Helsinki, 13 June 2018

Substance name: Tin sulphate
EC number: 231-302-2
CAS number: 7488-55-3
Date of Latest submission(s) considered[1]: 20 March 2017
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of Tin sulphate (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

Based on Article 46(1) of Regulation (EC) No 1907/2006 (Regulation (EC) No 1907/2006), you are requested to submit the following information on the registered substance, tin sulphate:

Substance identity

1. Maximum contents of relevant impurities Arsenic, Cadmium, Nickel, Lead and Antimony for each Registrant;

Human health

2. Sub-chronic toxicity study (90-day), oral route (test method: OECD TG 408), in rats, including additional specific investigations on mineral status, using the registered substance, tin sulphate or the analogue substance, tin chloride (CAS no. 7772-99-8) as further specified in Appendix 1;

3. *In vivo* mammalian bone marrow chromosomal aberration test, oral route (test method: OECD TG 475) in rats, using the registered substance, tin sulphate;

Exposure related requests

4. Exposure-related requests: clarification and detailed justification of the tonnages for each exposure scenario;

5. Exposure-related requests (consumer exposure): clarification of exposure scenario.

You have to provide an update of the registration dossier(s) containing the requested

[1] This decision is based on the registration dossier(s) at the end of the 12 month evaluation period / This decision is based on the registration dossier(s) on the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

information, including robust study summaries and, where relevant, an update of the Chemical Safety Report by **20 March 2020**. The full study report(s) have to be submitted for the sub-chronic toxicity study and the genotoxicity study. The deadline takes into account the time that you, the Registrant(s), may need to agree on who is to perform any required tests.

The reasons of this decision and any further specifications are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

Who performs the testing

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all Registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

Appeal

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

Authorised[3] by Leena Ylä-Mononen, Director of Evaluation

[3] 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

Based on the evaluation of all relevant information submitted on tin sulphate and other relevant available information, ECHA concludes that further information is required in order to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health and the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in order to clarify the CMR concern.

In this document tin sulphate and tin(II) sulphate are used synonymously.

0. ANALYSIS OF THE READ-ACROSS APPROACH

Description of the read-across approach

For the endpoints repeat-dose toxicity, carcinogenicity, reproductive toxicity and mutagenicity a read-across approach has been proposed in the dossier with tin(II) chloride anhydrous or dihydrate (CAS no. 7772-99-8/10025-69-1). Additionally, for genotoxicity, a read-across with tin(II) bis(methanesulphonate) (CAS no. 53408-94-9) has been used.

The proposed read-across is based on an analogue approach with the target substance tin sulphate and the source chemicals tin(II) chloride or tin(II) bis(methanesulphonate).

The proposed read-across hypothesis is that the target and the source substances have similar toxicological properties because they dissociate into the common tin cation Sn^{2+} and a non-common counter-ion are predicted to have no toxicological effects.

Assessment of the read-across justification

Tin sulphate and tin(II) chloride share structural similarity. The prediction is supported by similar physico-chemical properties and toxicological data for tin(II) chloride. Moreover, the non-common anions sulphate and chloride are considered of known low systemic toxicity. ECHA therefore agrees that data generated with tin sulphate can be used for evaluating the hazard of tin(II) chloride and *vice versa*.

Therefore, results from the existing sub-chronic toxicity study, reproductive toxicity and genotoxicity studies on tin(II) chloride are considered appropriate for tin sulphate.

With regards to the read-across with tin(II) bis(methanesulphonate), although structural similarity is shared with tin(II) sulphate, ECHA is of the opinion that the available toxicological data on both compounds do not allow to conclude on the relevance of using data on tin(II) bis(methanesulphonate) to assess tin(II) sulphate toxicity due to differences in the quality, methodology and investigated endpoints in the available studies. Moreover, the lack of toxicokinetics data (e.g. bioavailability) and the potential differences in physico-chemical properties raise uncertainties on the appropriateness of the read-across between the two substances since potential differences in bioavailability could lead to potential differences in the toxicity. Therefore, the results of the studies

available with tin(II) bis(methanesulphonate) are only used in the decision as supportive information. The assessment of the read-across justification is elaborated below.

- Substance identity issues

There is no issue identified with regard to substance identity as tin sulphate and tin(II) chloride anhydrous or dihydrate, tin(II) bis(methanesulfonate) are all salts of inorganic tin and mono-constituent substances.

