SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Tin sulphate

EC No. 231-302-2

CAS RN 7488-55-3

Evaluating Member State: France

Dated: 30 June 2023

Evaluating Member State Competent Authority

French Agency for Food, Environmental and Occupational Health Safety (ANSES) on behalf of French Ministry of Environment
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Year of evaluation in CoRAP: 2016

Before concluding the substance evaluation, a Decision to request further information was issued on: 10 March 2017

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Further information on the substance evaluation process here:

https://echa.europa.eu/regulations/reach/evaluation/substance-evaluation

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B, the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Table list

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Tin sulphate (hereafter "the Substance") was originally selected for substance evaluation to clarify concerns about:

- suspected CMR (mutagenicity, carcinogenicity)
- suspected sensitiser
- consumer use
- high (aggregated) tonnage

During the substance evaluation process, the following additional concerns were identified:

- acute toxicity
- risk for the environment
- irritation

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A targeted compliance check decision for the Substance was issued in March 2016, requesting information on the composition of the Substance, a description of analytical methods and a long-term toxicity study on plants. The information provided in the dossier update was compliant.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the Substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

The conclusion covers the concerns identified, with the exception of reproductive toxicity, as a data gap on reproductive toxicity study has been identified and a compliance check (CCH) performed by ECHA is suggested.

Table 1: CONCLUSION OF SUBSTANCE EVALUATION

Conclusions	Tick box
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

As risks were identified and because further data on reprotoxicity is anticipated based on identification of a data gap for this endpoint, a re-evaluation of the safe use of the Substance will be necessary. Depending on the risks identified and the population exposed, the evaluating MSCA will decide on the necessity of performing a risk management option analysis (RMOA). If performed, the appropriate options will be assessed, and the most relevant Risk Management Measures (RMMs) will be identified (see below).

4.1.1. Harmonised Classification and Labelling

The Substance is a chemical that has no **current Annex VI entry** in the CLP regulation (EC 1272/2008). Acute toxicity, corrosion, skin sensitisation, repeated dose toxicity and aquatic chronic toxicity were the main hazards identified following exposure to the Substance.

The harmonised classification for these endpoints is not considered as a priority (art. 36 of CLP). Based on the report on ECHA's dissemination website (from 2 December 2022, see table 9 of this document), most of the notifications consider these classifications. The opportunity to propose a CLH will be evaluated in a further RMOA where such information will be considered.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable

4.1.3. Restriction

Not applicable

4.1.4. Other EU-wide regulatory risk management measures

Not applicable

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable

5.2. Other actions

Not applicable

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating MSCA. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2: FOLLOW-UP

Follow-up action	Date for intention	Actor
RMOA	If necessary, when the new data generated under CCH will have become available.	France
CLH dossier	The eMSCA will not yet prepare a harmonised classification proposal for the Substance at this stage. Presently the evaluating MSCA recommends a compliance check first comprising toxicity to reproduction. Therefore, the evaluating MSCA will await the outcome of this process. Once the results are available a harmonised classification proposal for the Substance will be considered	France

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance was originally selected for substance evaluation to clarify concerns about:

- Suspected CMR (mutagenicity, carcinogenicity)
- Suspected sensitiser
- Consumer use
- High (aggregated) tonnage

During the substance evaluation process, the following additional concerns were identified:

- acute toxicity
- risk for the environment
- irritation

Table 3: List of evaluated endpoints

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Acute toxicity	**Concern identified.** Self-classification for acute toxicity. Classification and labelling warranted, either self or harmonised.
Irritation/Corrosion	**Concern identified.** The Substance in solution identified as corrosive. Classification and labelling warranted, either self or harmonised.
Sensitisation	**Concern confirmed.** Self-classification as Skin Sens. 1. No further action. Classification and labelling to be initiated.
Mutagenicity	**No concern**: based on the new data generated.
Carcinogenicity	**No concern**: no effects identified in the 90-day study to substantiate carcinogenicity.
Repeated dose toxicity	**Concern identified:** Concluded based on the new data generated. Classification and labelling warranted, either self or harmonised.
Reproductive toxicity	**Concern unresolved**: Data gap identified for reproductive toxicity. CCH suggested.
Aquatic toxicity	**Concern identified**: Classification as Aquatic Chronic 2 warranted, either self or harmonised.
Risk for the environment	**No concern**: based on the new generated data. No risk identified.
Consumer use	**No concern**: based on updated scenario. No risk identified.
High aggregated tonnage	**No concern**: the tonnage for the Lead Registrant was downgraded during 2022. Nevertheless, the tonnage band of the substance stays at > 1000 tpa to cover all registrations.

7.2. Procedure

The Substance was included in the Community Rolling Action Plan (CoRAP) for evaluation in 2016.

All the physico-chemical, human health and environmental hazards that were part of the registration dossier were evaluated.

The evaluating MSCA met the lead registrant of the substance: The evaluating MSCA had access to several additional studies during the course of the evaluation and received also clarifications from the registrants on different topics.

Based on the evaluation of the available data, the evaluating MSCA concluded that there was a need to request further information to clarify the concerns related to substance identity, consumer and environmental exposure, reproductive and mutagenic potential. Therefore, eMSCA prepared a draft decision to request further information. The decision was agreed by the member state Committee in June 2018.

The substance evaluation conclusion was prepared based on the updated registration dossier from August 2021 and additional information received until June 2022. In addition, a literature review from 2013 to 2019 was performed on Pubmed.

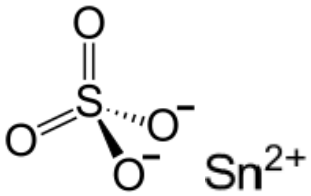
7.3. Identity of the substance

Table 4: Substance identity

Public name:	Tin sulphate
EC number:	231-302-2
CAS number:	7488-55-3
Index number in Annex VI of the CLP Regulation:	none
Molecular formula:	$SnSO_4$
Molecular weight range:	214.773 g/mol
Synonyms:	Stannous sulphate; Tin(2+) sulphate; Tin(II) sulphate

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



Analytical information is provided to confirm the compositions and the structure of substances of each registrant. It is noted, however, that **no sufficient information is available for some of the registrants to demonstrate that the substance is in agreement with the boundary composition**. Two registrants should also update their declarations, as the substance was wrongly declared as Tin (+IV) bis (sulphate) (EC n°

242-952-1, CAS n° 19307-28-9) whereas the analytical data are consistent with tin (+II) sulphate (EC n° 231-312-2, CAS n° 7488-55-3). More information is available in the confidential document (information not included in the present document but available for authorities on IUCLID). Moreover, most of the registrants did not provide any information on the **particle size distribution of the substance**.

Table 5: Boundary composition

Constituent **Constituents**	**Typical concentration**	**Concentration range**	**Remarks**
Tin (II) sulphate $SnSO_4$ EC no.: 231-302-2 CAS no.: 7488-55-3	-	≥ 80.0% - ≤ 100% w/w	
Impurity **Constituents**	**Typical concentration**	**Concentration range**	**Remarks**
Heavy metals and typical metals impurities of Sn		≥ 0.0 % - ≤ 0.5% w/w	Maximum 100 ppm per metal

7.4. Physico-chemical properties

Table 6: Overview of physicochemical properties

Property	Value
Physical state at 20°C and 101.3 kPa	**Value used for SEV:** Crystalline white odourless solid at 20°C and 1 atm
Melting / freezing point	**Value used for SEV:** no melting point, decomposition before melting at 378.0°C. *The melting point was determined according to OECD 102 guideline. No melting point is reported because decomposition occurs before melting at 378.0°C*
Density	**Value used for SEV:** 4.15 g/cm^3 at 20 °C. *Density was determined according to EPA OPPTS 830.7300 (Density / Relative Density / Bulk Density) guideline*.
Water solubility	**Value used for SEV:** 188.0 g/L at 19°C (pH not determined). *Water solubility reported in the peer reviewed handbook (CRC Handbook 88$^{th)}$ (No method or guideline specified).The solutions of tin (II) sulphate have been prepared with a concentration of 352 g/L at 20 °C, by adding water to the salt instead of the contrary (Donaldson, J. D.; Moser, W.; J. Chem. Soc. 1960, 4000-4003). An excess of water enhances the formation of poorly soluble salts, presumably tin (II) hydroxide*.
Partition coefficient n-octanol/water (Log K_{ow})	Not required

Surface tension	**Value used for SEV:** none. *Surface tension was determined according to OECD 115 guideline using ring method. Experimental study gives a result of 73 mN/m at 20 °C at 169.0 g/L (90% water solubility). The result is not acceptable as the concentration greatly exceeds the maximum concentration of 1 g/L recommended in OECD Guideline 115.*
Particle size distribution (Granulometry)	**Value used for SEV:** > 100 µm = 0% >13 µm = 94% D50=20 µm *Particle size distribution was determined with a study similar to DIN 55992-1 according to ISO/IEC 17025.* *Experimental study shows a particle size distribution such as:* *> 100 µm = 0%* *>63 - <100 µm = 14.99%* *>25.48 - <63 µm = 23.0%* *>12.41 - <25.46 µm = 55.76%* *>6.39 - <12.41 µm = 5.6%* *>3.19 - <6.39 µm = 0.43%* *>1.6 - 3.19 µm = 0.03%* *However, it should be noted that not all registrants characterized the granulometry of the substance. No nanoform has been registered. The present evaluation dossier does not cover nanoforms of the substance, and the granulometry should be specified as a range in the boundary composition to make this point explicit.*
Dissociation constant	Tin (II) sulphate is an inorganic salt, very soluble in water and remains only in dissociated ionic form in water, it does not therefore have a measurable dissociation constant. **Value used for SEV:** none. *Tin (II) sulphate is an inorganic salt, very soluble in water and remains only in dissociated ionic form in water, it does not therefore have a measurable dissociation constant.*
pH	**Value used for SEV:** pH = 2.25 for 1% concentration at 20°C. pH was determined according to OECD Guideline 122 guideline. Experimental study gives a result of pH=2.25 for 1% w/w concentration and pH=1.8 for 2.5% w/w concentration at 20 °C.
Flammability (Flash point)	*In accordance with column 2 of REACH Annex VII, Flash point (required in section 7.9.) does not need to be conducted as the substance is a solid.*
Auto flammability (Self-ignition temperature)	**Value used for SEV:** not self-heating and no self-ignition up to 400 °C. *Experimental study using Grewer Oven according to UN Test N.4 on tin (II) sulphate (99% purity) shows no exothermic effects up to 400 °C.*
Explosive properties	**Value used for SEV:** not explosive. *Experimental study using DSC measurements of tin (II) sulphate (99% purity) according to OECD Guideline 113 and EU A.14 shows no significant exothermic effects up to 500 °C.*

Oxidising properties	**Value used for SEV:** not oxidising. *Experimental study performed on tin (II) sulphate (99% purity) according to UN Test O.1 shows the burning time of the mixtures of the test item with cellulose (4:1 and 1:1) was greater than the burning time of the reference mixture of potassium bromate and cellulose (3:7).*

7.5. Manufacture and uses

7.5.1. Quantities

Table 7: Aggregated tonnage

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

The substance stannous sulphate is imported in the EU in 100-1000 tonnes per year.

7.5.2. Overview of uses

According to the ECHA dissemination website, this substance is used in the formulation of cement preparations, chemical industry and for electroplating industry.

Table 8: Uses

USES	Use(s)
Uses as intermediate	In chemical industry
Formulation	- Formulation in mixture in the Cement industry for reduction of chromium in the cement - Formulation as such or in mixture in electroplating industry for metal surface treatment products including galvanic and electroplating products - Formulation in the chemical industry
Uses at industrial sites	- Use in a mixture or as such in electroplating industry as metal surface treatment product, adhesives, sealants or as in intermediate (PC 1, 14, 19) - use in mixture or as such in industrial building and construction work (PC0) - use as such or in mixture in manufacture of chemicals (PC1, 19, 21, 32, 0)
Uses by professional workers	Professional building and construction work – indoor and outdoor: PC 0 (reduction agent for chromium in cement)
Consumer Uses	Do it yourself product, indoor or outdoor: PC0 (reduction agent for chromium in cement)
Article service life	- Article used by consumers (AC 4): Stone, plaster, cement, glass, and ceramic articles -Article used by workers and consumers (AC1, 2, 3, 7, 38): Vehicles, Machinery, mechanical appliances, electrical/electronic articles, electrical batteries and accumulators, metal articles, packaging material for metal parts, releasing grease/corrosion inhibitors

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

There is no harmonised classification for Tin (II) sulphate.

7.6.2. Self-classification

- In the registration (Lead registrant, joint submission, June 2022)*:*

Acute Tox. 4, H332 "Harmful if inhaled".

Skin Irrit. 2, H315 « Causes skin irritation » ;

Eye damage 1, H318 "Causes serious eye damage".

Skin Sens. 1, H317 "May cause an allergic reaction".

STOT RE 1, H372 "Causes damage to organs <lung> through prolonged or repeated exposure".

Aquatic chronic 3, H412 "Harmful to aquatic life with long lasting effects."

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory (from the ARN 313)*:*

Table 9: Notifications of classifications

Hazard class and category code	Hazard statement code	Number of notifications (as provided on ECHA's website the 2/12/22
Acute Tox. 4	H302	1 out of 33
Acute Tox. 4	H332	1 out of 33
Eye Irrit. 2	H319	26 out of 33
Skin corr. 1B	H314	1 out of 33
STOT SE 3	H335 (respiratory tract/lungs)	1+1 out of 33
Muta. 2	H341	6 out of 33
Repr. 2	H361d (reduction in the ossification of the fetal skeleton)	3 out of 33
STOT RE 1	H372 (lung)	1 out of 33
STOT RE 2	H373 (cardiovascular)	2 +4 out of 33
Aquatic Acute 1	H400 M-factor=10.00	5 out of 33
Aquatic Acute 1	H400	8 out of 33
Aquatic Chronic 1	H410	6 out of 33
Aquatic Chronic 3	H412	1 out of 33

7.7. Environmental fate properties

7.7.1. Degradation and environmental distribution

The following table resumes parameters about E-fate and behaviour of the metallic substance needed for performing the environmental risk assessment according to the table 2 of ECHA (2008).

Table 10: E-fate and behaviour parameters used for the environmental risk assessment of the tin (II) sulphate

Parameter	Unit	Value	Remark	Reference
Water solubility	[$g.L^{-1}$]	188	AT 19°C, pH not reported	*C.f.* section 7.4
Vapour pressure – Vp	[Pa]	1E-06	Minimum value in EUSES considering that the substance is not volatile	
Henry coefficient - HENRY	[$Pa.m^3.mol^{-1}$]	4E-06		
Octanol-water partitioning coefficient - K_{ow}	[-]	Not appropriate for metals	-	ECHA (2008)
Biotic and abiotic degradation	[-]	0	Biotic and abiotic degradation rates should be set to zero for metals	ECHA (2008)
Partition coefficient for soil: water – $Kp_{soil:water}$	[$L.kg^{-1}$]	1905	No soil sorption data were available for Sn, adsorption of Sn is assumed to be comparable with Pb	Bockting *et al.* (1992), cited in van Vlaardigen *et al.* (2005)
Partition coefficient for suspended matter: water – $Kp_{suspended\ matter:water}$	[$L.kg^{-1}$]	371535	-	

As mentioned by Van Vlaardigen *et al.* (2005), the partitioning of heavy metals (inorganic tin included) in sediment and soils has been the subject of several RIVM reports in the last decade. For tin, the partitioning coefficients mentioned in Table 10: have been used by Van Vlaardigen *et al.* (2005) to calculate the environmental risk limits for inorganic tin. These values have been also selected by the evaluating MSCA for the environmental risk assessment of tin (II) sulphate.

