~~Confidential~~

Helsinki, 24 November 2022

Addressees
Registrants of JS Sb metal-i2a as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
15/06/2021

Registered substance subject to this decision ("the Substance")
Substance name: Antimony
EC/List number: 231-146-5

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 ***03 March 2025***.

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

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

1. In vivo mammalian alkaline comet assay also requested below (triggered by Annex VIII, Section 8.4., column 2)

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

2. In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in mice, inhalation route, on the following tissues: liver and lung.

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

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

In the requests above, the same study has been requested under different Annexes. This is because some information requirements may be triggered at lower tonnage band. In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band. For the highest tonnage band, the reasons why the standard information requirement is not met and the specification of the study design are provided. Only one study is to be conducted; all registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the others under Article 53 of REACH.

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

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

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

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

Appendix 1: Reasons for the decision

Contents

Reasons related to the information under Annex VIII of REACH

1. In vivo mammalian alkaline comet assay

1 Appropriate in vivo mutagenicity studies must be considered under Annex VIII, Section 8.4., Column 2 in case of a positive result in any of the in vitro genotoxicity studies under Annex VII or VIII to REACH.

1.1. Triggering of an in vivo genotoxicity study

2 Your dossier contains positive results for the in vitro cytogenicity test (2021) which raise the concern for chromosomal aberrations.

3 Therefore an appropriate in vivo follow up genetic toxicity study is necessary to address the concern(s) identified in vitro.

1.2. Information provided to fufill the information requirement

4 The description of the information provided, the assessment of this information, the test selection and the specification of the study design are described in request 2.

Reasons related to the information under Annex IX of REACH

2. In vivo mammalian alkaline comet assay

5 Under Annex IX, Section 8.4, Column 2, the information requirement for an appropriate in vivo somatic cell genotoxicity study is triggered if 1) there is a positive result in any of the in vitro genotoxicity studies in Annex VII or VIII and 2) there are no appropriate results already available from an in vivo study.

2.1. Triggering of an in vivo genotoxicity study

6 In relation to the first condition, your dossier contains positive results for the in vitro micronucleus test (2021) which raise the concern for chromosomal aberrations. In relation to the second condition, as explained in detail below, there is no appropriate result from an in vivo study.

7 Therefore an appropriate in vivo somatic cell genotoxicity study is necessary to address the concern(s) identified in vitro.

2.2. Information provided to fufill the information requirement

8 You have adapted this information by referring to a weight of evidence under Annex XI, Section 1.2. In support of your weight of evidence adaptation you provided the following sources of information in the form of in vivo somatic genotoxicity study records with analogue substances:

(i) two NTP 1-year micronucleus studies (2017) via inhalation in mouse and rat with the analogue Antimony trioxide (ATO) EC 215-175-0
(ii) two micronucleus studies, single and repeated dose (1998, publication) via oral route in mouse with the analogue substance ATO
(iii) a micronucleus study in bone marrow (2005/6) via oral route in rat with the analogue Substance ATO
(iv) a 21-day erythrocyte micronucleus test in bone marrow (2007, publication) via oral route in rat with the analogue Substance ATO
(v) a 21-day bone marrow chromosome aberration test, (2007, publication) via oral route in rat with the analoge Substance ATO
(vi) a bone marrow chromosome aberration test (1992, publication) via oral route in mouse with the analogue Substance ATO
(vii) a bone marrow chromosome aberration test (1993, publication) via oral route in mouse with the analogue Substance ATO
(viii) a bone marrow chromosome aberration test in bone marrow (2005/6) via oral route in rat with the analogue ATO
(ix) two NTP 1-year comet assay studies (2017) via inhalation in mouse and rat lung with the analogue Substance ATO
(x) a UDS study (1998, publication) in rat via oral route with the analogue Substance ATO
(xi) a SCE study (1997, publication) in human lymphocytes with the analogues Substance antimony trichloride (ATC, EC 233-047-2)

9 Based on the presented sources of information, you argue that the data provides sufficient evidence to assess the genotoxicity of Sb substances and that substances releasing Sb^{3+} are not genotoxic in vivo.

10 Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

11 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

12 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 on the corresponding information requirement.