- Structural similarity

The target and source substances share the common tin cation Sn^{2+}. Potential differences come from non-common counter-ions suphate, chloride or methanesulphate.

- Physico-chemical data relevant for the toxicological endpoints

Based on the available data, no major differences have been identified in the following physico-chemical properties of target and source compounds tin(II) chloride and tin(II) bis(methanesulphonate): molecular weight, solubility, form, melting point and vapour pressure.

In general at pH>3, tin(II) ions in aqueous solution tend to form hydrolytic species and scarcely soluble species (e.g. tin hydroxide). According to Cigala *et al*., 2012, the chloride and the sulphate ions showed comparable binding abilities with the formation of complex species at low pH values (pH < 5) whereas solution containing carbonate anions forms strong complexes with Sn(II) throughout the entire pH range often hampering the formation of hydrolytic species even at low carbonate concentrations. Potential differences in behaviour in solution between tin(II) bis(methanesulphonate) and tin(II) sulphate is thus expected but is of unknown consequences on their bioavailability.

- Toxicokinetic data

There are no specific data on the absorption, distribution, metabolism or excretion of tin(II) sulphate or tin(II) bis(methanesulphonate). From various Sn(II) compounds (e.g. tin(II) chloride), absorption of Sn(II) via the oral route has been shown to be low (<5%). Ingested tin is largely unabsorbed and excreted mainly in the faeces, with the absorbed fraction eliminated slowly in the urine. Inorganic tin typically distributes mainly to bone, but also to the liver and kidneys (WHO, 2005).

The nature of the inorganic tin compound and its oxidation state appears to determine the extent of absorption. Study by Hiles *et al*., 1974, shows that Sn(II) salts (citrate fluoride, pyrophosphate) have a higher absorption that Sn(IV) salts (citrate, fluoride). However, the associated anion appears to have little or no effect on the absorbed fraction.

In conclusion, no major differences in the toxicokinetic of tin(II) chloride and tin sulphate is expected. With regard to tin(II) bis(methanesulphonate), although no data are available, due to the high solubility of this compound, a similar bioavailability could be

expected.

- Comparison of toxicological data

Experimental data obtained with tin sulphate, tin(II) chloride, or tin(II) bis(methanesulphonate) indicate that substances have similar acute toxicological profiles.

A published 28-day oral toxicity study in rats is available with both tin sulphate and tin(II) chloride. The results suggest similar systemic toxicity profiles on the investigated endpoints. The LOAEL observed in the study was around 120 mg/kg bw based on liver, anaemia and body weight effects (De Groot *et al*., 1973).

Regards to tin(II) bis(methanesulphonate), a 28-day oral sub-chronic toxicity study (OECD TG 407) is available in rats showing no effects up to the highest dose used: 125 mg tin/kg bw/d.

90-day sub-chronic toxicity studies by oral route are available with tin(II) bis(methanesulphonate) (OECD TG 408, ECHA disseminated website) and tin(II) chloride (De Groot *et al*., 1973). A comparison of the studies may suggest that tin(II) chloride exerts effects at lower dose levels than tin(II) bis(methanesulphonate) and that some target organs are different (anaemia observed with tin(II) chloride only and neurobehavioral effects observed with tin(II) bis(methanesulphonate)). Nevertheless, ECHA considered that it is not possible to conclude and to compare the results observed in these studies due to differences in their reliability and methodologies: differences in guideline and GLP status, rat strains, investigated endpoints, dose levels, dose spacing and level of information available.

The quoted studies are further detailed in section 2 below.

Conclusion

On one hand, based on the above considerations, it can be concluded that the results of the toxicity studies conducted with tin(II) chloride are likely to predict the properties or expected effects of tin(II) sulphate.

On the other hand, although tin(II) bis(methanesulfonate) shared structural similarity with tin(II) sulphate, this is not sufficient to accept the read-across. The read-across is not supported by toxicological data and tin(II) sulphate may be of higher reactivity and toxicity. Moreover, uncertainties come also from the lack of information on the bioavailability of the tin(II) compounds. Therefore, the results of the oral sub-chronic repeated dose toxicity study, reproductive toxicity study and genotoxicity studies with tin(II) bismethanesulfonate should be considered as supportive evidence only.