7.7.2. Bioaccumulation

According to Howe and Watts (2005), inorganic tin compounds may be bio-concentrated, but data are limited. The authors cited the study of Thompson *et al.* (1972) which estimated that the bio-concentration factors of inorganic tin were 100, 1000, and 3000 for marine and freshwater plants, invertebrates, and fish, respectively. Seidel *et al.* (1980), also cited in Howe and Watts (2005), demonstrated that marine macroalgae can bio-concentrate the Sn^{4+} ion by a factor of 1900. Those data should be considered with caution, as no detailed on the study is provided in Howe and Watts (2005).

More recently, Ikemoto *et al.* (2008) assessed the biomagnification of trace elements (including tin (Sn)) in the aquatic food web in the Mekong delta. In this study, the authors reported the concentrations of trace elements of the various biota (fifteen fish species, five crustacean species, one gastropod specie, phytoplankton, particulate organic matter, filtered water column) that make up the food web in the mainstream of the Mekong Delta. The food web structure was established based on Stable Carbon and Nitrogen Isotope Analysis and indicated that the food web of the mainstream of the Mekong Delta consisted of three trophic levels. The Sn-concentrations in water were 0.033 to 0.059 $\mu g.L^{-1}$, *i.e.* mean of 0.046 $\mu g.L^{-1}$. The mean Sn-concentration in crustacean species and fish species were 0.0752 and 0.0838 $\mu g.g^{-1}_{dwt}$, respectively. Based on these results, a bioaccumulation factor (BAF) can be calculated for crustaceans and fishes as:
$BAF = [Sn]_{fish/crustacean} / [Sn]_{water\ column}$

With the following results:

$BAF_{crustacean} = 1634\ L.kg^{-1}_{dwt}$

$BAF_{fish} = 1821\ L.kg^{-1}_{dwt}$

The trophic level-dependent accumulation of Sn was not found in organisms collected from the Mekong River. However, the absence of biomagnification should be considered with caution. Indeed, other elements measured by the authors were not biomagnified or diluted through the food chain in the Mekong Delta, contrary to previous studies considering the food chain of another ecosystem. The authors concluded that more research of the influences of the elements on the ecosystems and human life is required for various ecosystem of the world.

The bioconcentration and bioaccumulation factors mentioned above for algae, invertebrates, and fish are in the same degree of magnitude, and indicate that Sn may be bioconcentrated with BCF/BAF ranged from 100 to 3000 $L.kg^{-1}$.

As a conservative approach, and considering that to our knowledge no data is currently available on the potential regulation of internal concentration of Sn in aquatic organisms through active regulation, storage, or combination of both processes, the potential bioconcentration of tin (II) sulphate should be considered for the environmental risk assessment using a BCF/BAF of 1821 $L.kg^{-1}$.

7.8. Environmental hazard assessment

In accordance with ECHA guidance on information requirements and chemical safety assessment (2008), since ecotoxicity data are lacking for tin (II) sulphate, read-across for ecotoxicity data from other inorganic tin was considered.

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

Table 11: Toxicity of inorganic tin compounds to fish

Tested substance	Organism / Species	Endpoint	Value	Source / Reliability
Acute toxicity				
Tin dichloride ($SnCl_2$)	Goldfish (*Carassius auratus*)	7d-LC_{50} (embryo-larval test)	2.14 $mg.L^{-1}$ of measured Sn	Birge (1978) cited in Howe and Watts (2005) RI=3

Tin dichloride ($SnCl_2$)	Carp (*Cyprinus carpio*)	96h-EC_{50} (hatching success)	294.57 mg.L^{-1} of $SnCl_2.2H_2O$ 155 mg.L^{-1} of Sn	Kapur and Yadav (1982) cited in Van Vlaardigen *et al.* (2005) and in Howe and Watts (2005) RI=3
Tin dichloride ($SnCl_2$)	Mud dab (*Limanda*) [marine]	96h-LC_{50}	>1 mg.L^{-1} of Sn **>0.035 mg.L^{-1} of measured dissolved Sn**	Taylor *et al.* (1985) cited in Howe and Watts (2005) RI=2
Sn^{2+}	Largemouth bass (*Micropterus salmoides*)	8d-LC_{50} (embryo-larval test)	1.9 mg.L^{-1} of Sn	Birge *et al.* (1978b) cited in Howe and Watts (2005) RI=3
Tin dichloride ($SnCl_2$)	Zebrafish (*Danio rerio*)	120h-LC_{50} (Embryo development) [OECD 212]	22.8 µM 118.71*22.8E-03 = **2.71 mg.L^{-1} of Sn**	Sisman et al. (2009) RI=2 **[Key study]**
Tin dichloride ($SnCl_2$)	Carp (*Cyprinus carpio*)	NOEC (hatching success)	7.8 mg.L^{-1} of $SnCl_2.2H_2O$ 4.1 mg.L^{-1} of Sn	Kapur and Yadav (1982) cited in Van Vlaardigen *et al.* (2005) RI=3
Sn^{2+}	Rainbow trout (*Oncorhynchus mykiss)*	28d-LC10 (mortality)	7.55E-02 mg.L^{-1} of Sn	Birge *et al.* (1981) cited in Van Vlaardigen *et al.* (2005) RI=2-3
Sn^{2+}	Rainbow trout (*Oncorhynchus mykiss)*	28d-LC50 (mortality)	0.4 mg.L^{-1} of Sn	Birge *et al.* (1978) cited in Howe and Watts (2005) RI=2-3

Data on acute toxicity of inorganic tin to freshwater and marine fish revealed that the sensitivity of freshwater compared to marine fish species could be considered as equivalent. Hence, both set of data have been pooled.

Birge *et al.* (1978; RI=3) assessed the effects of several elements, including $SnCl_2$, on the goldfish *Carassius auratus* in embryo-larval bioassays in laboratory-controlled conditions. After 7 days of exposure, the LC50 was 2.14 mg.L^{-1} of measured Sn.

Kapur and Yadav (1982; RI=3) assessed the effects of some heavy metal salts, including tin salts, on the hatching success and the proportion of normal/abnormal development in the carp (*Cyprinus carpio*). Eggs were exposed to $SnCl_2$ in triplicate conditions (pH = 7.51; 16°C; Hardness = 360 mg $CaCO_3$.L^{-1}; DO = 5.6 mg.L^{-1}; BOD_5 = 1.2 mg.L^{-1}) to a nominal concentration range from 25 to 500 mg.L^{-1} of tin chloride ($SnCl_2$,$2H_20$), equivalent to a nominal concentration ranging from 13.1 to 263 mg.L^{-1} of Sn. After 96h of exposure, the

EC_{50} for hatching success was 294.57 mg.L^{-1} of tin chloride, equivalent to 155 mg.L^{-1} of Sn.

One valid publication is available investigating the short-term toxicity of tin dichloride to marine fish. Taylor *et al.* (1985; RI=2; GLP-compliant) assessed the acute toxicity of tin chloride with the dab (*Limanda limanda*), after 96h of exposure. The study was performed in controlled conditions (pH = 7.7; 12°C; flow through system; 34.5‰ of salinity; DO = 7.9 mg.L^{-1}). During the test medium preparation, the authors observed that tin chloride precipitated in contact with the saline medium. However, in this case, the turbidity was insufficient to mask the sublethal response of the test animals, and it was noted that the dabs, the only species tested, suffered from some laboured ventilation, possibly induced by the high turbidity. This study indicated that, at the maximum concentration of dissolved tin it was possible to maintain in seawater, i.e. 0.035 mg.L^{-1} of dissolved Sn, no mortality occurred over a 96 h period.

Sisman *et al.* (2009; RI=2) evaluated the possible teratogenic and genotoxic effects of $SnCl_2$ in adult zebrafish and their embryos and larvae. The teratogenic study included analysis of morphological malformations. A toxicity test was performed for zebrafish embryos and larvae with mortality and embryo development as endpoints. An early life stage toxicity test was performed in accordance with the OECD test guideline 212. 2-hpf eggs were exposed until 120-hpf to a nominal concentration range from 10 to 250 µM (eq. to 1.19 to 29.7 mg.L^{-1} of Sn). The LC_{50} (120-hpf) was 22.8 µM, eq. to 2.71 mg.L^{-1} of Sn. In addition, study results also revealed that exposure to doses lower than the LC_{50} did not significantly cause malformations during the embryonic stages (*i.e.,* 6 to 120-hpf).

In the RIVM report published by Van Vlaardigen *et al.* (2005), the Kapur and Yadav study (1982) was included in the chronic toxicity section of tin to freshwater organisms with a NOEC for reproduction of 7.8 mg $SnCl_2$/L. However, the NOEC reported in the RIVM report was derived by extrapolation of concentration-effects relationship based on the 96h-LC50 (see also above) and there is no information on the exposure duration that could justify considering the study as a chronic one. Therefore, the endpoint was not considered as reliable and a reliability index (RI) of 3 was attributed to the study.

Birge *et al.* (1978; RI=3) assessed the effects of several elements, including SnCl2, on the rainbow trout in embryo-larval bioassays in laboratory-controlled conditions. After 28 days of exposure, the LC50 was 0.4 mg.L-1 of measured Sn. In the RIVM report published by Van Vlaardigen et al. (2005), a 28d-LC10 of 0.076mg/L of Sn was reported from the Birge *et al.* (1981; RI=3) study. This value was derived by the statistical probit method from the previous study. However, a number of parameters were not reported, as the survival rate in the controls before and after hatching, concentration measurements of the substance during the test and the typical minimum average total length of control fish. Moreover, some criteria deviated from the OECD 210 guideline, as 1/the treatment period from fertilization for 4 days post-hatching instead of the 60 days post-hatching period recommended by the guideline, 2/abnormal individuals counted as dead individuals, 3/ temperature higher than the recommended one (13±0.5°C instead of 10±1.5°C).

<u>Relevant acute toxicity endpoint value for the risk assessment</u>:

96h-LC50 (marine fish) >0.035 mg.L^{-1} of Sn (Taylor *et al.,* 2005)

120h-LC_{50} (fish) = 2.71 mg.L^{-1} of Sn (OECD 212) (Sisman *et al*., 2009)

<u>Relevant chronic toxicity endpoint value for the risk assessment</u>:

The provided information is not sufficient to carry out a complete assessment of chronic data, nevertheless the data is reported for information:

28d-LC10 fish of 0.076mg/L of Sn (Birge *et al.* (1981) cited in Van Vlaardigen *et al.* (2005))

7.8.1.2. Aquatic invertebrates

Table 12: Toxicity of inorganic tin compounds to aquatic invertebrates

Tested substance	Organism / Species	Endpoint	Value	Source / reliability
Acute toxicity				
Sn^{2+}	Pulmonate snail (*Taphius glabratus*)	24h-NOEC (behaviour)	10 $mg.L^{-1}$ of Sn	Harry et Aldrich (1963) cited in Howe and Watts (2005) RI=3
$SnCl_2$	Oligochaete (*Tubifex tubifex*)	24h-EC_{50} (immobilization)	157.8 $mg.L^{-1}$ of Sn (*)	Khangarot (1991) cited in Van Vlaardigen *et al.* (2005) RI=3
		48h-EC_{50} (immobilization)	140.3 $mg.L^{-1}$ of Sn (*)	
		96h-EC_{50} (immobilization)	21.2 $mg.L^{-1}$ of Sn (*)	
$SnCl_2$	Oligochaete (*Tubifex tubifex*)	96h-LC_{50} (mortality)	30 $mg.L^{-1}$ of Sn	Fargasova (1994) cited in Van Vlaardigen *et al.* (2005) RI=2
Na_2SnO_3			27.5 $mg.L^{-1}$ of Sn	
$SnCl_2$	Midge (*Chironomus plumosus*)		3.6 $mg.L^{-1}$ of Sn	
Na_2SnO_3			**3.0 $mg.L^{-1}$ of Sn**	
$SnCl_2$	Amphipod (*Crangonyx pseudogracilis*)	48h-LC_{50} (mortality)	71.8 $mg.L^{-1}$ of Sn	Martin et Holdich (1986) cited in Van Vlaardigen *et al.* (2005) RI=3
		96h-LC_{50} (mortality)	50.1 $mg.L^{-1}$ of Sn	
Sn^{2+}	Daphnia (*Daphnia magna*)	24h-LC_{50} (mortality)	37 $mg.L^{-1}$ of Sn	Khangarot *et al.* (1987) RI=3
		48h-LC_{50} (mortality)	19.5 $mg.L^{-1}$ of Sn	
$SnCl_2$	Daphnia (*Daphnia magna*)	48h-EC_{50} (immobilization)	55 $mg.L^{-1}$ of Sn	Biesinger et Christensen (1972) cited in Van Vlaardigen *et al.* (2005) RI=3
$SnCl_2$	Daphnia (*Daphnia magna*)	48h-EC_{50} (immobilization)	21.56 $mg.L^{-1}$ of Sn	Khangarot et Ray (1989) cited in Van Vlaardigen *et al.* (2005) RI=3

$SnCl_2$	Marine crustacea (*Idotea balthica*)	106h-LC_{50} (mortality)	96 $mg.L^{-1}$ of Sn	El-Nady et Atta (1996) cited in Van Vlaardigen *et al.* (2005) RI=3
Chronic toxicity				
$SnCl_2$	Daphnia (*Daphnia magna*)	21-d LC_{50} (mortality)	42 $mg.L^{-1}$ of Sn	Biesinger et Christensen (1972) cited in Van Vlaardigen *et al.* (2005) RI=2-3
		21-d EC_{50} (reproduction)	1.5 $mg.L^{-1}$ of Sn	
		21-d NOEC (reproduction)	0.18 $mg.L^{-1}$ of Sn	

(*) Precipitation observed in the test solution.

Khangarot (1991; RI=3) assessed the acute toxicity of several metal salts, including $SnCl_2$, to a freshwater tubificid worm, *Tubifex tubifex*. Tubificid worms were exposed to a concentration range of metal salt in controlled conditions (30°C; pH = 7.6; DO = 5.8 $mg.L^{-1}$; Total hardness = 245 $mg.L^{-1}$ of $CaCO_3$). After 24, 48, and 96 hours of exposure, the following EC50(immobilization) were calculated:

24h-EC_{50}(immobilization) = 157.8 mg $.L^{-1}$ of total Sn

48h-EC_{50}(immobilization) = 140.3 mg $.L^{-1}$ of total Sn

96h-EC_{50}(immobilization) = 21.2 mg $.L^{-1}$ of total Sn

It should be noted that test solution of tin showed precipitation 2-3 hours after the addition of the tin salt ($SnCl_2.2H_2O$). As no analysis has been performed for measuring the Sn-concentration in the test medium, EC_{50} value should be considered with caution, because of a possible underestimation of the tin toxicity on tubificid.

Fargasova (1994; RI = 2) assessed the toxicity of Sn^{2+} ($SnCl_2.2H_2O$) and Sn^{4+} (Na_2SnO_3) with *Tubifex tubifex* and *Chironomus plumosus*. For each species, the organisms were exposed to tin salts during 96h of exposure in laboratory-controlled conditions. The following LC_{50}(96h) were calculated:

- For *Tubifex tubifex*:
    - 96h-LC_{50} = 30.0 $mg.L^{-1}$ of total Sn^{2+}
    - 96h-LC_{50} = 27.5 $mg.L^{-1}$ of total Sn^{4+}
- For *Chironomus plumosus*:
    - 96h-LC_{50} = 3.6 $mg.L^{-1}$ of Sn^{2+}
    - 96h-LC_{50} = 3.0 $mg.L^{-1}$ of Sn^{4+}

Relevant endpoint value:

- 96h-LC_{50}(*Tubifex tubifex*) = 27.6 $mg.L^{-1}$ of total Sn.
- 96h-LC_{50}(*Chironomus plumosus*) = 3.0 $mg.L^{-1}$ of total Sn.