13 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 8.4., column 2 includes similar information that is produced by an in vivo chromosomal aberration tests (OECD TG 475) or an in vivo micronucleus tests (OECD TG 474) or study to detect DNA strand breaks (OECD TG 489). These OECD TGs require to investigate the following key elements:

- Detection and quantification of cytotoxicity and the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei or DNA strand breaks in mammals (*in vivo*).

14 The in vivo UDS study (xi) and in vivo SCE study (xii) are not in vivo cytogenicity tests and do no inform on the above key elements. So this information cannot contribute to the weight of evidence for this information requirement.

15 The sources of information (i) to (ix) may provide relevant information on detection and quantification of chromosomal aberrations in cultured mammalian cells.

16 However, the reliability of these sources of information is significantly affected by the following deficiency:

2.2.1. The proposed read-across approach does not allow a reliable conclusion on the properties of the Substance

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

18 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

2.2.1.1. Scope of the grouping of substances (category)

19 You provide a read-across justification document in IUCLID Section 13.

20 For the purpose of this decision, the following abbreviations are used for the category members:

21 <u>"Metallic antimony":</u>

- Sb – powder, CAS RN 7440-36-0 (EC No. 231-146-5)
- Sb- massive, CAS RN 7440-36-0 (EC No. 695-029-4)

22 Trivalent antimony substances:

- ATO: diantimony trioxide, CAS RN 1309-64-4 (EC No. 215-175-0)
- ATS: antimony sulfide, CAS RN 1345-04-6 (EC No. 215-713-4)
- ATEG: antimony tris(ethylene glycolate), CAS RN 29736-75-2 (EC No. 249-820-2)
- ATC: antimony trichloride, CAS RN 10025-91-9 (EC No. 233-047-2)

23 Pentavelent antimony substances:

- SHHA: Sodium hexahydroxoantimonate, CAS RN 33908-66-6 (EC No. 251-735-0)
- SAA: Sodium antimonate, CAS RN 15432-85-6 (EC No. 239-444-7)
- APC: Antimony pentachloride, CAS RN 7647-18-9 (EC No. 231-601-8)
- APO: Antimony pentoxide, CAS RN 1314-60-9 (EC No. 215-237-7)
- PHHA: Potassium hexahydroxoantimonate, CAS RN 12208-13-8 (EC No. 235-387-7)

24 You justify the grouping of the substances as:

- "Sb 3+ or 5+ will exhibit strong electrophilic characteristics, and be taken up as the (oxyan)ion after release from the parent compound due to hydrolysis of ionic bonds" and "Considering the specificity of interactions between a chemical and a cell, the differences in valence/ionic species may need to be considered for the purpose of read-across for genotoxicity evidence";
- "the moiety (functional group) of each Sb substance that will normally influence the physico-chemical properties, and the bio-availability of the substance" and "The functional groups will dictate the ease with which Sb oxyanions are released from a substance and made available for systemic uptake". You conclude that "The difference in moieties can be omitted for the purpose of read-across for genotoxicity evidence".
- "the impurity profile is relatively comparable across the various Sb substances, and that there is no reason to discriminate between these on the basis of (im)purity for purposes of read-across for genotoxicity evidence".
- "The differences in physical form and particle sizes can be omitted for the purpose of read-across of genotoxicity evidence".
- "the genotoxicity data available on the Sb substances reveal a general trend of no (in vivo) genotoxicity. Mechanistic information indicates that the in vitro genotoxicity observed in some cases are most likely the result of indirect mechanisms, which differ between Sb 3+ and Sb 5+ substances. Whereas Sb 3+ substances appear to induce oxidative stress or interfere with DNA repair processes, Sb 5+ substances are of lower potency and refractile to binding to DNA".

25 In relation to the category, you state "As genotoxicity information is available from more than one source substance, and used for more than one target substance, the read-across approach applied to fill in genotoxicity data gaps for Sb 3+ and 5+ substances is a category (as opposed to analogue) or group one". You subdivide the category based on water solubility and bio-elution tests and you conclude that Sb metal, all Sb^{3+} substances and and Sb^{5+} pentoxide have similar properties (being practically insoluble) which justify the prediction. ECHA understands that this is the applicability domain the grouping and will assess your predictions on this basis.