1. MAXIMUM CONTENTS OF RELEVANT IMPURITIES SUCH AS ARSENIC, CADMIUM, NICKEL, LEAD AND ANTIMONY FOR EACH REGISTRANT

According to the "Guidance for identification and naming of substance under REACH and CLP", impurities present in a concentration > 1% should be specified and impurities that are relevant for classification and/or PBT assessment shall always be specified irrespective of the concentration. Regarding the starting materials used in the manufacturing processes and bibliographic data on tin sulphate, presence of Arsenic, Cadmium, Nickel, Lead and Antimony is expected to contribute to the compositional profile of the registered substance. All these impurities are of toxicological concern and assigned to harmonised classification or self-classification. According to their level in the registered substance, these impurities can be relevant for the classification and the risk assessment.

Consequently, for the registered substance, each Registrant is required to specify a maximum concentration for each impurity. Information shall be included in section 1.2. of the IUCLID dossier in "specific Registrant composition".

Consideration of Registrant(s)' comments

In your comments you agreed with the request.

2. SUB-CHRONIC TOXICITY STUDY (90-DAY), ORAL ROUTE (TEST METHOD: OECD TG 408), IN RATS, INCLUDING ADDITIONAL SPECIFIC INVESTIGATIONS ON MINERAL STATUS, USING THE REGISTERED SUBSTANCE TIN SULPHATE OR THE ANALOGUE SUBSTANCE TIN(II) CHLORIDE (CAS no. 7772-99-8)

The Concerns identified

In the technical dossier, no sub-chronic or chronic repeated-dose toxicity study is available according to current guidelines and GLP status either on tin(II) chloride or sulphate. Available data are limited, of low quality or performed at low dose levels only.

Several target organs have been identified in the available limited sub-chronic toxicity studies but no dose-response and critical effects for DNELs setting could be identified due to the limitations of the studies.

Some concerns on the ability of inorganic tin salts to interfere with the status of calcium, iron, copper and zinc has been raised in the literature and need also to be clarified.

Moreover, concerns on immunotoxicity (lymphocytes), neurotoxicity (behavioral effects) and male reproductive toxicity (testis) have been identified in the sub-chronic toxicity study performed with tin(II) bis(methanesulphonate) that were neither investigated nor clarified by the available data on tin sulphate or tin(II) chloride raising additional concerns on these endpoints.

Finally, equivocal carcinogenicity results have been observed in a chronic toxicity study performed with tin(II) chloride that raised concern on the potential carcinogenicity of the registered substance.

Although there are indication that tin sulphate may cause adverse effects, the available data are insufficient to derive scientifically based DNELs/DMELs.

Why new information is needed

In the technical dossier, no guideline repeated dose toxicity study is available. Published data are limited, of low quality, or performed at low dose level only. The studies available were all performed by oral route.

The 90-day sub-chronic toxicity study performed with tin(II) chloride in rat caused changes in liver, kidney, pancreas, heart, spleen, testicles, growth retardation and anaemia (NOAEL ~ 7.5 - 33 mg/kg bw/day, De Groot *et al*., 1973). The exact doses of exposure (in mg/kg bw/day) were difficult to estimate due to the study designs used and to the lack of information in the published data. Furthermore, it is not clear from the study which organs were investigated for histopathology. The haematological system is identified in this study as a target organ for tin(II) chloride but no information on the potential reversibility of the effects are available in this study. A concern remains on the severity of this adverse effect and its reversibility (central or pheripheral anemia).

Additionally, effects observed in a 90-day OECD guideline toxicity study performed with tin(II) bis(methanesulphonate) on grip strength and reduced lymphocytes count in several organs were not investigated in any tin(II) chloride or tin sulphate sub-chronic studies and should be further investigated with the substance of interest.

Interference with the status of iron, copper and zinc have also been observed in animals (Pekelharing, 1994). The mode of action is not totally clear, but could involve altered absorption/retention of these trace elements.