Martin and Holdich (1986; RI = 3) performed tests on the acute toxicity of metal salts to freshwater amphipod, *Crangonyx pseudogracilis* Bousfield (Amphipoda), 48- and 96-h LC_{50}

values were determined for several metal salts, including Sn(II). The study was performed in controlled conditions (semi static test; 13°C; Total hardness = 50 mg.L^{-1} of $CaCO_3$; pH = 6.75; DO = 9.6 mg.L^{-1}). The LC50(48h) and the LC50(96h) were 71.8 and 50.1 mg .L^{-1} of total Sn, respectively.

Khangarot *et al.* (1987; RI=3) assessed the acute toxicity of heavy metal, including tin with *daphnia magna* in laboratory-controlled conditions. The LC_{50}(24h) and LC50(48h) was 37 and 19.5 mg.L^{-1} of Sn, respectively.

Biesenger and Christensen (1972; RI = 2-3) assessed the toxicity of several metal salts, including $SnCl_2$, to *Daphnia magna* in controlled conditions (pH = 7.74; Total hardness = 45.3 mg.L^{-1} $CaCO_3$; DO = 9 mg.L^{-1}). 12h-old daphnia were acutely (48h) and chronically (21d) exposed to a concentration range of tin salt. At the end of the tests, the following toxicity endpoints were calculated.

- 48h-LC_{50} = 55 mg.L^{-1} of total Sn;
- 21d-LC_{50} = 42 mg.L^{-1} of total Sn
- 21d-EC_{50}(reproduction) = 1.50 mg.L-1 of total Sn
- 21d-EC_{16}(reproduction) = 0.35 mg.L-1 of total Sn
- 21d-NOEC (reproduction) = 0.18 mg.L-1 of total Sn

Khangarot (1989; RI=3) assessed the acute toxicities of several metal salts, including $SnCl_2$, to *Daphnia magna*. Daphnids were exposed to a concentration range of metal salt in controlled conditions (20°C; pH = 7.6; DO = 5.6 mg.L^{-1}; Total hardness = 240 mg.L^{-1} of $CaCO_3$). After 24, and 48 hour of exposure, the following EC50 (immobilization) were calculated:

24h-EC_{50} (immobilization) = 38 mg .L^{-1} of Sn

48h-EC_{50} (immobilization) = 21.56 mg .L^{-1} of total Sn

El-Nady et Atta (1996; RI=3) exposed marine isopod (*Idotea baltica*) to different concentration levels of metals, including inorganic tin. The toxicity of inorganic tin was studied at different concentration levels between 1 to 135 mg.L^{-1}. The acute lethality of tin to the species was examined and found to be LC_{50}(24h) = 96 mg.L^{-1}.

<u>Relevant acute toxicity endpoint value for the risk assessment</u>:

96h-LC_{50} (midge) = 3.0 mg.L^{-1} of total Sn (Fargasova *et al.*, 1994)

<u>Relevant chronic toxicity endpoint value for the risk assessment</u>:

The provided information is not sufficient to carry out a complete assessment of chronic data, nevertheless the data is reported for information:

21d-NOEC (daphnids reproduction) = 0.18 mg.L-1 of total Sn (Biesinger et Christensen (1972) cited in Van Vlaardigen *et al.* (2005))

7.8.1.3. Algae and aquatic plants

Table 13: Toxicity of inorganic tin compounds to algae and aquatic plants

Tested substance	Organism / Species	Endpoint	Value	Source
$SnSO_4$	Green algae (*Pseudokirchnerella subcapitata*) [OECD201, GLP]	72-h EC_{50} (growth rate)	**>4.4 mg.L^{-1} of Sn**	Unpublished study report #3 (2011) RI=2
		72-h EC_{10} (growth rate)	**<0.024 mg.L^{-1} of Sn**	
$SnCl_2$	Green algae (*Ankistrodesmus falcatus*)	8d-EC_{50} (growth inhibition based on cell yield)	12 mg.L^{-1} of Sn	Wong *et al.* (1982) cited in Van Vlaardigen *et al.* (2005) RI=3
$SnCl_4$		8d-EC_{50} (growth inhibition based on cell yield)	2 mg.L^{-1} of Sn	
		8d-NOEC (growth inhibition based on cell yield)	0.053 mg.L^{-1} of Sn	
$SnCl_2$	Green algae (*Scenedesmus quadricauda*)	4h-EC_{50} (Cell number)	14 mg.L^{-1} of Sn	
$SnCl_2$	Cyanobacterium (*Anabaena doliolum*)	9d-EC_{10} (growth rate)	25 mg.L^{-1} of Sn	Dubey and Rai (1990a) cited in Van Vlaardigen *et al.* (2005) RI=3
$SnCl_2$	Cyanobacterium (*Synechocystis aquatilis*)	96h-EC_{10} (growth rate)	0.030 mg.L^{-1} of Sn	Pawlik-Skowronska *et al.* (1997) cited in Van Vlaardigen et al. (2005) RI=2-3
$SnCl_2$	Marine Diatom (*Sketelotoma costatum*)	72h-EC_{50} (growth inhibition based on cell yield)	0.2 mg.L^{-1} of total Sn	Walsh *et al.* (1985) cited in Howe and Watts (2005) RI=3
	Marine Diatom (*Thalassiosira guillardii*)	72h-EC_{50} (growth inhibition based on cell yield)	0.2 mg.L^{-1} of total Sn	
Sn (1)	Ciliate (*Tetrahymena pyriformis*)	9h-EC_{50} (growth inhibition)	90 mg.L^{-1} of total Sn	Sauvant *et al.* (1995) cited in Howe and Watts (2005) RI=3

(1) - Salt not stated.

The authors of the Unpublished study report #3 (2011; RI=2) performed a GLP-compliant study on the effect of Tin (II) sulphate (SnSO4) on the Growth of *Pseudokirchneriella subcapitata* according to the test guideline OECD 201. The test item was dissolved in sterilised growth medium. For the determination of algal growth three replicates for each concentration and six replicates for controls (test medium only) were exposed to nominal concentrations spaced by a factor of 3.16: 100, 316, 1000, 3160 and 10 000 µg SnSO4/L

(equivalent to 55, 174, 551, 1742 and 5514 µg Sn/L). The concentrations of total tin in the aqueous phase were chemically analysed in the algae cultures at test start and after 72 h. At the beginning of the test, the measured concentrations were between 54.4 and 92.8 % and between 26.2 and 69.2% of the nominal values at the end of the experiment. Therefore, mean measured concentrations (geometric mean) were used for the evaluation. A concentration dependent inhibition could not be observed for the range of concentrations tested. Over the test period of 72 hours the EC_{50} values for growth rate and yield were > 4.42 $mg.L^{-1}$ of Sn, equivalent to > 8.00 $mg.L^{-1}$ of $SnSO_4$. Nonetheless, the NOEC for yield and growth rate were estimated to be < 0.024 $mg.L^{-1}$ of Sn (equivalent to 43.6 $µg.L^{-1}$ of $SnSO_4$). With no clear dose/response relationship, these results should be considered with caution. However, it is important to note that the present PNEC water derived from the fish study (Sisman *et al.,* 2009) covers this endpoint. Moreover, according to the R10 guidance, the PNEC water cannot be derived from an algae chronic endpoint when no data on other trophic levels are available. As a consequence, a weight of evidence approach was applied taking into account the Unpublished study report #3 (2011), and less-reliable data described in the Table 13: .

Wong *et al.* (1982; RI=3) assessed the effects of tin compounds on algae in laboratory controlled conditions in order to assess tin compounds (including $SnCl_2$ and $SnCl_4$) effects on the reproduction (biomass, *i.e.* cell number) after 8d of exposure to a concentration ranging up to 50 $mg.L^{-1}$ of Sn, using only the test specie *Ankistrodesmus falcatus*. The following results were obtained.

For *Ankistrodesmus falcatus* var. *acicularis*

- 8d-EC_{50} (biomass) = 12 $mg.L^{-1}$ of Sn^{2+}
- 8d-EC_{50} (biomass) = 2 $mg.L^{-1}$ of Sn^{4+}

Pawlik-Skowronska *et al.* (1997; RI=3) assessed the impact of inorganic tin on the planktonic cyanobacterium *Synechobacterium aquatilis*. Test species were exposed in laboratory-controlled conditions to inorganic tin, to concentrations ranging from 1 to 10 $mg.L^{-1}$ of Sn. Growth (cell density) was measured as endpoint after 96h of exposure. No ECx nor NOEC/LOEC were calculated by the authors. EC_{10}(96h; growth) = 0.03 $mg.L^{-1}$ of total Sn was calculated by Van Vlaardigen *et al.* (2005) based on results from Pawlik-Skowronska *et al.* (1997).

Walsh *et al.* (1985; RI=3) reports effects of stannous chloride on growth and survival of two species of marine unicellular algae, *Skeletonema costatum* and *Thalassiosira pseudonana*. In laboratory-controlled conditions, marine algae were exposed to a range of five concentrations. Concentrations of tin compounds in stock solutions were estimated by measurement of elemental tin. Inorganic tin was only slightly toxic: the EC_{50} (72h) were 0.3 $mg.L^{-1}$ of $SnCl_2$ for both marine algae, which were equivalent to 0.2 $mg.L^{-1}$ of Sn.

Sauvant *et al.* (1985; RI=3) assessed the toxicity of Sn to *Tetrahymena pyriformis* in laboratory-controlled conditions. The growth inhibition was estimated after 3, 6, and 9h of exposure, and the following EC_{50} were calculated:

EC_{50}(3h; growth inhibition) = 132 $mg.L^{-1}$ of Sn

EC_{50}(6h; growth inhibition) = 80 $mg.L^{-1}$ of Sn

EC_{50}(9h; growth inhibition) = 90 $mg.L^{-1}$ of Sn

<u>Relevant endpoint value for the risk assessment</u>:

72h-EC50 (growth rate, cyanobacteria) > 4.4 $mg.L^{-1}$ of Sn (Unpublished study report #3, 2011)

The provided information is not sufficient to carry out a complete assessment of chronic data, nevertheless the data is reported for information:

EC_{10}(96h; growth) = 0.03 mg.L^{-1} Pawlik-Skowronska *et al.* (1997) cited in Van Vlaardigen *et al.* (2005)

7.8.1.4. Sediment organisms

No data.

7.8.1.5. Other aquatic organisms

Table 14: Toxicity of inorganic tin compounds to other aquatic organisms

Tested substance	Organism / Species	Endpoint	Value	Secondary source	Source
$SnCl_2$	Amphibians (*Gastrophryne carolinensis*)	7d-LC50 (embryo-larval test)	0.09mg Sn.L^{-1} (measured)	Howe and Watts (2005)	Birge (1978) RI=3

Birge (1978) assessed the effects of several elements, including $SnCl_2$, on the toad *Gastrophryne carolinensis* in embryo-larval bioassays in laboratory-controlled conditions. After 7 days of exposure, the LC50 was 0.09 mg.L^{-1} of measured Sn.

7.8.2. Terrestrial compartment

7.8.2.1. Terrestrial plants

Table 15: Toxicity of inorganic tin compounds to terrestrial plants

Tested substance	Organism / Species	Endpoint	Value	Source
$SnCl_2$	Rape (*Brassica napus*)	21-day NOEC (Shoot Height, Shoot Fresh Weight, Number of Emerged Seedlings) [OECD 208]	>1000 mg.kg^{-1}_{dwt} of Sn (nominal)	Unpublished study report #1 (2017) RI=2 **[Key study]**
	Soybean (*Glycine max*)	21-day NOEC (Shoot Height, Shoot Fresh Weight, Number of Emerged Seedlings) [OECD 208]	>1000 mg.kg^{-1}_{dwt} of Sn (nominal)	
	Carrot (*Daucus carota*)	28-day NOEC (Shoot Height) [OECD 208]	**125 mg.kg^{-1}_{dwt} of Sn (nominal)**	
	Sugar Beet (*Beta vulgaris*)	21-day NOEC (Shoot Fresh Weight) [OECD 208]	**125 mg.kg^{-1}_{dwt} of Sn (nominal)**	

	Oats (*Avena sativa*)	21-day NOEC (Shoot Height, Shoot Fresh Weight, Number of Emerged Seedlings) [OECD 208]	>1000 $mg.kg^{-1}_{dwt}$ of Sn (nominal)	
	Onion (*Allium cepa*)	28-day NOEC (Shoot Height, Shoot Fresh Weight, Number of Emerged Seedlings) [OECD 208]	>1000 $mg.kg^{-1}_{dwt}$ of Sn (nominal)	

In the unpublished study report #1 (2017), four Dicotyledonae (*Brassica napus, Glycine max, Daucus carota and Beta vulgaris*) including one nitrogen fixating species (*Glycine max*) and two monocotyledonous (*Avena sativa* and *Allium cepa*) terrestrial plant species were exposed to $SnCl_2$ mixed with soil, for 14 to 21 days after 50% germination in the control, in line with OECD testing guideline 208 (2006) and GLP. All the validity criteria were met.

However, the following points were raised:

• The number of seeds per test pot was higher than recommended by OECD TG 208 in pots of this size, for *Brassica napus* (recommended: 3 seeds per pot; in the study: 5), *Glycine max* (recommended: 1-2 seeds per pot; in the study: 3), and *Beta vulgaris* (recommended: 1-2 seeds per pot; in the study: 5). Similarly, 12 cm diameter pots were used instead of the recommended 15 cm. This may have affected the growth of the plants, especially for plants with the additional stress of exposure to the test item. However, no effects on mortality, emergence and phytotoxicity were observed for any tested plant species at any test concentration (only effects on fresh weight were observed), and the validity criteria were met for all plant species.

• The study has been conducted with a low content of organic material in the artificial soil (i.e., 0.94% organic carbon). The standard organic carbon content of 2% (relating to 3.4% standard organic matter content) was used to convert the endpoints to a standard soil (see Section R.16.5.4).

• The relative humidity was occasionally slightly under 45%. Nevertheless, no adverse effect was observed.

• A control replicate of *Daucus carota* was considered in the study report as an outlier without further information. The percentage emergence has not been calculated with this replicate and this could have affected the validity criteria especially on the emergence of control seedlings. Nevertheless, enough data on at least three species from different taxa of one monocotyledon and two dicotyledons have been provided as required by the regulatory requirement under REACH (Chapter R.7c) and the OECD 208 guideline.

For the reasons explained above the study is classified RI=2.

Table 16: Toxicity of inorganic tin compounds to soil macro-organisms

Tested substance	Organism / Species	Endpoint	Value	Source
$SnCl_2$	Annelid (*Eisenia fetida)*	10 wk-NOEC (mortality)	22754 $mg.kg^{-1}_{wwt}$ (nominal)	Fischer *et al.* (1997) RI=3
		10 wk-NOEC (reproduction)	18961.6 $mg.kg^{-1}_{wwt}$ (nominal)	

Fischer *et al.* (1997; RI=3) assessed the effects of several elements, including $SnCl_2$, on the annelid *Eisenia fetida*. After 10 weeks of exposure, the LC50 was 0.09 $mg.L^{-1}$ of measured Sn. However, this study does not follow the OECD TG 222. Indeed, in the study, a peaty marshland soil and horse manure in proportions 1:1 (m/m) with a moisture content of 65 to 70% were used, which does not correspond to the soil type recommended by the guideline. Moreover, there is no replicate in the controls, the 400 individuals were grouped in the same soil. Thus, the coefficient of variation of reproduction in the controls cannot be calculated. In addition, the mortality of the adult controls is not reported in the publication. The average temperature varies between 20 and 30°C instead of the recommended temperature of 20 ± 2°C. The age of the worms as well as their synchronization is not reported and the worms' weight less than 250 grams. Therefore, the study is classified RI 3. Nevertheless, this study shows that earthworms are not expected to be the most sensitive soil species.