26 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects as well as similar degradation products by a potential reductive cleavage. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

27 We have identified the following issues with the prediction of toxicological properties:

2.2.1.2. Missing supporting information on the formation of common compound

28 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

29 Supporting information must include toxicokinetic information on the formation of the common compound, bridging studies to compare properties between the Substance and the category members.

30 As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s). In this context, information characterising the rate and extent of the (bio)transformation of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common (bio)transformation product and to assess the impact of the exposure to the parent compounds.

31 In your justification document, you refer to recent aqueous solubility data and in vitro bioelution assays conducted using artificial gastric fluid for your antimony substances ([redacted], 2019). The bioaccessibility data from the in vitro bioelution assays show that, for the group of practically insoluble antimony substances, it is antimony metal powder that may be expected to have one of the highest 'oral' bioaccessibility. You also refer to a draft report [redacted], 2017 which indicates that as a generalization uptake efficiency is <1%. However, differences in absorption were observed for some substances in the category (for example ATO versus ATC). The authors consider that differences in the solublity and the counter ion of the antimony compound impacts absorption in vivo.

32 Your dossier does not include toxicokinetic information on the formation of the common compound or bridging studies to compare properties between the Substance and the category members.

33 ECHA considers that the in vitro bioaccessibility data does not provide information on systemic absorption and bioavailability. Furthermore, there is indication available showing that the counterion may impact absorption in vivo. Therefore, it cannot currently be assessed whether the in vitro bioaccessibility results provide the basis for predicting in vivo genotoxicity. Further information would be needed to confirm the relevance of the in vitro bioaccessibility results for predicting in vivo toxicological properties following the oral route of exposure. Such information to allow comparison between the substances could include information from in vivo toxicokinetics and information on the toxicodynamic properties of the substances within the group. In the absence of this information, it is not possible to translate bioaccessibility into in vivo bioavailability which is of interest to justify the read-across predictions. Therefore, you have not addressed whether differences in absorption impact your read across hypothesis.

34 Furthermore, you have no bridging studies available in your dossier addressing the same type of mutagenicity. Hence, a comparison is not possible.

35 Therefore, you have not provided sufficient supporting information to scientifically justify your read-across hypothesis.

2.2.1.3. Data density

36 Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances".

37 According to the Guidance on IRs and CSA, Section R.6.2.1.5., one of the factors in determining the robustness of a category is the density and distribution of the available data across the category. To identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available.

38 You have provided in vivo cytogenicity studies for a single category member (ATO). Based on these studies you claim that there is a trend of lack of in vivo genotoxicty within the category.

39 Information for one category member is not sufficient to establish a trend across the category consisting of 7 substances. Therefore, the information provided is not sufficient to conclude that the toxicological property under investigation is likely to follow a regular pattern.

2.2.1.4. Adequacy and reliability of studies on the category member

40 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TGs 474, 475 or 489. Therefore, the following specifications must be met:

41 The study must qualify as "adequate data from an in vivo cytogenicity test". The in vivo study must be either a micronucleus test or a chromosomal aberration test, performed according to OECD TG 474, 475 or 489[2]. The key parameters of these test guidelines include:

a) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that is tolerated without evidence of toxicity (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia). The highest dose can also be a dose that produces toxicity in the bone marrow (e.g. a reduction in the proportion of immature erythrocytes among total erythrocytes in the bone marrow or peripheral blood).

However, in all the *in vivo* chromosomal aberration and *in vivo* micronucleus studies listed above (studies i. to ix.), this key parameter is not reported.

b) It is not appropriate to perform the test if there is evidence that the test substance, or a relevant metabolite, will not reach the target tissue.

However, in all *in vivo* chromosomal aberration and *in vivo* micronucleus studies listed above (studies i. to ix.), it has not been demonstrated that target tissue exposure to the test substance has occured.

c) At least 200 metaphases must be analysed for each animal for structural chromosomal aberrations including and excluding gaps (OECD TG 475).