Interference with calcium homeostasis has also been reported at very low dose level with tin(II) chloride. Indeed, decreased calcium concentration in serum and bones and reduced compressive bones strength has been observed in several studies by Yamaguchi *et al.* 1978, 1979, 1980a/b, 1981a/b, 1982. Two hypotheses have been suggested by the authors; a direct effect on bone cells or an indirect effect on parathyroid hormone. According to EFSA opinion (2005) it is likely that effect on bones (reduced compressive bones strength) are not systemic effects caused by the absorbed tin but are rather manifestations of deficiency of one or more trace elements. Clarification of the interference of tin(II) sulphate with calcium, iron, copper and zinc needs to be assessed in order to clarify the relevance of these possible mode of action for human health risk assessment.

Available limited long term studies suggest that tin(II) chloride is not carcinogenic. However, one study (NTP, 1982), performed in mice and rats concludes that C-cell thyroid adenomas and carcinomas may have been treatment related in rat. C-cells are

neuroendocrine cells in the thyroid of which primary function is to secrete calcitonin and parathyroid hormone. Both hormones play a significant role in rats in the maintenance of calcium homeostasis. In this study, an increase in one type of lymphoma was also reported in mice above historical control values. In the other available long-term toxicity study performed in rat in 1980, thyroid tumors were not seen after 115-week but only low doses were investigated. Therefore, a concern remains on the possible effects of tin salts on lymphocytes, thyroid and calcium homeostasis that could lead to potential carcinogenesis.

Effects on testis has been observed in sub-chronic toxicity studies at the highest dose tested (315 mg/kg bw/d of tin(II)chloride, tin(II)oxide) in De Groot (1973 et al.) or 0,2% tin(II) bismethanesulphonate with a marked general toxicity in another study by De Groot (1973). Effects on testis were also observed in a one-generation toxicity study performed with tin(II) bis(methanesulphonate) in rat treated in diet at the high dose level of 300 mg/kg bw (study disseminated on ECHA website). No effects on reproductive organs were observed in the available 3-generation study performed with tin(II) chloride up to the highest dose tested of around 30 mg/kg bw/d. However, as only low doses were tested in this 3-generation toxicity study, this may explain the absence of effects. Therefore, a concern remains on potential effects of tin salts on both testis and spermatogenesis that would need further investigation on reproductive toxicity of tin sulphate if confirmed in the requested 90-day toxicity study.

In conclusion, a critical effect and dose-response relationship, relevant to the identified CMR concern, cannot be established based on the available information. Therefore, it is deemed that more information is needed.

What is the possible regulatory outcome

The existing data are not sufficient to characterise dose-response for human health risk assessment for tin sulphate and further investigation is needed. Indeed, sub-chronic and chronic studies available in the dossier were limited and not performed according to current guidelines. The new requested study could possibly lead to derive a more severe DNEL for systemic effects for workers and consumers. Moreover, the necessity of a classification as STOT RE for the haematological system or other target organs would be clarified with this new study.

Furthermore, in case where effects on the male reproductive organs are confirmed, an extended one-generation reproduction study (EOGRTS) may be requested.

The clarification of the potential effects on thyroid, calcium homeostasis and lymphocytes will help to elucidate equivocal carcinogenic findings observed in both rats and mice after long-term exposure.

Therefore, ECHA judged that more information is required to clarify the concern identified. An *in vivo* 90-day sub-chronic toxicity study appears proportionate to clarify the identified concerns.

Considerations on the test method and testing strategy

Test material

You commented that the use of tin(II) chloride would be more appropriate for read-across to other Sn(II) compounds than using tin(II) sulphate. No argumentation was provided to support this statement.

ECHA considers that both compounds can be used for the study as read-across is accepted between the substances and similar behaviour and toxicological properties are expected.

Based on self-classification provided in the registration dossier, tin(II) sulphate may be more appropriate since tin(II) chloride is self-classified as skin corr. 1B (based on pH in solution) and tin(II) sulphate is not. Nevertheless, ECHA is of the opinion that based on the pH measurements available for tin sulphate in solution (a 2% solution has a pH of 1.8) the same classification as for tin(II) chloride should apply.

Therefore, ECHA leaves it to you, the Registrants, to decide whether to use tin(II) chloride or tin(II) sulphate for the testing. A certificate of analysis of the test material including the content of impurity shall be provided.