Table 17: Toxicity of inorganic tin compounds to soil micro-organisms

Tested substance	Organism / Species	Endpoint	Value	Source
$SnCl_2$	Microbial inoculum	9d-EC_{10} (respiration inhibition)	6.8 $mg.kg^{-1}_{dwt}$ of Sn (measured, initial)	Lighthart *et al.* (1983) cited in Van Vlaardigen et al. (2005) RI=3
$SnCl_2$	Microbial inoculum	20d-NOEC (N-mineralisation inhibition)	297 $mg.kg^{-1}_{dwt}$ of Sn	Liang et Tabatabai (1977) cited in Van Vlaardigen *et al.* (2005) RI=3
$SnSO_4$	Microbial inoculum	8-9 y-NOEC (N-mineralisation inhibition)	234 $mg.kg^{-1}_{dwt}$ of Sn	Wilke (1989) cited in Van Vlaardigen *et al.* (2005) RI=3
Sn_2SO_4	Microbial inoculum	8-9 y-NOEC (nitrification)	59 $mg.kg^{-1}_{dwt}$ of Sn	Wilke (1989) cited in Van Vlaardigen *et al.* (2005) RI=3

For all the soil micro-organisms studies listed in Table 17, the following points were raised:

- Results from the studies cannot be normalized to standard organic matter soil. Therefore, the Reliability Index is set to 3 for all these studies.

- The results obtained in Lighthart *et al.* (1983) study have been carefully assessed considering the low endpoint values. This study shows several non-compliances with recommendations of the OECD TG 216 (21/01/2000) and OECD TG 217 (21/01/2000), which lead to important methodological biases within the experimentation. At first, the soil was dried before the preparation of the microcosms, which is problematic concerning the representativeness of the microbial flora naturally present in the soil and of its initial activity. The inoculation of the soil with an aqueous extract of fresh soil is questionable,

despite the authors wait 9 days before launching their treatment with the different metals. Indeed, it is unlikely that the soils treated this way will recover to their natural state with a reinstallation of the native microbial communities. It would have been necessary to work with fresh soils with naturally established microbial communities. Indeed, autoclaved, and re-inoculated soils are not representative of initial microbial communities present in soil and thus the intrinsic activity of the soil. In addition, the authors do not specify whether they have verified that the carbon contained in the biomass of the soil microcosms is greater than or equal to 1% of the total organic carbon content after inoculation. This information would have been valuable considering the inoculation method of the microcosms. The number of replicates (n=3) is insufficient given the preparation methodology used, it would have been necessary to work with n=6 replicates. It is noted that the coefficient of variation in control is of very acceptable value (CV=4%), but it was estimated from 30 individuals (without separate replicates). Except for the *Rifle* soil, the amount of water used during soil rehydration (70%) is far above the natural values measured during sampling and the maximal WHC preconized in OECD TG 216 and 217; these conditions are therefore not representative of natural conditions as the variations regarding the amount of water in the soil microcosms strongly influence microbial activity. At last, the microcosms are hermetically sealed during the incubation period, these elements are contrary to the recommendations of the OECD 216 and OECD TG 217.

In the light of this study, terrestrial microorganisms could be the most sensitive species in soil compartment (the endpoint is 100-fold lower than for plants) but the Lighthart's study is considered as **not reliable** for the reasons explained above. However, it cannot be excluded that microorganisms are the most sensitive species, and that reliable data on microorganism would lead to the derivation of a lower PNEC. Therefore, the proportionality of the requirement of a new soil microorganisms' study was investigated. Regarding the properties of the substance, tin (II) sulphate falls within hazard category 3 of the Guidance R7c, Table 7.11-2. Indeed, the lowest aquatic EC50 is above the 1 mg/L limit. Therefore, toxicity data on soil microorganisms could not be requested under compliance check to clarify this point.

However, tin is naturally present in soil. According to Geochemical Atlas of Europe (Salminen *et al*., 2005), the median of Sn on 848 sample points in European topsoil is 3 mg. kg^{-1}_{dwt} Sn. If the $PNEC_{soil}$ was derived from the Lighthart study (i.e., $PNEC_{soil}$ (AF=50) = 0.136 mg. kg^{-1}_{dwt} Sn), the $PNEC_{soil}$ would be more than one order of magnitude under the European background threshold and therefore unrealistic.

Several other arguments regarding soil exposure are also reported in section **7.13.2** and show that there will be no added value to request a new study on microorganisms. Indeed, calculating the risk ratio with the $PNEC_{soil}$ derived from the Lighthart study (RI=3) which is 20-fold time lower than the one derived from the Unpublished study report#24, shows that the final conclusions will remain unchanged.

Therefore, the endpoint value derived from the OECD 208 plant study is used to derive the PNEC for the soil risk assessment.

<u>Relevant endpoint value for the risk assessment</u>:

28d-NOEC (terrestrial plant) = 266 mg.kg^{-1}_{dwt} of Sn (nominal, standard C_{org} 2%) (Unpublished study report #24, 2016)

7.8.3. Microbiological activity in sewage treatment systems

The authors of the unpublished study report #2 (2011; RI=1) performed a GLP-compliant study on the effects of tin (II) sulphate on STP-microorganisms, according to OECD TG 209.

As inoculum microorganisms from a sewage treatment plant fed with municipal wastewater were used.

The test item was given to the synthetic sewage with a concentration of 62.5, 125, 250, 500 and 1000 mg SnSO4 per litre. The content of the vessels was stirred and aerated for 3 h at 20 ± 2 °C. Two replicates were prepared for controls (synthetic sewage and inoculum only), solitaire vessels were used for the treated assays.

The total microbial respiration rate of the activated sludge incubated with concentrations of 62.5 to 1000 mg SnSO4 per litre was found to be within 72.5 and 118.2 mg O2/(L*h) after three hours. The respiration rate was significantly inhibited by the test item. The results show, that up to a concentration of 500 mg SnSO4 per litre, the respiration inhibition was found to be < 20 %. Therefore, 500 mg were assessed as EC_{20}.

The EC50 of tin (II) sulphate (SnSO4) on the total microbial respiration rate (total oxygen uptake including heterotrophic and nitrification uptake) of an activated sludge is 1194 mg/L (95 % CL not available).

Relevant endpoint value for the risk assessment:

EC_{50} (respiration inhibition) = 1194 mg.L^{-1} of $SnSO_4$, *eq.* to 650.9 mg.L^{-1} of Sn (unpublished study report #2, 2011)

EC_{20} (respiration inhibition) = 500 mg.L^{-1} of $SnSO_4$, *eq.* to 276.4 mg.L^{-1} of Sn (unpublished study report #2, 2011)

7.8.4. PNEC derivation and other hazard conclusions

Table 18: PNEC derivation and other hazard conclusions

Hazard assessment conclusion for the environment compartment	Hazard conclusion	Remarks/Justification
Freshwater	$PNEC_{freshwater}$ = 2.71 µg.L^{-1} of Sn	Assessment factor: 1000 (three acute toxicity data available) Extrapolation method: Assessment factor method based on 120h-LC_{50} (fish) = 2.71 mg.L^{-1} of Sn (Sisman *et al.*, 2009) The chronic studies have not been used for the derivation of the PNEC because the provided information of the test does not allow a complete assessment of them. Nevertheless, a derivation of PNEC based on chronic data would lead to value closed to the actual PNEC (3 µg/L)
Marine water	$PNEC_{Marine\ water}$ = 0.271 µg.L^{-1} of Sn	Assessment factor:10000 (three acute toxicity data available from freshwater and saltwater species) Extrapolation method: Assessment factor method based on 120h-LC_{50} (fish) = 2.71 mg.L^{-1} of Sn (Sisman *et al.*, 2009)

Sediments (freshwater)	$PNEC_{sediment}$ = 875.5 $mg.kg^{-1}_{wwt}$ of Sn	Extrapolation method: Equilibrium partitioning using $LogKp_{susp/water}$ = 5.57, *i.e.,* $Kp_{susp/water}$ =371535 $L.kg^{-1}$ according to ECHA guidance – appendix R.7.13-2
Sediments (marine water)	$PNEC_{marine\_sediment}$ = 87.5 $mg.kg^{-1}_{wwt}$ of Sn	
Sewage treatment plant	$PNEC_{STP}$ = 6.51 $mg.L^{-1}$ of Sn	Assessment factor: 100 Extrapolation method: Assessment factor method based on EC50 (respiration inhibition) = 650.9 $mg.L^{-1}$ of total Sn (unpublished study report #2, 2011)
Soil	$PNEC_{soil}$ = 2.66 $mg.kg^{-1}_{dwt}$ of Sn	Assessment factor: 100 Extrapolation method: Assessment factor method based on 28d-NOEC (terrestrial plant) = 266 $mg.kg^{-1}$ of Sn (unpublished study report #1, 2016)

7.8.5. Conclusions for classification and labelling

Regarding acute toxicity data, LC50 for fish, EC50 for invertebrates and EC50 for algae are ranging from 1 to 10 mg/L. Based on these data no classification for acute toxicity is needed.

According to the Guidance on the Application of the CLP Criteria, Annex I, Table 4.1.0 section (b), in the case substances for which adequate chronic toxicity data are not available (iii), **tin(II) sulphate should be classified, based on acute data, as Aquatic Chronic 2 H411** and evaluating MSCA advises the Registrants to apply this classification.

The chronic studies have not been used for the above suggested classification because the provided information of the test does not allow a complete assessment of them. Nevertheless, as they would lead to a more severe classification, they would be re-assessed in the frame of a classification dossier, considering how the missing information/deviation could impact the classification.

7.9. Human Health hazard assessment

Data basis

The conclusion and evaluation were based on the aggregated dataset retrieved in 2017 and the last updated version of the CSR of 15 June 2022. In addition, a literature search has been performed in Medline with tin (II) sulphate between 2017 and 2022.

In addition, this evaluation also takes previous international evaluations or reviews into account, in particular EFSA (2018) assessment on tin chloride.

Read-across approach

For the endpoints repeated-dose toxicity, carcinogenicity, reproductive toxicity, and mutagenicity a read-across approach has been proposed in the registration 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 by the registrants. For repeated-dose toxicity by inhalation, a read-across with tin(II) oxide (synonym: tin monoxide) has also been proposed. For acute toxicity by inhalation, a read-across with tin (II) oxalate is also proposed.

The proposed read-across hypothesis is that tin(II) sulphate and tin(II) chloride, tin(II) monoxide or tin(II) bismethanesulphonate have similar toxicological properties because they all dissociate into the common tin cation Sn^{2+} which is responsible of the effects. The

non common counter-ions are predicted to have no impact on the toxicological profile of the substances.

Table 19: Identity of the substances proposed for read-across

Substance	CAS No	EC No	Structure	Comments
Tin (II) chloride (synonym : stannous chloride, tin dichloride, tin protochloride)	7772-99-8	231-868-0	$SnCl_2$	Registered
Stannous chloride dihydrate	10025-69-1	600-045-1	$SnCl_2.2H_2O$	Pre-registered
Tin(II)bis(methanesulfonate)	53408-94-9	401-640-7	$C_2H_6O_6S_2Sn$	Registered
Tin(II) oxide (synonym: stannous oxide)	21651-19-4	244-499-5	OSn	Registered
Tin(II) oxalate	814-94-8	212-414-0	$C_2H_2O_4.Sn$	Registered

Physico-chemical properties

Based on the available data, no major differences have been identified in the physico-chemical properties of tin(II) sulphate and tin(II) chloride or Tin(II) bis(methanesulfonate) (molecular weight, form, melting point and vapour pressure).

However, for tin(II) oxide, differences in solubility in water has been noted compared to the other tin(II) compounds. In addition, particles of tin(II) oxide are of lower sizes (nano or particles< 10µm) than tin(II) sulphate (94% between 10 and 100 µm); this issue regarding the size is not covered in the current dossier.

In general at pH>3, tin(II) ions in aqueous solution tend to form hydrolytic species and forms 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 (e.g. bismethanesulphonate) forms strong complexes with Sn(II) throughout the entire pH range often hampering the formation of hydrolytic species even at low carbonate concentrations. Potential difference in behaviour in solution between tin(II) bis(methanesulphonate) and tin(II) sulphate is thus expected but it is of unknown consequences on their bioavailability.

Table 20: Physico-chemical properties of category members (ECHA disseminated database)

Substance	Tin (II) sulphate	Tin (II) chloride, anhydrous	tin(II)chloride, dihydrate[1]	Tin(II)bis (methanesulfonate)	Tin(II) oxalate	Tin(II) oxide
Form (ambient temperature)	Solid	Solid	Solid	Solid	Solid	Solid
Molecular weight	214.8	189.6	225.65	308.7	210.76	134.7
Melting point	Decompose at > 378°C	246°C	38°C	250°C	368°C	Decompose before melting
Vapour pressure	Test not required (melting point > 300°C)	25mmHg at 427.9°C	-	< 10^{-6} Pa	0.000000172 mmHg at 25°C	Test scientifically not necessary
Density	4.15 g/cm³ at 20°C	3.9 g/cm³ at 20°C	2.71 g/cm³ (temperature not specified)	2.4 g/cm³ at 20°C	7.9 g/cm³at 20°C	6.3 g/cm³ at 25°C
Dissociation constant	Log K=7.8	Log K=7.8	No information	No information	pKa=0.0003 at 23°C	Not feasible
Water solubility	Soluble > 178g/l	Soluble (178g/l at 20 °C)	Soluble (> 100 g/ml at 20°C)	Soluble (> 1000 g/l)	5.97mg/l at 20°C	Insoluble (<0.1mg/l, pH7, 25°C)

[1] IPCS inchem information (https://inchem.org/documents/icsc/icsc/eics0738.htm)

Toxicokinetics

There are no specific data on the adsorption, distribution, metabolism or excretion of tin Tin(II) sulphate, tin(II)bis(methanesulphonate), tin(II) oxalate or tin(II) oxide.

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. In the present case, all the compounds have the same oxidation sate (Sn^{2+}).

Based on the physico-chemical properties available, no major differences in the toxicokinetic of tin(II) chloride, tin(II) sulphate or tin(II) bis(methanesulphonate) is expected. However, the bioavailability of tin(II) oxide and to a lesser extent tin(II) oxalate may differ as differences in solubility have been observed.

Comparison of data from human health endpoints

In a published 28-day dietary toxicity study in Wistar rats, the toxicity of various inorganic tin compounds was compared for some toxicological parameters. No effects were observed with insoluble tin(II) monoxide up to the highest dose. Similar effects on body weight, food efficiency, anaemia and liver were observed in animals fed at the same dose level with stannous chloride dihydrate, oxalate and sulphate (De Groot *et al.,* 1973). Stannous chloride also induces distended intestine at the highest dose level. Actual dose levels in mg/kg is not available in the study.

A 28 day sub-chronic toxicity study (OECD TG 407) is available for Sprague-Dawley rats with tin(II)bis(methanesulphonate). The NOAEL in this study was the highest dose used: 125 mg tin/kg bw/d as tin(II) bis(methanesulfonate).

90-day sub-chronic toxicity studies by oral route are available with tin(II) bis(methanesulphonate) and tin(II) chloride. The studies were performed according to OECD test guideline 408 in rats.

In the study performed with tin(II) bismethanesulphonate, the rats were exposed by gavage at 0, 50, 150 and 450 mg/kg bw day (Unpublished study report#4, 2007). At the test day 20 the 450 mg/kg bw/day was lowered to 300 mg/kg bw/day for male animals. Marked toxicity was noted at the top dose, including severe clinical signs, body weight changes effects and death. Severe clinical signs were noted and in addition several animals had a dilated intestinal tract. According to the authors, local damage to the gastro-intestinal tract is the likely cause of death. Treatment with 150 mg/kg, 450/300 mg Tin(II)methanesulfonate/kg bw/day, by oral route caused changes in a number of amino acids and demonstrated enzyme changes, with an strong dose-related effect (no further information). The grip strength of the rats at the top dose was also reduced in both sexes at the end of the exposure period at the top dose. The NOAEL was considered to be 150 mg/kg/day tin (II) bismethanesulphonate (corresponding to 58 mg/kg tin considering correction for molecular weight) and the LOAEL 300 mg/kg (corresponding to 115 mg/kg tin, using molecular weight correction =300*118.7/308.7).

