to investigate 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy. These include information after prenatal exposure on embryonic/foetal survival (number of live foetuses; number of resorptions and dead foetuses, post-implantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal), but also information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.
The sources of information ii., iii. and iv. are not relevant as they do not inform on detailed observations for structural malformations or variations nor on the embryonic/foetal survival.

The source of information i. provides relevant information, but there are siginficant deficiencies affecting its reliability, as described above.

Therefore it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 414 study. Consequently, your adaptation is rejected and the information requirement is not fulfilled.

3. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex IX to the REACH Regulation.

You provide the following justification for waiving this study, which we have taken to be an adaptation according to Annex IX, Section 9.1, Column 2:
'*Testing for this endpoint is not considered to be necessary as the CSR does not indicate a risk to aquatic organisms when considering the environmental risk mitigation measures. Furthermore, iodine is a natural ubiquitously present essential trace element. It is highly mobile and cycles through all environmental compartments via a range of mechanisms including disproportionation to different oxidation states by abiotic and biotic mechanisms coupled with binding to organic matrices and biological organisms. These act to significantly mediate the aquatic toxicity when compared to laboratory conditions.*'

We have assessed this information and identified the following issues:

As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity to study on aquatic invertebrates must be performed unless the Chemical Safety Assessment demonstrates that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1). The justification must be documented in the Chemical Safety Assessment.

In particular, the Chemical Safety Assessment must take into account the following elements to support that long-term toxicity testing is not required:

- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information.

The substance meets the criteria to be classified as hazardous (on the basis of the 48-hour Daphnia EC50 of 7.5mg/l study in your registration and because this inorganic substance is not readily biodegradable) but you have not reported the exposure assessment. In your CSR you specify parameters for local releases to the environment for the different stages in the life cycle of the substance. You also calculate PNECs for freshwater and freshwater sediment.

To reach the conclusion that the risks are controlled, we understand that you rely on the argument that iodine is natural essential trace element that is ubiquitous in the environment.

You did not demonstrate that the substance released in the various life cycle stages does not cause adverse effects, i.e. either that (a) PECs are below the PNECs or (b) the release would not cause an adverse impact taking into account the naturally-occurring background levels.

Therefore your Chemical Safety Assessment does not demonstrate that the risks of the Substance are adequately controlled. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1., Column 2.

Therefore, the information you provided do not fulfil the information requirement.

In your comments on the draft decision you agreed to conduct this study.

4. Long-term toxicity testing on fish

Long-term toxicity testing on fish is a standard information requirement in Annex IX to REACH.

You provide the following justification for waiving this study, which we have taken to be an adaptation according to Annex IX, Section 9.1, Column 2:
'*Testing for this endpoint is not considered to be necessary as the CSR does not indicate a risk to aquatic organisms when considering the environmental risk mitigation measures. Furthermore, iodine is a natural ubiquitously present essential trace element. It is highly mobile and cycles through all environmental compartments via a range of mechanisms including disproportionation to different oxidation states by abiotic and biotic mechanisms coupled with binding to organic matrices and biological organisms. These act to significantly mediate the aquatic toxicity when compared to laboratory conditions.*'

We have assessed this information and identified the following issues:

As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity testing on fish must be performed unless the Chemical Safety Assessment demonstrates that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1). The justification must be documented in the Chemical Safety Assessment.

In particular, the Chemical Safety Assessment must take into account the following elements to support that long-term toxicity testing is not required:

- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information.

The substance meets the criteria to be classified as hazardous (on the basis of the 48-hour Daphnia EC50 of 7.5mg/l study in your registration and because this inorganic substance is not readily biodegradable) but you haven't reported the exposure assessment. In your CSR you specify parameters for local releases to the environment for the different stages in the life cycle of the substance. You also calculate PNECs for freshwater and freshwater sediment.

To reach the conclusion that the risks are controlled, we understand that you rely on the argument that iodine is natural essential trace element that is ubiquitous in the environment.

You did not demonstrate that the substance released in the various life cycle stages does not cause adverse effects, i.e. either that (a) PECs are below the PNECs or (b) the release would not cause an adverse impact taking into account the naturally-occurring background levels.

Therefore your Chemical Safety Assessment does not demonstrate that the risks of the Substance are adequately controlled. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1., Column 2.

Therefore, the information you provided do not fulfil the information requirement.

In your comments on the draft decision you agreed to conduct this study.

Appendix D: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[7].

B. Test material

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

1. Selection of the Test material(s)

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

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

Appendix E: General recommendations when conducting and reporting new tests for REACH purposes

A. Testing strategy for aquatic toxicity testing

You are advised to consult ECHA Guidance R.7b, (Section R.7.8.5) which describes the Integrated Testing Strategy, to determine the sequence of aquatic toxicity tests and testing needed.

Appendix F: Procedure

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

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

The compliance check was initiated on 18 June 2019.

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

ECHA took into account your comments and did not amend the requests.

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

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

Appendix G: List of references - ECHA Guidance[9] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[10]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[11]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[12]

[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[12] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix H: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

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

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