Species selection

According to OECD TG 408, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

Route of exposure

The study shall be performed by oral route of exposure to determine the most relevant potential systemic effects. Inhalation route is not considered as appropriate to investigate potential systemic effects as only 1% of the particles are respirable according to your comments. Moreover, oral route is considered as more appropriate than the inhalation route since in case effects on the male reproductive organs are confirmed in the study, an extended one-generation reproduction study (EOGRTS) may be requested as a follow-up. The most appropriate route to conduct an EOGRTS is for the present substance the oral route.

Diet content

Iron, copper, and zinc have been shown to have a protective effects against tin(II) chloride induced anaemia (De Groot, 1973). Thus, diet shall contain a known level of iron, copper, calcium and zinc and representative of a normal rat diet (not supplemented). Furthermore, the tin content in the diet shall be determined.

Special investigations

Further investigations of effects of tin sulphate on copper, zinc, iron metabolism, calcium interaction and effects on enzymes are considered as necessary:

The haematological examination and clinical chemistry recommended in the latest version of OECD test guideline 408 shall be investigated. Additionally serum levels of iron, copper and zinc, transferrin saturation, serum parathyroid hormone (PTH) level, acid phosphatase activity and serum calcitonin level shall be measured.

Calcium and phosphate content in bones shall also be investigated in case statistical significant disturbance of serum calcium level is induced by tin sulphate in the study.

Special emphasis shall be placed upon potential effects on the stages of spermatogenesis, the histopathology of interstitial cell structure and sperm staging in order to be able to detect possible effects on testes and sperm. Indeed, these parameters were not investigated in any studies already performed with tin(II) sulphate or tin(II) chloride. ECHA recommends you to follow the latest draft version of OECD TG 408 (points 39-41) for spermatogenesis investigations.

Furthermore, the investigation of the reversibility of the potential haemolytic effects induced by tin(II) sulphate shall be considered.

Dose level

A range-finding study shall be considered by the oral route if needed prior to the 90-day study. This will be helpful in identifying a suitable concentration range for the 90-day toxicity study.

Study report

You are requested to submit the full study report for the information requirement 2. This will allow the evaluating MSCA to fully assess the provided information, and to efficiently clarify the concern(s).

Consideration on alternative approaches

The request is suitable and necessary to obtain information that will allow to clarify whether there is a risk for human health. More explicitly, there is equally no suitable alternative of obtaining this information. Where the data, once obtained, confirms that there is a risk for humans, it will allow authorities to consider further risk management and DNEL setting. ECHA notes that there is no experimental study available that will generate the necessary information without testing on vertebrate animals.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, you are required to carry out the following study: Sub-chronic toxicity study (90-day), oral route (test method: OECD TG 408), in rats, including additional specific investigations on mineral status, using the registered substance, tin sulphate **or** the analogue substance, tin chloride (CAS no. 7772-99-8).

Consideration of other comments by the Registrant(s) on the study

In your comments you agree to perform a 90-day toxicity study but you proposed to include or combine the study in/with an Extended One Generation Reproductive Toxicity Study according to OECD TG 443. You further argued that in addition to the situation described by ECHA regarding fertility of male animals, a published study (Yousef et al., 2005) is showing adverse effects of tin dichloride to the fertility of male rabbits. You are of the opinion that the combination of a sub chronic oral toxicity study and an extended one-generation reproduction toxicity study would reduce the number of animals significantly.

ECHA considers that the use of the results of the 90-day toxicity study and the genotoxicity study (ref. to request 3) to decide the need for an EOGRTS and to trigger the appropriate study design of this study is the most proportionate option for compliance with the "3 Rs principle" (Replacement, Reduction, and Refinement of animal testing). As highlighted in section 3 in the note to Registrant(s), reproductive concern has been identified and may need to be clarified after the submission of the requested studies.

3. *IN VIVO* MAMMALIAN BONE MARROW CHROMOSOMAL ABERRATION TEST, ORAL ROUTE (TEST METHOD: OECD TG 475), IN RATS, USING THE REGISTERED SUBSTANCE TIN SULPHATE

Concern

In the registration dossier, the mammalian cell gene mutation assay performed with tin(II) chloride (OECD TG 476; Myhr *et al*., 1991) was negative. Positive result was found in an *in vitro* mammalian chromosome aberration study (OECD 473) after 3-h exposure duration with metabolic activation and after 20-h exposure without metabolic activation (negative after 3h treatment), performed with tin sulphate.