One of the reason to request a 90-day study with tin(II) chloride or sulphate, following 1st round of the substance evaluation (SEv) was to assess the read-across hypothesis. In the available new 90-day study performed with tin(II) chloride (Unpublished study report#5, 2021), dose levels were 0, 830, 2500 or 6000 ppm in diet, corresponding to 0, 57.3/73.3,

176/234, 449/670 mg/kg in male/females, respectively. Effect level (LOAEL) was the top dose 449 mg/kg (corresponding to 281 mg tin/kg bw, using molecular weight correction factor =681*118.7/189.6) with decreased locomotor activity as the main adverse effect. The NOAEL was 234 mg/kg.

Conclusion for systemic toxicity

A comparison of these studies suggests that tin chloride is less toxic than tin(II) bis(methanesulphonate) as no marked toxicity was noted in the new study at similar dose levels. Tin (II) bismethanesulphonate may have a higher bioavailability compare to tin(II) chloride. There are some evidence that tin (II) sulphate would behave similarly as tin(II) chloride. Differences in the toxicity profile between tin(II) chloride or sulphate and other tin(II) oxide compounds have been reported in the De Groot study (1973) by oral route. No systemic effects were observed in the study with tin(II) oxide, whereas at the same dose level, systemic toxicity was observed with tin(II) sulphate. These results suggest that the **systemic toxicity of tin salts is function of the solubility**.

Conclusion for local toxicity

No data are available to compare potential differences in local effects between tin(II) sulphate and tin(II) oxide **by inhalation route**. Local effects due to accumulation of insoluble particles in the lungs have been observed with tin(II) oxide. These effects are not expected with soluble particles of tin(II) sulphate. Nevertheless, because of the very low pH (<2) of tin(II) sulphate in solution, local effects are expected in lungs. It is particularly challenging to anticipate if local effects induced by accumulation of particles in lungs will be a worst case compared to local effects induced by irritating/corrosive properties of the test material.

Conclusion on read-across

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 toxicological properties of tin(II) sulphate.

Although tin(II) bis(methanesulfonate) shared structural similarity with tin(II) sulphate, bioavailability may be higher with this compound compared to tin(II) sulphate. Therefore, the results obtained with tin(II) bismethanesulfonate should be considered with caution.

By contrast, **tin(II) oxide may be of lower bioavailability than tin(II) sulphate for systemic toxicity and may underestimate systemic toxicity**. The read-across proposed with tin(II) oxide for local effects is not supported as differences in physico-chemical properties, bioavailability and potential differences in mode of action leading to local toxicity by inhalation does not justify the read-across.

Table 21: Data matrix

	Tin (II) sulphate	Tin (II) chloride	Tin (II) bis(methanesulfonate)	Tin(II) oxide	Tin(II) oxalate
CAS n°	7488-55-3	7772-99-8/10025-69-1	53408-94-9	21651-19-4	814-95-8
EC n°		231-868-0	401-640-7	244-499-5	212-414-0
Acute toxicity	Rats LD50= 2207 mg/kg 4(secondary literature)	Rats Oral: gavage OECD 423 LD_{50} = 1910 mg/kg 2 (reliable with restriction) **Acute tox. 4**	Rats Oral: gavage OECD 401 LD_{50} = 1621 mg/kg **Acute tox. 4**	No data	Rats Inhalation OECD 436 LC50=2mg/l 2 (reliable with limitations) **Acute Tox. 4**
Skin irritation or skin corrosion	*In vitro* skin corrosion, OECD 431 Not corrosive Waiving for skin irritation test. pH-value of 2.5 w/w % solution of $SnSO_4$ is < 2. So it is assume that the substance is irritating or corrosive to the skin. **Skin irrit 2 (self-classification)**	Waiving based on pH data **Skin Corr. 1B (self-classification)**	NZ rabbits OECD 404 Not irritating 1 (reliable without restriction) **Skin Corr. 1B** (harmonised classification)	No data	*In vitro* skin corrosion, (Unpublished study report#6, 2018) OECD 431 Corrosive **Skin Corr. 1C** Rabbit (Unpublished study report#7, 2013) OECD 404 Not irritating (unchanged solid material)
Eye irritation	Waiving pH-value of 2.5% w/w solution of SnSO4 is < 2. So it is assume that the substance causes corrosive or severe irritant effect in eyes. **Serious eye damage**	Corrosive, pH determined to be 1.82 at 2% w/w; Rabbits (NZw) Males OECD 404 **Serious eye Damage** 1(reliable without restriction)	NZ rabbits OECD 405 **Serious eye damage** 1(reliable without restriction)	No data	Rabbits OECD 405 Not irritant (unchanged solid material) **Serious eye damage (self-classification)**
Skin sensitisation	Human patch test report **Sensitising (self-classification)**	Human patch test report with tin (II) sulphate **Sensitising**	Guinea-pigs OECD 406 2(reliable with restriction) **Sensitising**	Human patch test report with tin (II) sulphate **Sensitising**	Human patch test report with tin (II) sulphate **Sensitising**
Short-term repeated	Rat (Wistar) De Groot, 1973	Rat (Wistar) De Groot, 1973	Rats (SD) OECD 407	Rat (Wistar) De Groot, 1973	No data

dose toxicity study (28-d)	28-day toxicity study Oral:diet Doses: 0, 0.03, 0.1, 0.3, 1 % Sn in the diet NOAEL: 0.1% based on bw and haematological findings at ≥ 0.3% 3(unreliable)	28-day toxicity study Oral:diet Doses: 0, 0.03, 0.1, 0.3, 1 % Sn in the diet NOAEL: 0.1% based on bw and haematological findings at ≥ 0.3% 3(unreliable)	oral: gavage Doses: 0, 5, 25, 125 mg/kg NOAEL = 125 mg/kg bw 4 (secondary literature)	28-day toxicity study Oral:diet Doses: 0, 0.03, 0.1, 0.3, 1% Sn in the diet NOAEL: 1% 3(unreliable) Rat (Wistar) Unpublished study report#17, 2015 Inhalation Doses: 2.3, 9.2, 89 mg/m^3 NOAEC: 9.2 mg/m^3 (systemic) LOAEC: 2.3 mg/m^3 (local)	
Short-term repeated dose toxicity study (90-d), oral route	No data	Rats (Crl:WI(Han)) Unpublished study report#5 (2021) OECD 408 Oral: diet 0, 57.3, 176, 449 mg/kg in males and 0, 73.3, 234, 670 mg/kg in females NOAEL= 176 mg/kg based on locomotor activity impairments at 449 mg/kg 2(reliable with limitation) Rats (F334/N) NTP (1982) Oral: diet NOAEL: 0.19% based on decreased bw, gastric irritation 2(reliable with restriction)	Rats (SD) Unpublished study report#4 (2007) OECD 408 Oral: gavage 0, 50, 150, 450/300 mg/kg bw/d NOAEL= 50 mg/kg based on marked general toxicity including death, local gastric irritation at 300 mg/kg and changes in amino acids and enzymes at 150 mg/kg 4 (secondary literature)	No data	No data
***In vitro* gene mutation study in bacteria or in mammalian cells**	No data	Ames, Priva *et al. (*1991) Similar to OECD 471 Negative, 2(reliable with restriction) Mammalian cell gene mutation test, Mouse lymphoma cells Myhr *et al.*, 1991 OECD 476	Ames Unpublished study report#8 (1987) and #9 (1988) OECD 471 Negative 2 (reliable with restriction, No TA102 or E.coli strain)	No data	No data

		Negative 2(reliable with restriction)			
***In vitro* micronucleus study or cytogenicity study in mammalian cells**	Chromosome aberration test, human lymphocytes Unpublished study report #10, 2012 OECD 473 **Positive** with and without S9 1(reliable without restriction)	-	Chromosome aberration test, human lymphocytes Unpublished study report#18, 1987 OECD 473 **Positive** without S9 No information on cytotoxicity 2 (reliable with limitations)	No data	No data
***In vivo* mutagenicity**	Chromosomal aberration assay in bone marrow OECD 475 Unpublished study report#15 (2019) Oral: gavage 0,500, 1000, 2000 mg/kg Negative 2(reliable with limitations)	Chromosomal aberration test in bone marrow Unpublished study report#11, 1974 Similar to OECD 475 SD rats oral: gavage; 0 to 1300 mg/kg Negative 2 (reliable with limitations) SD rats Unpublished study report#12 (1974) Oral: gavage 0-1300 mg/kg bw Similar to OECD 478 (Rodent dominant lethal test) Equivocal 2 (reliable with limitations)	Micronucleus assay in erythrocytes CF-1 mouse Unpublished study report#14 (1986) and #13 (1989). oral: gavage (1000 mg/kg) or ip 50 mg/kg bw Similar to OECD 474 Negative after ip, equivocal after gavage 2(reliable with restriction)	No data	No data
Carcinogenicity	No data	Rat (F344/N) and mice (B6C3F1) NTP (1982) Similar to OECD 451 Oral: diet Equivocal 2(reliable with restriction)	No data	No data	No data
Reproductive	No data	CPB:WU rats Unpublished study report#19 (1979)	Wistar rats One-generation reproduction toxicity	No data	No data

toxicity study		Similar to OECD 416 Oral:feed 0 (control), 5, 10, 19 mg/kg NOAEL parental and reproductive > 19 mg/kg LOAEL developmental: ≥ 5 mg/kg 2(reliable with restriction)	study Unpublished study report#20, 2010 oral: feed Similar to OECD 415 LOAEL around 300 mg/kg based on lesions in the testes in F1. NOAEL= 100 mg/kg 2 (reliable with restriction)		
Prenatal development al toxicity	No data	Rat, rabbits, mice, and hamster OECD 414 not teratogenic up to 50 mg/kg Unpublished study report #21 (1972) 2(reliable with restriction)	No data	No data	No data

7.9.1. Toxicokinetics

There are no data on the absorption, distribution, metabolism or excretion of tin(II) sulphate. Nevertheless, general discussions are available on tin toxicokinetics in the following reviews: ATSDR, 2005; EFSA, 2005; JECFA, 2006; WHO, 2005.

The summary below is the summary of the information included in the report by WHO, 2005. Since then, no new data on toxicokinetics of tin has become available.

"In humans and laboratory mammals, absorption of inorganic tin from the gastrointestinal tract is low (generally less than 5%), but is influenced by dose, anion (compound solubility), and the presence of other substances. Unabsorbed ingested tin is mostly (95–99%) excreted in the faeces within 48 h. Absorbed tin distributes mainly to the bone, but also to the lungs, liver, and kidneys. Limited evidence suggests that inorganic tin does not readily cross the blood–brain barrier. Absorbed tin is mainly excreted in the urine, with some additional biliary excretion occurring. In mice, the biological half-life of absorbed inorganic tin was approximately 30 days."

7.9.2. Acute toxicity and Corrosion/Irritation

Summary and discussion of acute toxicity and irritation/corrosion

Acute toxicity

There is no reliable data available on tin (II) sulphate acute toxicity by oral route.

By oral route, tin (II) sulphate is reported to have an LD_{50} of 2207 mg/kg bw in a review (Gigiena I Sanitariya, 1986). A few details are available on these data (no information on strain, sex, doses, number of animals). On this basis, no classification was proposed by the lead registrant. It has to be noted that tin(II) chloride is acutely toxic by oral route leading to some uncertainties on this conclusion for tin(II) sulphate.

By inhalation route, based on the acute toxicity study available in rats with tin oxalate (unpublished study report#23, 2012), the registrants classified tin(II) sulphate as Acute Tox. 4, H332. The LC_{50} obtained was 2 mg/L in this study performed according to OECD TG 436. In the absence of more reliable data, evaluating MSCA agreed to the proposed classification, noting the **potential uncertainties on the read-across** (no justification provided).

Human data

As reported in EFSA report (2018), a dose-related increase in incidence of acute gastrointestinal irritation was already statistically significant at the lowest concentration of 161 mg Sn/kg tomato juice (corresponding to a bolus dose of 40 mg Sn). EFSA considered that the development of acute effects was probably due to the total bolus dose of tin rather than the concentration in food *per se*. From case reports, gastrointestinal adverse effects were reported after exposure to concentrations from 131 mg Sn/kg food. The symptoms included nausea, abdominal cramps, vomiting, headache, chills, and diarrhoea. Onset of symptoms was observed within two hours of consumption and the symptoms lasted for 2–48 h.

Corrosion/irritation

Skin

The dossier contains only an *in vitro* skin corrosive test performed with tin(II)sulphate which was negative. The study was similar to OECD TG 431. The test material was tested as a powder moistened with water (25 mg test material moistened with 25µL Water). However, there are limitations in the study as the positive control (potassium hydroxide) was only positive after 3 min but not after 60 minutes of exposure (positivity criteria not met as viability was above 15%). Therefore, the reliability of the study is questionable.

Table 22: 3 min treatment

3 min	Negative Control		Test Item		Positive Control	
	Tissue 1	Tissue 2	Tissue 1	Tissue 2	Tissue 1	Tissue 2
Absolute OD550 values	1.693	1.588	1.608	1.529	0.208	0.211
	1.727	1.580	1.585	1.541	0.215	0.212
	1.700	1.571	1.643	1.500	0.224	0.221
OD550 (mean of 3 aliquots)	1.707	1.580	1.612	1.523	0.216	0.215
OD550 (mean of 2 replicate tissues)	1.643*		1.568		0.215	
Mean relative tissue viability [%]	100		95		13**	
Inter tissue viability difference [%]***	7.7		5.7		0.4	

Table 23: 60 min treatment

60 min	Negative Control		Test Item		Positive Control	
	Tissue 1	Tissue 2	Tissue 1	Tissue 2	Tissue 1	Tissue 2
Absolute OD550values	1.292	1.726	1.188	1.224	0.256	0.322
	1.335	1.678	1.172	1.218	0.269	0.327
	1.379	1.713	1.183	1.221	0.269	0.317
OD550 (mean of 3 aliquots)	1.335	1.706	1.181	1.221	0.264	0.322
OD550 (mean of 2 replicate tissues)	1.521*		1.201		0.293	
Mean relative tissue viability [%]	100		79		19**	
Inter tissue viability difference [%]***	24.4		3.3		19.6	

* mean OD550 ≥ 0.8
** mean relative tissue viability of the 3 min. positive control ≤ 30%

In addition, although tin(II) sulphate as a solid may not be corrosive, tin (II) sulphate in solution has a very low pH (<2) and is expected to be corrosive. In a 2% solution tin (II) sulphate has a pH of 1.8 and this acidic pH would probably cause irritating or corrosive effects. The substance is reported to be irritating in human under occlusive dressing but no details on the test material was provided (solution or powder). On the same basis, tin(II) chloride has been classified as Skin corr. 1B (from the lead registrant's dossier, same Registrant as Tin (II) sulphate), because of the low pH of a solution of tin chloride in water, a classification of the substance as corrosive is needed. No justification on the sub-categorisation is provided and no other data are available. Overall, the evaluating MSCA concludes that a **classification of tin (II) sulphate as skin corrosive is warranted**.

It may be noted that article 5(1) of CLP on the identification and examination of available information on substance states "The information shall relate to the forms or physical states in which the substance is placed on the market and in which it can be reasonably expected to be used". In the case of tin (II) sulphate, workers exposure to both solid and liquid forms is expected, as shown by the proposed exposure scenarios modelled for both forms, **this fully justifies the need for classification**.

Eye
The waiving for eye irritation study was based on the following justification in the CSR: "Column 2 adaptation based on pH < 2". As a worst-case, the **Registrant proposed to self-classify the substance Eye dam. 1, H318 and evaluating MSCA agrees with this conclusion and classification**.

Respiratory tract
No relevant information is available.