However, in the *in vivo* chromosomal aberrations studies vi., vii., viii. and ix., only

[2] ECHA Guidance R.7a, Table R.7.7–3, p.558

100 metaphases were analysed and therefore this key parameter was not met.

d) The proportion of immature among total (immature + mature) erythrocytes must be determined for each animal (by counting a total of at least 500 erythrocytes for bone marrow and 2000 erythrocytes for peripheral blood) (OECD TG 474).

However, in the *in vivo* micronucleus studies studies i., ii., iii., and iv. listed above, you did not count a total of at least 500 erythrocytes for bone marrow and 2000 erythrocytes for peripheral blood.

e) At least 4000 immature erythrocytes per animal must be scored for the incidence of micronucleated immature erythrocytes (OECD TG 474).

However, in the *in vivo* micronucleus studies i., ii., iii. and iv. listed above, only 1000 cells were score for micronuclei.

f) The proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes must be reported for each group of animals (OECD TG 474).

However, in the *in vivo* micronucleus studies i., ii., iii. listed above, you did not report this proportion for each group of animals.

g) The study includes a positive control group and historical negative/positive control data. The study must include at least one indicator of cytotoxicity (e.g., inflammation, cell infiltration, apoptotic or necrotic changes) when increases in DNA migration are observed (OECD TG 489);

However, in study ix. no positive control group and no historical control data was reported. No cytotoxicity measurements are provided.

42 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TGs.

2.2.1.5. Conclusion on the read-across approach

43 For the reasons above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). all the sources of information are vitiated by significant deficiencies as they breach the conditions set out in Annex XI, Section 1.5.

2.2.2. Conclusions on the weight of evidence and whether the data fulfil the information requriment

44 In summary, the sources of information (i.) to (ix.) provide limited relevant information on detection and quantification of cytotoxicity and the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei in cultured mammalian cells (in vitro) or or DNA strand breaks in mammals (in vivo). However, for the reasons explained in Section 2.2.1., these sources of information have significant reliability issues and cannot contribute to the conclusion on the information requirement for in vivo genotoxicity.

45 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for in vivo genotoxicity. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

46 In its proposals for amendment, one of the Member State Competent Authorities (MSCAs) pointed at recent decisions taken under Article 46 REACH (SEv decisions) regarding further information on the Substance and the analogue Substance ATO. It mentioned that the information to be generated may further substantiate an adaptation based on grouping and read-across and therefore information shall not be requested in this compliance check decision before the conclusion of the substance evaluation processes.

47 However, currently there is a data gap in your registration, as there is no adequate in vivo information to follow-up the positive result available from a in vitro micronucleus study. Consequently, this decision requests information needed to bring the registration into compliance with the relevant information requirement. As neither of the SEv decisions already requests the standard information for the Substance, and it is uncertain whether the information to be generated may substantiate an adaptation, ECHA has no option but to request you to submit the information required under REACH.

2.3. Test selection

48 According to the Guidance on IRs and CSA, Section R.7.7.6.3., the mammalian erythrocyte micronucleus test ("MN test", OECD TG 474) or the mammalian bone marrow chromosomal aberration test ("CA test", OECD TG 475) are suitable to follow up a positive in vitro result on chromosomal aberration if the Substance or its metabolite(s) will reach the target tissue. Alternatively, the in vivo mammalian alkaline comet assay ("comet assay", OECD TG 489) is a suitable test to be performed.A proposal for amendment (PfA) was submitted by one of the Member States Competent Authorities (MSCAs) to request only the comet assay, instead of giving the choice between three tests.

49 Based on the information provided in the dossier, the genotoxic effect observed in the in vitro test(s) is observed with and without metabolic activation. The ability to induce micronuclei in the absence of metabolic activation gives rise to a concern that the Substance will be mutagenic at the site of contact. In the in vivo follow up study, the potential effect of the parent (non-metabolised) substance on target tissue(s) can be detected in the comet assay, as site of contact tissues are analysed in this assay. On the contrary, the two other in vivo tests, i.e. OECD TG 474 and 475, may not detect the effect of the parent substance as exposure of the bone marrow (i.e. the target organ of these tests) to the Substance is uncertain, and likely to be much lower than exposure of lung tissues at the site of contact.