Genotoxicity potential of tin(II) chloride has been assessed in many *in vivo* assays available in the registration dossiers and in literature. However, only one limited old study performed with tin(II) chloride has a reliability index 2. This study shows negative results in a chromosomal aberration test and uninterpretable results in a rodent dominant lethal assay (inconsistent or negative results obtained with the positive control). The limitations in the study give uncertainties in the obtained results. The other *in vivo* studies performed with tin(II) chloride were not considered as reliable. Two *in vivo* studies performed with tin(II) bis(methanesulphonate), were also provided in the dossier and are considered very limited as only one dose was tested in both studies. Furthermore, as elaborated in section 0 of the draft decision, a read-across with tin(II) bis(methanesulphonate) is not accepted as such but only as supportive information.

Therefore, based on the available data, no conclusion can be set on the mutagenic potential of the tin(II) sulphate and on risk assessment (DNEL or DMEL derivation). Furthermore, carcinogenicity concerns have been identified for the substance as lymphomas in mice and thyroid C-cell tumours in rats may have been treatment related.

Based on the available data, genotoxic mechanism of carcinogenicity cannot be excluded. A genotoxic potential of the substance would support that the tumours observed in the carcinogenicity study are treatment-related. Therefore, it is judged that more information is required in order to state on possible genotoxic classification and risk characterisation linked to carcinogenicity potential of the substance.

Why new information is needed

Tin(II) sulphate tested positive for chromosomal aberration *in vitro*. There are a number of *in vivo* mutagenicity studies conducted with the related substances, tin(II) chloride and tin(II) bis(methanesulphonate), but not on the registered substance itself. However, the available *in vivo* studies are generally of limited quality and it is currently not possible to reliably conclude on the *in vivo* genotoxicity of tin(II) sulphate. Therefore, further testing for germ cell mutagenicity is required to clarify this concern.

What is the possible regulatory outcome

Positive results in the requested study could lead to a classification for genotoxicity in somatic cells. As no information is available on the ability of tin(II) sulphate to reach the germ cells, further testing such as a transgenic rodent assay (TGR) will be necessary to classify the substance in category 1B.

Positive results may also impact risk assessment (DNEL or DMEL derivation) and related risk management measures.

Furthermore, potential carcinogenicity concern has been raised in a long-term repeated-dose toxicity study (lymphomas and thyroid C-cells tumours). Positive *in vivo* results in the requested study will support the conclusion that tin sulphate may be a mutagen carcinogen.

Considerations on the test method and testing strategy

Test material

The purity of tin(II) sulphate should be representative of registered technical tin(II) sulphate. The certificate of analysis including the content of impurity used in technical tin(II) sulphate shall be provided.

Species selection

According to the test method OECD 475, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

Route of exposure

ECHA considers that the oral route is the most appropriate route.

Consideration of alternative approaches

The request for the *in vivo* mammalian bone marrow chromosomal aberration test is suitable and necessary to obtain information that will allow to clarify whether there is a risk for human health.

More explicitly, there is no equally suitable alternative way available of obtaining this information. Where the data, once obtained, confirm that there is risk for mutagenic effects for tin(II) sulphate, it will allow authorities to consider further regulatory risk management like classification and/or identification of the substance as an SVHC. ECHA notes that there is no experimental study available that will generate the necessary information without testing on vertebrate animals.

According to the ECHA Guidance on information requirements and chemical safety assessment (version 4.1, October 2015) Chapter R.7a, section R.7.7.6.3, the mammalian erythrocyte micronucleus test (OECD TG 474) or the mammalian bone marrow chromosomal aberration test (OECD TG 475) are suitable to follow-up a positive *in vitro* result on chromosomal aberration if the test substance or its metabolite(s) will reach the target tissue. Alternatively, the *in vivo* mammalian alkaline comet assay (OECD TG 489) is a suitable test to be performed.

The mammalian erythrocyte micronucleus test and the mammalian bone marrow chromosomal aberration test are both able to detect chromosomal aberrations, whereas the comet assay is an indicator assay detecting putative DNA lesions. Hence, ECHA considers that the most appropriate test to follow-up an *in vivo* concern for chromosomal aberration is either the mammalian erythrocyte micronucleus or the mammalian bone marrow chromosomal aberration test. Toxicokinetics data are available and demonstrate a bone marrow exposure. Nevertheless, tin sulphate may interfere with erythropoiesis and may lead to false positive results with the mammalian erythrocyte micronucleus test.