7.9.3. Sensitisation

The registration dossiers did not contain any study for skin sensitisation, only a secondary source (WHO Food additives series: 55, 2005). According to that secondary source, tin salts are sensitising to skin based on reported positive patch test with tin (II) sulphate. Based on this information the registrant applies a self-classification as Skin Sens.1, H317. However, as previously noted by the Health council Netherland (2005), only a limited number of patch test reports are available. Indeed, it seems that only one case of occupational allergic contact dermatitis has been described in the literature.

A LLNA is available with tin chloride in Basketter *et al.* (1999) in which the test material was not further specified. The test was positive with SI values of 4.1, 6.5, and 6.3 at 5, 10 and 25% respectively. These results support the self-classification proposal of the registrant and the alert in human.

Evaluating MSCA agrees with the classification proposal Skin Sens. 1, H317.

7.9.4. Repeated dose toxicity

Animal data

Table 24: Summary of repeated-dose toxicity studies, oral administration

REPEATED DOSE TOXICITY_ORAL			
Method	**Type of effect**	**Remarks**	**Reference**
28-d Toxicity Study in rats Similar to OECD TG 407 prior to GLP 10/sex/dose Wistar rats oral, diet 4-week exposure 0, 300ppm, 1000 ppm, 3000 ppm, 10000ppm in the diet equivalent to around 12, 40, 120 and 400 mg/kg bw per day using default values for dose calculations (Table R.8-17 of ECHA guidance chapter R8) Parameters: Body weight and food consumption were recorded weekly. Haematological examinations were made on all rats on day 27. Weight and histological examination of liver, kidneys, heart, and spleen. Limitations: No information on actual tin dose level, some results are not reported.	Tin(II) monoxide No observed effects. NOAEL= 1000 ppm Tin(II) chloride, sulphate, oxalate **At 10000ppm** • Growth retardation • Decrease food efficiency • slight anaemia in both sexes (Hb, Ht, clinical signs) • Histopathological changes in liver in both sexes (homogeneous liver cell cytoplasm and oval cell type hyperplasia of bile ducts) **At 3000 ppm** • Growth retardation • Slight anaemia in both sexes In addition, rats fed on diets containing 1% tin chloride showed slightly distended small and large intestines. **NOAEL for tin(II)sulphate, chloride or oxalate: 1000 ppm**	2 (reliable with limitations) Test materials: **Tin(II) sulphate, Tin(II) chloride, dihydrate, Tin(II) oxalate, tin(II) monoxide**	De Groot, 1973a (28-day study sub party)

<u>90d Toxicity Study in rats</u> Similar to OECD 408 prior to GLP 10/sex/dose Wistar rats oral, diet 13-week exposure 0, 300, 1000, 3000, 10 000ppm in the diet equivalent to approximately 12, 40, 120 and 400 mg/kg bw per day using default values for dose calculations (Table R.8-17 of ECHA guidance chapter R8) End points monitored: survival, body weight, food intake, haematology (haemoglobin, haematocrit, total erythrocytes, total and differential leukocytes), serum chemistry (transaminases, alkaline phosphatase, bilirubin), urinalysis, organ weights (heart, kidney, liver, spleen, brain, gonads, thymus, thyroid, adrenals), and gross and microscopic pathology. Microscopic examinations were performed on rats fed with the 2 highest levels of tin chloride, 1% of tin oxide and on the controls. In the rats fed the intermediate levels of tin chloride, only the liver, kidneys and stomach were examined. Limitations: No information on actual tin dose level; Tin in the standard diet was no determined; only few organs were weight and list of organs examined for histopathology not provided; low haematological and biochemical parameters investigated; histopathological results not reported	<u>Stannous oxide:</u> No observed effects **NOAEL= 1000 ppm** <u>Stannous chloride:</u> **At 10 000ppm** - Mortality: 4 males. All rats sacrificed at week 9. Moderate testicular degeneration, severe pancreatic atrophy, brain, liver and bile-duct changes in prematurely dead animals - Anaemia (↓ Hb by 20%, ht by 6% compare to control) - Reduced food consumption - Abdominal distension on week 1 - Low of bw at week 8 **At 3 000ppm** - abdominal distension during the first 2 weeks - reduced food consumption - anaemia (decrease Ht by 4%) - liver changes (bile duct epithelium proliferation) - ↓ alkaline phosphatase (AP) **NOAEL = 1000ppm** In another study of De Groot, 1973b, Copper and iron had a protective effect on the anaemia induced by stannous chloride tested at 10 000 ppm	2 (reliable with limitations) Test materials: **tin(II)chloride dihydrate, tin(II)oxide**	De Groot, 1973a (90-day study sub party)
<u>90d Toxicity Study in rats</u> 35 and 250 ppm Iron 0, 50ppm, 150ppm, 500 ppm or 2000ppm stannous chloride dihydrate male and female rats limitations: only short study summary available	**2000ppm:** - Growth depression - reduced appetite and food efficiency - anaemia - Pancreatic atrophy and histological changes in the liver, kidneys, spleen, testicles, and heart in some animals **500ppm** - Growth depression, - reduced appetite and food efficiency - transitory decrease in haemoglobin The degree of severity was usually more pronounced in animals receiving the low iron diets. NOAEL = 150 ppm e.q., to around 7.5 mg/kg bw per day.	4 (not assignable) Test material: **stannous chloride dihydrate**	De Groot, 1973c Summary from JECFA, 1982

Preliminary 13-week repeated-dose toxicity study Similar to OECD 408, GLP status unknown F344/N Rats Oral: diet 0, 500, 1000, 1900, 3800, 7500 ppm stannous chloride in rats (equivalent to 16-236 mg tin/day) and 0, 1900, 3800, 7500, 15000, 30000 ppm in mice (equivalent to 311-2457 mg Sn/kg) iron : 160 ppm; Zn : 0.4 ppm, Cu : 2.4 ppm 10 rats or mice/group/sex Limitations: no haematological or biochemical parameters were measured, necropsy only performed on the animals that survived at the end of the study. Tabulated data on microscopically findings not available in the NTP report. Tin in the standard diet was no determined	In rats - No effect on survival - ↓ bw gain (> 10%) at 7500 ppm - ↑ gross distention of cecum and reddened gastric mucosa at ≥ 3800 ppm - No histopathological findings. In mice - no effect on survival up to 30,000 ppm - ↓ bw gain > 30% at 30000 ppm - Gross distention of the cecum in 60-90% of the male mice at ≥ 3800 ppm - No histopathological findings. NOAEL = 1900 ppm in both species	2 (reliable with limitations) Test material: food grade **anhydrous Tin(II) chloride**	NTP, 1982
90-day oral toxicity study in rats According to OECD 408, GLP-compliant CD(SD) rats Oral: gavage 0, 50, 150, 450/300 mg/kg N= 10/sex/dose Limitations: - Because of the early deaths in the high dose male group, the dose level of the high dose male group was reduced from 450 to 300 mg Tin(II)methane-sulfonate/kg b.w./day on test day 20.	**450/300 mg/kg** - ↓ survival: 3/10 males died on test days 8, 11 or 13 and 4/10 females died on test days 38, 48, 67 and 80, respectively. - Ataxia, soft faeces and/or pale or pale-reddish faeces in both sexes. Pilo-erection, pale skin or body parts, laboured breathing, reduced motility, rough fur, inflated abdomen or salivation were also noted for several animals. - No effects on clinical biochemistry - No changes in the urinary status of rats - Dilated intestinal tract - In dead animals: macroscopic lesions noted in the spleen, stomach, intestinal tract, prostate, seminal vesicle , liver, lungs , adrenals, thymus, caecum, pancreas and kidney. Moderate to marked reduction of lymphocytes in the spleen, thymus, and lymph nodes in five of the 7 rats that died prematurely. - No organ weight changes - Histopathology: No changes were noted in the surviving high dosed animals. - ↓ fore- and hind limb grip strength by 43% in male and 45% in female rats at maximum approx. 1-2 hours after dosing **(**week 13) **150 mg/kg** - Changes in a number of amino acids and demonstrated enzyme changes (unspecified in the summary), with a strong dose-related effect. Not considered adverse by study authors as no other concomitant findings	2 (reliable with limitation) Test material: **Tin(II) bismethane sulphonate** Vehicle: 5% aqueous hydroxypropylmethylcellulose gel	Unpublished study report# 4, 2007

	NOAEL = 150 mg/kg		
<u>90-day oral toxicity study in rats</u> According to OECD 408, GLP-compliant Crl:WI(Han) rats Oral: diet N=10/sex/dose 0, 850, 2500 or 6000 ppm for 90 days (e.q., to 57.3/73.3, 175.7/234.1, 441/669.5 mg/kg for male/female, respectively) Limitations: Requested information on Zn, iron, copper content not investigated, transferrin, parathyroid hormone, acid phosphatase, serum calcitonin	**441/669.5 mg/kg** - No effect on survival, clinical signs, ophthalmoscopy, - ↓ bw gain in males at the top dose - ↑ alkaline phosphatase at the top dose - ↓ locomotor activity at the top dose - no anaemia, no effects on lymphocytes in any organs - No decrease in serum calcium level - No effect on spermatogenesis - No effect on organ weight - Slight increase in secretory depletion of acinar cells in pancreas - No other histopathological findings in any organs - a few blood samples indicate marked copper deficiency in males **175.7mg/kg** **-** ↓ bw gain in males - A few blood samples indicate small magnitude copper deficiency in males NOAEL = 57.3 mg/kg in males and 234 mg/kg in females	1 (reliable without limitation compared to OECD TG) Test material: **Tin(II) chloride, anhydrous**	Unpublished study report# 5, 2021

Hb: haemoglobin, Ht: haematocrit

Table 25: Summary of repeated dose toxicity studies, inhalation

REPEATED DOSE TOXICITY BY INHALATION ROUTE			
Method	**Type of effect**	**Remarks**	**Reference**
28-day toxicity study in rat According to OECD 412, GLP-compliant Rat (Wistar) Inhalation, 6h/d, 5d/w Doses: 2.3, 9.2, 89 mg/m^3 Restriction: - significant variance in dose and humidity - read-across with tin(II) sulphate for local pulmonary effect is not acceptable	- no effect on survival - no clinical signs - ↓ bw gain in males at ≥ 9.2 mg/m3 in females at all dose tested (statistical significance and severity not specified). - slight ↓ in food consumption at 87.9 µg/L. - ↑ mean activated partial thromboplastin times were evident for males exposed to 9.2 mg/m^3 and all females Lung - ↑ lung and bronchi relative weights in all groups. - Accumulation of pigmented and flocculent material within alveoli, variably accompanied by both diffuse and local aggregations of alveolar macrophages, and increased cellularity of the BALT, Larynx - pigment accumulation within the epithelium and *lamina propria* Lymph nodes: - tracheobronchial and mediastinal lymph nodes (increased general cellularity, with or without the accumulation of pigmented material) Kidneys - ↑ tubular pigment NOAEC: 9.2 mg/m^3 (systemic) according to study authors LOAEC: 2.3 mg/m^3 (local lung findings) according to study authors	2 (reliable with limitation) Test material : **Tin(II) oxide** Vehicle: air	Unpublished study report #17, 2015

Summary and discussion on repeated-dose toxicity

- Oral route

In a 28-day and 90-day sub-chronic toxicity studies performed with tin(II) chloride in rat, changes in liver, kidney, pancreas, heart, spleen, testicles, growth retardation and anaemia were noted (De Groot *et al*., 1973a/b/c). 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 report. Furthermore, it is not clear from the study which organs were investigated for histopathology. The haematological system and the liver are identified in this study as a target organ for tin(II) chloride. From this 90-day study a NOAEL of 40 mg/kg can be derived. Similar findings were noted with tin (II) sulphate as tin chloride in the 28-day study. Tin (II) sulphate was not tested for an exposure of 90 days.

In the preliminary 90-day study, performed by NTP, rats and mice were exposed to tin chloride at 0, 500, 1000, 1900, 3800 or 7500 ppm in both species and at 15,000 ppm and 30,000 ppm in mice only in diet. Haematology and biochemistry investigation was not

performed. Decreased body weight was noted in rats and mice at the top dose. Distension of the caecum and reddening of the mucosal surface of the stomach were noted in rats at the mid and top dose levels. Distension of the caecum was also noted in mice at ≥ 3800 ppm. No histopathological changes were noted in rats or mice.

Interference with calcium homeostasis has also been reported with tin chloride at very low dose level. Indeed, decreased calcium concentration in serum and bones and reduced compressive bones strength has been observed in several studies by Yamagushi *et al.* (1976, 1979, 1980a/b, 1981a/b, 1982). Two hypotheses have been suggested by the authors. The **decrease in calcium content may have been induced by parathyroid hormone, a calcium-regulating hormone, to maintain calcium homeostasis or by a direct effect of tin(II) chloride on bone cells**. According to EFSA (2005) opinion 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.

In addition, interference with the status of iron, copper and zinc have also been observed in animals with tin chloride (Pekelharing, 1994) exposed to tin compounds. The mode of action is not totally clear, but could involve altered absorption/retention of these trace elements. As conclude by EFSA in 2005, **there is evidence of reduced status of iron, zinc, and copper when rats are fed diets containing 50 mg Sn/kg diet or higher**.

90-day sub-chronic toxicity studies by oral route is available with tin(II) bis(methanesulphonate). The studies were performed according to OECD TG 408 in rats. The concentration used were 0, 50, 150 and 450 mg/kg bw day of Tin(II) bismethanesulphonate (unpublished study report #4, 2007), via oral gavage. At the test day 20 the 450 mg/kg bw/day was lowered to 300 mg/kg bw/day for male animals. Treatment with 450/300 or 450 mg /kg bw/day, p.o. resulted in ataxia, soft faeces and/or pale or pale-reddish faeces for all male and female animals starting on test day 1. Additionally, pilo-erection, pale skin or body parts, laboured breathing, reduced motility, rough fur, inflated abdomen, or salivation were noted for several animals. Three of 10 males and four of 10 females treated orally with 450 mg died. Macroscopic post mortem findings in the 3 males and 4 females treated orally with 450/300 or 450 mg that died prematurely showed macroscopic lesions in the spleen ((severely) reduced in size), stomach (dilated, aerated, (mucosa) red discoloured), intestinal tract (dilated, aerated), prostate (reduced in size), seminal vesicle (reduced in size), liver (several pale spots, black discoloured), lungs (emphysematous, multiple black foci (diameter 2 mm), (right and central upper lobes) red-black discoloured), adrenals (enlarged), thymus ((severely) reduced in size), caecum ((severely) enlarged), pancreas (pale) and kidney (reduced in size). Additionally, three high dosed female animals showed a dilated intestinal tract. All findings were considered to be test item-related. Treatment with 150, 450/300 or 450 mg Tin(II)methanesulfonate/kg bw/day, p.o. caused changes in a number of amino acids and demonstrated enzyme changes, with an strong dose-related effect (no further information). The fore- and hind limb grip strength of the rats at the top dose was reduced by 43% for the male and by 45% for the female at maximum approx. 1-2 hours after dosing in week 13. The **NOAEL was considered to be 150 mg/kg/day tin (II) bismethanesulphonate** (corresponding to **58 mg/kg tin** considering correction for molecular weight) and the LOAEL 300 mg/kg (corresponding to 115 mg/kg tin, using molecular weight correction =300*118.7/308.7).

Based on these studies, a critical effect and dose-response relationship for tin(II) sulphate cannot be established. Additionally, evaluating MSCA noted that the effects observed in a 90-day 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 (II) sulphate sub-chronic studies. Therefore, a sub-chronic toxicity study (90-day), oral route (test method: OECD TG 408), in rats, using the registered substance, tin (II) sulphate or the analogue substance, tin chloride (EC n° 215-689-5) was requested in an ECHA decision of the 13 June 2018.