50 Therefore, the comet assay is the most appropriate follow up test for the Substance.

51 Moreover, it is recommended that a micronucleus test (OECD TG 474) is combined with the comet assay.

2.4. Specification of the study design

2.4.1. Species

52 Regarding the performance of the comet assay, according to the test method OECD TG 489 rats are the preferred species. Other rodent species can be used if scientifically justified (OECD TG 489, paragraph 23). For the reasons specified below, considering the PfA submitted by one of the MSCAs, you should perform the study in mice.

53 After inhalation exposure to the analogue substance Antimony trioxide there was clear evidence of carcinogenicity in mice for lung tumours (NTP Technical Report [redacted]), however there was not a clear evidence of carcinogenicity in rats. It is possible that the carcinogenicity of antimony trioxide in mice is mediated by a genotoxic mechanism, as most

carcinogens, likely through the formation of antimony ions, which would also be produced by antimony metal (the counter ion is not of toxicological concern). In view of this common mechanism of production of antimony ions, there is a concern that mice would be more sensitive to the genotoxic effects of Antimony metal than rats, on the basis of the results of the carcinogenicity studies. Thus the study should be performed in mice.

2.4.2. Route of exposure

54 Having considered the anticipated routes of human exposure, and the need for adequate exposure of the target tissue(s), as raised in the PfA submitted by one of MSCAs, performance of the test by the inhalation route is appropriate.

55 The granulometry of the Substance metal powder shows that the particle size D10 is estimated at 2.4-2.7 µm; consequently the pulmonary and tracheobronchial regions of the human respiratory tract would be accessible to a significant proportion of the Substance metal powder. Inhalation of the powdered metal is therefore a relevant route of exposure. Further, workers are exposed by this route in industrial and professional settings, with PROCS 81, 23-26 and 28, indicative of exposure by the inhalation route.

56 Consequent to the concern for genotoxicity at the site of contact, there is a concern that the lung will be more sensitive to the Substance as compared with the gut, due to the greater robustness and regenerative capacity of the gut as compared to the lung. Separately, the analogue substance Antimony Trioxide causes tumours in the lung in mice exposed by inhalation (NTP Technical Report [redacted]); there is therefore a concern that the lung is susceptible to carcinogenesis from antimony compounds after inhalation exposure, and that this may be mediated by a genotoxic mechanism. Given that the Substance likely speciates into antimony ions, which would be in common with those produced by antimony compounds such as antimony trioxide, it follows that there is a concern that the lung is susceptible to genotoxicity and carcinogenicity after inhalation exposure to antimony metal. Therefore, the study should be performed by the inhalation route.

2.4.3. Target organs

57 In line with the test method OECD TG 489, the comet assay must be performed by analysing tissues from liver as primary site of xenobiotic metabolism and from lung as site of contact.

2.4.4. Germ cells

58 A subsequent germ cell genotoxicity study (TGR/OECD TG 488, or CA on spermatogonia/OECD TG 483, depending on the concern raised by the substance) may still be required under Annex IX, in case 1) an in vivo genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity.

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

References

The following documents may have been cited in the decision.

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

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

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

The Substance is listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2018.

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in an earlier substance evaluation decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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 31 August 2021.

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

In your comments, you agreed with the timeline to provide the information. ECHA took your comments into account and did not amend the request.

In your comments you ask "*why the information required is split between the two tonnage bands?"*. As explained under page 2 of this decision the same study has been requested under different Annexes. This is because the requested study is triggered already at Annex VIII due to the the concern for chromosomal aberrations raised by the available in vitro cytogenicity test. For the highest tonnage band (*i.e.*, Annex IX), the reasons why the information requirement is not met and the specifications of the study design are provided. Only one study is to be conducted.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

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

The Member State Committee unanimously agreed on the draft decision in its MSC-79 written procedure. ECHA adopted the decision under Article 51(6) of REACH.

Appendix 3: Addressees of this decision and their corresponding information requirements

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

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

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

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

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

1.2. Test material

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

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

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

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[4].

[3] https://echa.europa.eu/practical-guides
[4] https://echa.europa.eu/manuals