Thus, the mammalian bone marrow chromosomal aberration test is more sensitive than the mammalian erythrocyte micronucleus testto detect clastogenicity and is considered as the most appropriate follow-up for the *in vitro* mammalian chromosomal aberration test for tin sulphate.

Study report

. You shall submit the full study report for the information requirement 23. This will allow the evaluating MSCA to fully assess the provided information, and to efficiently clarify the concern(s).

Conclusion

Therefore, pursuant to Article 46(1) of the REACH Regulation, you are required to carry out the following study:

In vivo mammalian bone marrow chromosomal aberration test (test method: OECD TG 475) in rats, oral route with tin sulphate.

Consideration of Registrant(s)' comments

In your comments you agreed with the request.

Note to the Registrant(s)

Based on the results of this study and the 90-day sub-chronic toxicity study, further requirements on reproductive and developmental toxicity may be warranted.

4. EXPOSURE-RELATED REQUESTS: CLARIFICATION AND DETAILED JUSTIFICATION OF THE TONNAGES FOR EACH EXPOSURE SCENARIO

In order to clarify the pattern of uses and to conduct an appropriate risk assessment considering the whole tonnage values from the different Registrants as requested in section 10 of the CSR, the breakdown of the tonnage values shall be detailed for each contributing scenario.

Therefore, pursuant to Article 46(1) of the REACH Regulation, you are required to give clarifications and a detailed justification of the tonnages for each exposure scenario and to update the risk assessment in the registration dossier.

This information should be clarified if necessary in the confidential part of your dossiers in order to respect free competition rules.

Consideration of Registrant(s)' comments

In your comments you agreed with the request.

5. EXPOSURE-RELATED REQUESTS (CONSUMER EXPOSURE): CLARIFICATION OF EXPOSURE SCENARIO

In order to clarify the possible impact on human health of the service life of tin for consumers, you are required to add exposure scenarios regarding service life to closely evaluate the consumer exposure and to update the risk assessment part in the registration dossier.

For service life contributing scenario 1 (AC1, 2, 3, 7, 38), further description of use were not considered relevant due to process conditions. According to you, tin sulphate will no longer be present because tin sulphate will be oxidised and transformed to Sn4+ or Sn metal. Further clarification is necessary to accept or reject this statement and to perform a risk assessment on tin(II) sulphate if relevant.

For service life contributing scenario 3 (AC4), further description of use were not considered relevant due to process conditions. According toyou, tin sulphate will no longer be present. In cement mixture, tin sulphate is used as chromium reduction agent.

Tin sulphate will react with cement and humidity into insoluble hydroxide and changes to oxidation state Sn(IV). Due to missing use conditions, an inconsistent description of the physical state and lack of documentation for the exposure calculations, consumer exposure estimation is not possible.

Therefore, pursuant to Article 46(1) of the REACh Regulation, you are required to give clarifications and a detailed justification of the consumer use and service life exposure.

Consideration of Registrant(s)' comments

In your comments you agreed with the request.

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Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected CMR, suspected sensitiser, consumer use and aggregated tonnage, Tin sulphate CAS No 7488-55-3 (EC No 231-302-2) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2016. The updated CoRAP was published on the ECHA website on 22 March 2016. The Competent Authority of France (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

Pursuant to Article 45(4) of the REACH Regulation the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

In the course of the evaluation, no additional concerns were identified.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 21 March 2017.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation.

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

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took into account the comments from you, which were sent within the commenting period, and they are reflected in Appendix 1.

Proposals for amendment by other MSCAs and referral to Member State Committee

The evaluating MSCA notified the draft decision to the Competent Authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received proposals for amendment to the draft decision and modified the draft decision.

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendments. Proposals for amendments and your comments on the proposals for amendment were taken into account. The range-finding study by inhalation route proposed as a Tier I to choose the most appropriate route of exposure in request 2 has been dropped due to your comment on technical difficulties to conduct such a study.

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

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-59 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registrations is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossiers at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

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

3. In relation to the required experimental studies, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation.

4. In relation to the experimental studies the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

   Further advice can be found at
http://echa.europa.eu/regulations/reach/registration/data-sharing. If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the studies on behalf of all of them.