In order to clarify potential interference of tin(II) sulphate with calcium, iron, copper and zinc or calcium homeostasis, special investigations were requested in the 90-day study: *"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 (II) sulphate in the study. Furthermore, the investigation of the reversibility of the potential haemolytic effects induced by tin(II) sulphate shall be considered."*

The 90-day study requested in a decision following the first round of evaluation was submitted in 2021. Tin(II) chloride anhydrous was tested in male and female Crl:WI (Han) rats via oral dietary administration (Unpublished study report #5, 2021). The study was well-conducted and performed according to OECD TG 408. Groups of 10 rats per sex were given the substance at 0, 830, 2500 and 6000 ppm (equivalent to 57.3, 175.7, 449 mg/kg in males and 73.3, 234.1, 669.5 mg/kg in females) for 90 days. A 14-day preliminary study was used for dose setting. In addition, in the main study 6 rats/sex/groups were given tin(II) chloride anhydrous at the same dose levels for immunotoxicity testing. The diet contained 72 ppm Zinc, 140 ppm iron, 9.9 ppm copper. The left testis were examined in all males for the assessment of spermatogenesis, with CASA sperm counts, motility and morphology assessed.

Dose levels were chosen based on range-finding study where the following dose levels were tested: 0, 830, 2500 and 6000 ppm in males and females. As the slight decrease in male body weight gain was considered adverse in the range-findings study, the same dose levels were used in the main 90-day study. In the range-finding study, it was stated that the high dose levels of 6000 ppm was expected to produce little or no toxicity in animals. As little toxicity was observed at the top dose in the range finding study in males (slight decrease in body weight gain) and none in females, **it is questionable why a higher dose level was not use in the main study in order to produce to induce toxicity as recommended in the OECD test guideline**. The toxicokinetics performed in the main study in animals also suggest a **very low bioavailability of the test substance** and low level of exposure in the study even at the top dose. According to the recent ECHA advice on dose-level selection for the conduct of sub-chronic assays under REACH, the use of a dose level with minimal adversity in the range-finding study as the high dose in the main study is not acceptable.

Although the study was initially planned to be performed by oral gavage, the diet route was at the end chosen; the reason is unknown.

In the main study, no treatment-related mortality was observed. No effects on clinical signs or at ophthalmoscopy were noted. Mean cumulative body weight gain (day 1 through 90) was significantly decreased by 13 and 31% in males at 2500 and 6000 ppm. No significant adverse effect on body weight were noted in female up to the highest dose level (non-significant dose-related trend to decrease). For males at 2500 ppm, the significant decrease in body weight gain was mainly due to the first two-week of treatment. Nevertheless, as a trend for decrease was still observed from day 15 onward, the effect is considered adverse.

Table 26: Summary of the effects of tin(II) chloride on body weight gain (g) in males

Dose group (ppm)/days	1-8	8-15	15-22	22-29	29-36	36-43	43-50
0	44±4.6	40±4.2	28±3.4	24±4.2	22±3.7	20±6.3	-5.5±8.8

830	43±4.5	30±5.4	32±6.0	24±5.2	14±17	18±7.0	-3.3±8.7
2500	35±7.1*	34±4.5*	29±6.9	19±6.1	22±3.6	16±3.6	-5.2±5.8
6000	16±8.1*	20±9.5*	24±4.8	18±3.4*	21±4.3	12±6.0*	2.8±5.6
Dose group (ppm)/days	**50-57**	**57-64**	**64-71**	**71-78**	**78-85**	**85-90**	**1-90**
0	30±7.8	7.1±4.8	13±4.1	8.9±4.1	5.8±4.9	7.8±4.7	245±25.7
830	25±8.2	10±5.3	13±3.0	11±5.3	6.0±6.1	8.4±3.3	252±39
2500	27±3.5	7.6±3.2	9.9±3.3	8.6±4.1	2.7±2.8	7.2±3.2	212±13.0*
6000	22±5.2*	11±3.0	7.4±3.3*	5.2±3.7	4.9±2.7	4.2±3.8	168±11.9*

*p≤0.05

Table 27: Summary of the effects of tin chloride on body weight (g) in males

Dose group (ppm)/days	1 (pre-dosing)	8	36	64	90
0	163±16	254±21	368±28	420±35	455±37
830	164±13	255±22	364±47	414±64	468±53
2500	167±10	249±9.2	352±14	397±12	426±13
6000	160±9.3	222±15*	305±20*	353±17*	375±15*

No treatment-related effects in haematological parameters were noted in the study. Haemoglobin or haematocrit changes were not observed following exposure to tin(II) chloride. In animals showing a decrease in body weight compared to control, **a slight dose-related decrease in creatinine was noted at ≥ 2500 ppm**. No effects were noted in the immunotoxicity study (Keyhole limpet hemocyanin administered via intravenous injection. Analysis of anti-KLH antibodies (IgM and IgG)).

A significant increase in phosphatase alkaline was noted at the top dose in males (83IU/L vs 60UI/L in controls) and in females at the mid and top dose (50 and 58 IU/L, respectively, compared to 31 UI/L in controls).

No changes in organ weight, macroscopic or microscopic findings were noted in the study. However, a slight increase in acinar cell secretory depletion was noted in both male and females at the top dose (1/10 in controls vs 3/10 at 6000 ppm in males and 2/10 in controls vs 5/10 in females). Pancreas was not examined in the mid and high dose levels. Therefore, there is no information on the potential dose-response for this effect.

No effects on sperm parameters were noted in the study.

Toxicokinetics was also performed in the study. Exposure, as assessed by tin C_{max} and AUC_{0-24} values, tin levels increased with the increase in stannous chloride anhydrous dose level from 830 to 6000 ppm in males and females on day 1 and during week 13. No accumulation of tin was observed.

Spontaneous locomotor activity was measured at week 12 and recorded for 60 minutes and reported in 10-minute intervals. Locomotor activity was recorded with the room lights turned off and white noise switched on. The white noise generator was maintained (level recorded at the beginning and end of each session) at an appropriate level so that a sound meter registers between 60 and 80 dB (Decibels), during the course of the scheduled sessions. Animals were allowed to acclimatize in their holding cages to the white noise for at least 10 minutes prior to any procedure taking place in the room.
Recordings of activity was made using the Kinder Motor Monitor system with the following parameters reported:

- Basic movement: simple tally of all horizontal beam breaks
- Fine Movement: Measure of small movements such as grooming and head movements. Animal remains in a fixed point e.g. a single beam break with no other beams affected.

- Total Ambulation: Measure of large movements. When a new beam is blocked and the anchor beam is broken i.e. animal has relocated its whole body (e.g. a step forward). Total Ambulation = X Ambulation + Y Ambulation
- Total distance travelled Record of distance travelled around the cage. Total Distance Travelled = HD Periphery Distance + Center Distance
- Rearing (Event): Beam break on top grid.

Significant increase in basic movements, fine movement, total ambulations, total rears and total distance travelled were observed during the first (1 to 10 minutes) and second 10-minute (11 to 20 minutes) intervals for males given 6000 ppm compared with control. Basic movements, fine movements, and total distance travelled were also significantly decreased during the sixth 10-minutes interval (51 to 60 minutes) for males given 2500 or 6000 ppm. These observations were considered non adverse by the study authors because of the varying consistency (increased initially and then decreased at a later interval). In females, similar significant increases were noted during first 10 minutes in basic movements, total ambulations, total rears and total distance, at 6000 ppm. Based on combined sex data, the increase locomotor activity (basic movements, fine movements, total ambulations, total rears, total distance travelled) was still significant at 6000 ppm. **Based on these very consistent and significant findings in all parameters assessed, the increase in locomotor activity in both sexes is considered treatment related.**

No effects were noted on approach response, corneal tactile reflex test, touch response, auditory startle response, tail pinch, hindlimb foot splay, air righting ability, Quantitative forelimb and hind limb grip strength or pupillary response.

The concern identified with tin(II) bismethanesulphonate on grip strength, sperm and lymphocytes were not confirmed in this study. Indeed, no effect on sperm or estrous cycle were noted. In addition, no anaemia nor calcium serum level changes were induced by tin(II) chloride.

Specific analysis requested in the decision on iron, zinc, copper, transferrin saturation, parathyroid hormone, acid phosphatase or serum calcium calcitonin were not provided with the study report. Nevertheless, serum calcium levels were not affected in the study. No effects were noted in liver, kidney, or bones. Haematology parameters were unchanged in the study and no anaemia was observed.

Following request, Zinc and Copper were analysed in a few remaining plasma samples from the toxicokinetic part. In order to have a sufficient blood sample, the samples were pooled for each sex/group to be able to perform both the analysis on Copper and Zinc. Based on the available analysis, **a dose-related decrease in copper was noted in males**. No clear differences was noted in Zinc levels based on these pooled samples.

Table 28: Concentration of copper in blood (pooled analysis, ng/mL)

Copper (ng/mL)	Control	Low dose	Mid dose	High dose
Day 1	1280	1250	1340	1300
Day 91	1680	1280	1120	465

In contrast, to other sub-chronic toxicity study (e.g., NTP, 1982), gastro-intestinal tract disturbance were not observed in this study. This may support the hypothesis that gastrointestinal absorption inhibition may be related to the observed effects in haemoglobin levels or bone strength in the other short-term studies in rats. However, there are no data to support the hypothesis.

It is noted that gastric macroscopic lesions were observed in the NTP study (1982). In both dietary studies, anhydrous stannous chloride was used as test material. In the context of the NTP study (1982) the purity was approximately 98.5 %, whereas in the recently performed 90-day study a higher purity was certified. Potential difference in the content of

iron was identified (higher content in the NP study). However, this is not considered to be responsible of the difference of the results observed in this study compared to the others. Instead of this potential lower level of iron, no difference in test item preparation was identified, thought the exact diet composition in the NTP study was not available. No potential chelating compounds were identified in the diet in the 2022 study. Although the bioavailability was shown to be low, male exposure was observed in the 90-day study (2022). There were no toxicokinetics data available in the NTP, 1982 study. Overall, no significant difference in the study methodology was identified that could explain the differences in the effects observed on the GI tract and therefore affect the outcome of the recent 90-day study.

The NOAEL is considered to be 57.3 mg/kg in males and 234 mg/kg in females based on the adverse effect observed on locomotor activity in both sexes and body weight decrease and copper deficiency in males and the evaluating MSCA agrees with these values.

Human data
According to EFSA analysis (2018), the limited data available in humans on effects of stannous chloride on essential elements indicate that zinc status can be negatively affected. The conclusion is based on the study by Johnson *et al.* (1982). Daily doses of 50 mg tin/day during 40 days, corresponding to 0.7 mg Sn/kg bw per day, reduced significantly the retention of zinc while no effects were observed on other essential element (copper, iron, manganese, magnesium).

- Inhalation route

As Registrants have not classified the substance as corrosive and as data are insufficient to assess the local properties of tin (II) sulphate, a range-finding study was initially requested in the draft decision in order to identify appropriate dose levels for the 90-day study to be conducted and avoiding pain and distress of animals. It was further proposed to perform the 90-day study by the most relevant route to allow an identification of potential systemic effects of tin (II) sulphate.

The Registrants proposed to use the available 28-day inhalation toxicity study performed with Tin monoxide (CAS n° 21651-19-4, EC n° 244-499-5) to **classify tin (II) sulphate as STOT RE 1 for respiratory tract and kidney**. This classification aims to cover the identified concern on possible local effects to the respiratory tract after an inhalation exposure of workers to tin (II) sulphate and in order to avoid conducting the range-finding study requested in the initial draft decision.

In this 28-day study, male and female Wistar rats were exposed to dust of tin monoxide during 28-day (nose only), 6 hours per day and 5 days per weeks. The GLP study was conducted according to OECD TG 412. The dose tested were 0, 2.44, 9.19 and 87.9 µg/l (=mg/m^3). The following summary of results is available on ECHA disseminated website: *"There were no treatment related clinical signs observed during the detailed weekly physical examination. Lower body weight gain was evident for males exposed to 9.19 µg/L and 87.9 µg/L and for all females exposed to tin monoxide. Food consumption was also slightly reduced for males exposed to 87.9 µg/L. A statistically significant increase in group mean activated partial thromboplastin times were evident for males exposed to 9.19 and 87.9 µg/L and all females exposed to tin monoxide. Group mean venous blood oxygen saturation levels were increased for females exposed to 9.19 µg/L and both sexes exposed to 87.9 µg/L. Two hours after the completion of exposure in week 4, tin was detected in the plasma of a single male and female exposed to 9.19 µg/L and in all animals exposed to 87.9 µg/L. Tin was not quantifiable in control animals or animals exposed to 2.44 µg/L. Group mean lung and bronchi weights (adjusted for terminal body weight) were greater than control for all animals exposed to tin monoxide.*

Histopathological changes related to treatment were observed within the lungs (the accumulation of pigmented and flocculent material within alveoli, variably accompanied by

both diffuse and local aggregations of alveolar macrophages, and increased cellularity of the BALT), tracheobronchial and mediastinal lymph nodes (increased general cellularity, with or without the accumulation of pigmented material), larynx (pigment accumulation within the epithelium and lamina propria) and kidneys (increased tubular pigment). Observations within the larynx and lungs were considered to reflect the accumulation of inhaled test article, with attempted clearance by the local mononuclear-phagocyte system. Accompanying findings within the local lymph nodes and kidneys were considered to represent the subsequent systemic dissemination of test article. Findings were more pronounced, in terms of incidence and severity, amongst animals dosed with 87.9 µg/L, and displayed a clear dose-related response. Amongst animals dosed with 2.44 µg/L, findings were restricted to the lungs and tracheobronchial lymph nodes."

Evaluating MSCA agrees that a classification of tin(II) sulphate as STOT RE 1 would protect from potential local effects after repeated exposure but the rationale for classification is not justified for two main reasons. First, a read-across between tin monoxide and tin(II) sulphate is not supported (see above in the read-across section). Secondly, evaluating MSCA considers that effects observed in lung with tin(II) oxide might not be severe enough to meet the criteria for STOT RE 1 (lung).

In its comments the registrant highlighted that it is doubtful that it is technically possible to perform a toxicity study via inhalation route with unchanged tin (II) sulphate. Indeed, in the case of tin (II) sulphate, the registrant argues that almost all of the particles will be above 10 µm. Thus, the registrant considered that most of the test substance will reach the upper respiratory tract only. Moreover, they mentioned that since the substance has a very low pH in solution (<2), a study by inhalation is not suitable due to animal welfare protection. Evaluating MSCA notes that it is uncertain whether all the composition had similar granulometry. In addition, it is noted that there was no registration for nanosize particles of tin (II) sulphate.

The Member state committee acknowledged the technical difficulties to conduct a study by inhalation route with unchanged tin (II) sulphate. As the objective was to focus on potential systemic toxicity of tin (II) sulphate, the request for a range-findings study by inhalation was removed from the final decision. However, evaluating MSCA notes that the range-finding study by inhalation route would have allowed to appropriately identify potentially relevant effects for DNEL setting and further risk assessment. In addition, evaluating MSCA believes that a classification of the substance as **Skin Corr. (H314) as for tin (II) chloride would have been more appropriate to cover potential local effects**. Evaluating MSCA strongly encourage the lead registrant to provide a harmonised classification and labelling dossier for these endpoints. The evaluating MSCA will not yet prepare a harmonised classification proposal for the Substance. The evaluating MSCA will await the outcome of the CCH. Once the results are available a harmonised classification proposal for all endpoints will be considered.

Conclusion

Different studies of poor quality (Klimisch 2-3) for both 28 and 90d performed by oral route with Tin (II) chloride were available. Only specific parameters were investigated or the actual exposure was not possible to be determined. A more recent study was also performed requested in an ECHA decision (Unpublished study report#5, 2021). In these studies a gastric irritation, anaemia, and effects on liver were observed. There were also effects on calcium (effects on bones), zinc, copper and iron homeostasis reported.

Some testicular effects were also noted in 90d studies performed with both Tin (II) chloride and Tin(II) bismethanesulphonate.

Based on the effects seen in a study performed by inhalation route, **tin (II) sulphate should be classified as STOT RE 1 for respiratory tract and kidney.**

7.9.5. Mutagenicity

In vitro data available in the dossier and available literature data relevant for tin (II) sulphate (literature search ended July 2016) rating Klimisch 1 or 2 are presented. All the *in vivo* data presented in the dossier and available literature data relevant for tin (II) sulphate (literature search ended July 2016) are presented.

Table 29: Summary of mutagenicity data

MUTAGENICITY IN VITRO			
Method	**Type of effect**	**Remarks**	**Reference**
OECD test Guideline 471 (Bacterial reverse mutation assay) *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100, TA 1538, *E. coli* WP2 uvr. A (S9mix rat : with and without) Test concentrations: 33.3, 100, 333, 1000, 3333, and 10000 µg/plate Limitations: - purity of the test material not reported; - only 2-anthramine was used as positive control with S9 although a second positive control is need; - raw data not reported; - dose above the maximum recommended dose of 5000 µg/plate; - platings in duplicates instead of triplicates; - no historical control data; - missing GLP status.	Negative with and without metabolic activation	2 (reliable with restriction) Test material: **Tin chloride dihydrate**	Priva *et al.*,(1991)
OECD Guideline 471 (Bacterial reverse mutation assay) *S. Typhimurium* TA 1535, TA 1537, TA 98, and TA 100 (with and without rat metabolic activation) Test concentrations: 8 to 5000 µg/plate Limitations: only 4 instead of 5 strains recommended in the guideline, only plate incorporation method was used, raw data not reported, unclear if 2-aminoanthracene was used as positive control with S9 for all the strain although a second positive control is need, purity not reported;	Negative with and without metabolic activation	2 (reliable with restriction) Test material: **tin(II) bis(methanesulfonate)**	Unpublished study report #8 (1987)
OECD Guideline 471 (Bacterial reverse mutation assay) *S. Typhimurium* TA 1535, TA 1537, TA 98, and TA 100 (with and without rat metabolic activation) Test concentrations: 1.6 to 5000 µg/plate	Negative with and without metabolic activation	2 (reliable with restriction) Test material: **tin(II) bis(methanesulfonate)**	Unpublished study report #9 (1988)

Limitations: only 4 instead of 5 strains recommended in the guideline, only plate incorporation method was used, raw data not reported, unclear if 2-aminoanthracene was used as positive control with S9 for all the strain although a second positive control is need; low level of details in the IUCLID endpoint study summary, purity not reported			
Similar to OECD guideline 476 (*in vitro* mammalian cell gene mutation) L5178Y lymphoma cells: mouse (with and without rat met. Act.) Test concentrations: first exp : 10, 20, 30, 40, 50, 60, and 80 µg/mL (-S9) Second exp: 30, 40, 50, 60, 80, and 100 µg/mL (+S9) Precipitation observed at 80µg/mL and acidic shift at 60 µg/mL (-S9) Limitations: - purity of the test material was not stated; - No detailed results on cytotoxicity; - missing GLP status;	Negative with and without metabolic activation	2 (reliable with restriction) Test material: **stannous chloride**	Myhr *et al. (*1991)
Similar to OECD Guideline 473 (*in vitro* mammalian Chromosome aberration test) Lymphocytes: Human (met. Act. : with and without) Test concentrations: <u>Experiment 1:</u> 0.4, 0.8, 1.1, 1.4, 1.7, 2.0, 2.3, 2.6, 2.9, 3.2, 3.6, 4.0, and 5.0 µg/mL (-S9; 3 hr exposure and 17 hr recovery) and 15.0, 30.0, 40.0, 50.0, 60.0, 70.0, 80.0, 90.0, 100.0, 115.0, 130.0, 150.0, and 200.0 µg/mL (+S9; 3 hr exposure and 17 hr recovery) <u>Experiment 2</u>: 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, and 10.0 µg/mL (-S9; 20 treatment without recovery) and 25.0, 50.0, 75.0, 100.0, 120.0, 140.0, 160.0, 180.0, 200.0, 225.0, 250.0, and 300.0 µg/mL (+S9; 3 hour treatment and 17 hour recovery)	Negative without activation (3-hr exposure) Positive without metabolic action (20-h exposure) Positive with metabolic activation	1 (reliable without restriction) test material: **tin (II) sulphate**	Unpublished study report #10 (2012)

Table 30 Summary of *in vivo* genotoxicity studies (Klimisch 1 or 2)

MUTAGENICITY IN VIVO			
Method	**Type of effect**	**Remarks**	**Reference**
Similar to OECD guideline 475 (Mammalian bone marrow chromosomal aberration test) Male Rats: SD oral : gavage 5 males/group in treated groups and 3/group in controls Test I Exp 1 : 1 treatment at 4, 40, 400, 1300 mg/kg and examination at 6, 24 and 48h posttreatment Exp 2 : 5-day treatment at 4, 40, 400 mg/kg and examination 6-h posttreatment test II: 1300 mg/kg single dose Positive control: triethyleneamine, single ip dose Slide in duplicates 50 metaphases scored per animals Colchemid ip 4-h after treatment Mitotic index: 500 cells Limitations: - Prior to GLP - Low number of animals in treated and control groups; - No historical control data available in the study summary although it is stated that some increase of chromosomal aberration were observed but within normal range values; - Only 50 metaphases in duplicates scored per animals instead of 200 metaphase per animals recommended; - Mitotic indices obtained by counting 500 cells instead of 1000 cells recommended; No details on the type of aberration;	Negative	2 (reliable with restriction) test material: **stannous chloride, anhydrous**	Unpublished study report#11 (1974)
Similar to OECD 478 (Rodent Dominant Lethal Test), prior to GLP Rats: SD oral: gavage 2 females for 1 male in test I 10 males per week Test I: - Exp 1 : 1 treatment at 4, 40, 400 mg/kg, sacrifice of animals at 6, 24, and 48 hours after treatment - Exp 2 : 5-day treatment at 4, 40, 400 mg/kg 6 hours after last treatment Test II: Single acute dose of 1300 mg/kg	<u>Test I, EXP I:</u> Fertility index : Uninterpretable due to negative result in positive control Average corporea lutea: positive control only positive at weeks 1, 3, 4, 6. Statistically significant decrease at all dose at week 8.	2 (reliable with restriction) test material: **stannous chloride, anhydrous**	Unpublished study report #12 (1974)

Following treatment, the males were sequentially mated to 2 females per week for 8 weeks (7 weeks in the subacute study). Females were killed 14 days after separating from the male, and at necropsy the uterus was examined for early deaths, late foetal deaths, and total implantations. Corpora lutea, early foetal deaths, late foetal deaths and total implantations per uterine horn were recorded. Positive control: triethyleneamine, single ip dose Limitations: - Prior to GLP; - Test material characterisation is lacking; - Lack of experimental details ; - 2 virgin female were mating with one male instead of one male to one female; - Only 200 implants minimum instead of 400 implants were analysed; - No individual data; - Only 4 females instead of 10 recommended; - Data on clinical signs and toxicity not reported; - Dominant lethal frequency were not calculated; - Concurrent and historical control for sub chronic study not reported; - Only average of historical controls for acute study; - Fetus weight was not reported; - Positive control: for test I, exp I, and test II for many parameters and weeks, negative and positive controls were in the same range or positive control was negative; For test I, exp II, no positive control data was provided;	Preimplantation losses: positive control above negative control at week 5, 6 and 8. Increase preimplantation losses at weeks 6 and 7 in treated animals. Post implantation losses: positive control negative at weeks 5, 6 and 8. <u>Test I, EXP II:</u> Fertility index: no effects Corporea lutea: non-dose related statistically significant increase at all dose level at week 6. Preimplantation losses: increase at weeks 3 and 6 in treated animals Post-implantation losses: no effect <u>Test II</u> Fertility: positive control positive only at week 2 and 4. Corporea lutea : positive control was negative Preimplantation losses: increase at week 4, inconsistent results with positive control. post implantation losses: increase at week 6 in treated group. Inconsistent results obtained with positive control		
Similar to OECD 474 (mammalian Erythrocyte Micronucleus test) CF-1 mouse Oral, gavage One treatment of 0 or 1000 mg/kg bw (actual ingested) Positive control cyclophosphamide (50 mg/kg) 5 animals/sex/group	Negative Isolated increase in micronuclei in 2 males after 72h (unknown significance)	2 (reliable with restriction) Test material: **tin(II) bis(methan**	Unpublished study report#13 (1989)

Limitations: - Only one dose tested; - Both the negative and positive controls data appear to be high in comparison with up to date control data from other testing laboratories; - No target organ toxicity by a change of the PCE/NCE ratio could be observed in any of the treatment groups; - The fluctuation of the re-scoring results for one male animal showing significant increase in MN-PCE frequency might be indicative for less experienced staff scoring the cells; - only 1000 PCE per animal were scored instead of 2000 recommended;	No proof of bone marrow exposure	**esulphonate)**	
Similar to OECD 474 (mammalian Erythrocyte Micronucleus test) NMRI mouse Intraperitoneal route Single treatment 50 mg/kg bw, assessment at 24, 48 and 72h 15 animals/sex in treated group and 5 animals/sex in controls groups Positive control: cyclophosphamide Limitations: - prior to GLP - short reporting - Only one dose was tested; - Both the negative and positive control data appear to be high in comparison with up to date control data from other testing laboratories (negative mean: 0.8-1.2‰); - missing test item characterisation; - intraperitoneal route of exposure;	Negative Isolated increase in micronuclei in 2 males after 24h (unknown significance) Increase PCE/NCE ratio after 72-h exposure	2 (reliable with restriction) Test material: **tin(II) bis(methanesulphonate)**	Unpublished study report #14 (1986)
According to OECD guideline 475 (Mammalian bone marrow chromosomal aberration test), GLP Han Wistar male rats Oral: gavage, single administration (dosing volume: 10 ml/kg) 6 rats per groups 500, 1000, 2000 mg/kg (subgroup 1) 2000 mg/kg (subgroup 2) Bone marrow sample: 16 hours (subgroup 1) or 42 hours (subgroup 2) after administration Positive control: cyclophosphamide, 20 mg/kg (3 rats) Limitations: - No historical control data for positive control at 20 mg/kg. Only data at 30 and 35 mg/kg cyclophosphamide available. Low number of study available for negative historical control range (n=8 at 16-hour time point and n=6 at 42-hour time point)	Negative At 2000 mg/kg: clinical signs of piloerection. No clinical signs of toxicity at 500 or 1000 mg/kg. Mitotic index (MI) (cytotoxicity): no evidence of bone marrow toxicity. Systemic exposure confirmed at all dose levels based on bioanalysis (rat plasma concentration)	2 (reliable with limitations) Test material: **Tin(II) chloride anhydrous** Purity: confidential Vehicle: corn oil	Unpublished study report#15 (2019)

Summary and discussion of mutagenicity

- Gene mutation in bacteria

Tin(II) dichloride dihydrate did not show an increase in revertant rates in any of the tester strains with or without metabolic activation. The results were summarised and published in a peer-reviewed journal (Priva *et al.*, 1991).

Data on tin(II) bis(methanesulfonate) need to be considered with care, since as stated in the read-across justification, although tin(II) bis(methanesulfonate) shared structural similarity with tin(II) sulphate, bioavailability may be higher with this compound compare to tin(II) sulphate. Therefore, the results obtained with tin(II) bismethanesulfonate should be considered with caution. The data with tin(II) bis(methane sulfonate) were negative in two unpublished study reports in bacterial reverse mutation assays (Unpublished report#9, 1988; Unpublished report#8, 1987). Both references were considered reliable with restrictions.

- *In vitro* mammalian cell gene mutation

Tin(II) chloride dihydrate (purity not reported) was assayed for the ability to induce mutations at the thymidine kinase (tk) locus (5-trifluorothymidine TFT resistance) in L5178Y mouse lymphoma cells (Myhr *et al.,* 1991). No relevant increase in mutation frequency could be observed in any of the cultures. Some erratic increase in mutant frequency were observed, but without any dose response correlation or reproducibility in parallel cultures, thus were considered in the IUCLID endpoint summary of no biological relevance. Since no significant increase in mutation colonies was observed, a colony sizing was not performed. The study was similar to OECD TG 476, but not conducted according to GLP and without further characterisation of the test item.

- *In vitro* mammalian chromosome aberration/micronucleus tests

In an unpublished study report#10 (2012), tin (II) sulphate (purity 99%) was tested in an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes. Duplicate cultures of pooled blood lymphocytes from three female healthy donors were exposed to tin (II) sulphate at concentrations of 2-5 µg/mL (-S9) and 25-200 µg/mL (+S9). Changes for osmolality or pH were checked in the cytotoxicity range finding experiments. In two independent main experiments with 3 and 20 hours exposure duration, chromosome aberration frequencies were scored in three out of four concentrations. No marked changes in osmolality or pH were observed in the range finding experiments up to concentrations of 1500µg/mL. In the first experiment with 3 hours exposure duration and S9, an increase in chromosomal aberrations frequency exceeding the historical control range was observed. However, the increase is not dose-dependent and, if viewed in isolation, is considered equivocal. The highest concentrations showed 45% and 44% cytotoxicity without and with metabolic activation, respectively. In the second experiments, a statistically significant and dose-dependent increase in the aberration frequency also exceeding the historical control range, was observed in the 3-hour treatment with S9 and the 20 hour treatment without S9 mix. Positive and negative control aberration frequencies were within the range of historical control data. **Tin (II) sulphate was therefore considered clastogenic under the conditions of this assay by induction of structural chromosome aberrations** when tested for 3 hours in the presence of S9 and for 20 hours in the absence of S9. The study is considered valid and relevant without restriction.

- *In vivo* chromosome aberration/micronucleus test

In a testing series, the US Food and Drug Administration commissioned the conduct of *in vitro* and *in vivo* genetic toxicity tests in rats with tin chloride (purity not reported) (Unpublished study report#11, 1974):

- in *an in vivo* chromosome aberration test (prior to GLP similar to old version of OECD TG 475), 5 adult Sprague-Dawley rats were assigned in each treatment group. Animals received two types of treatment schedules: acute treatment (single treatment; sacrifice of animals at 6, 24, and 48 hours after treatment) at doses of 4, 40, 400mg/kg bw (Tier I), at a dose of 1300mg/kg bw (Tier II) or subacute treatment (5 treatments 24 hours apart; sacrifice 6 hours after last treatment) at doses of 4, 40, 400mg/kg bw. The dose of 400mg/kg bw was reported to be the

LD5. The test item was dissolved in 0.85% saline and given via gavage. Positive control animals received a single i.p. injection of triethylene amine. Bone marrow cells were extracted from the femora, washed, fixed, and stained. A total of 50 metaphases per animal were scored for the presence of structural aberrations, the mitotic index was determined by counting at least 500 cells. The acute study did not show aberration frequencies exceeding the normal range value (1-3%). The aberration frequencies in the positive control animals were significantly higher than in the negative control animals, demonstrating the sensitivity of the animal strain for chromosomal damage. The subacute study showed a **non-dose-dependent increased frequency of chromosomal aberrations but still within the normal range values**. Due to the missing test item characterisation, the low number of metaphases scored per animal in the *in vitro* CA assay and the low number of animals used per dose group, this study is considered reliable with restriction and should only be used in a weight of evidence approach.

- in a dominant lethal assay in male and female Sprague Dawley rats (prior to GLP, similar to old version of OECD TG 478), the clastogenic effects of stannous chloride (purity not stated) was investigated. Animals received two types of treatment schedules: acute treatment (single treatment; sacrifice of animals at 6, 24, and 48 hours after treatment) at doses of 4, 40, 400mg/kg bw (Tier I), at a dose of 1300mg/kg bw (Tier II) or subacute treatment (5 treatments 24 hours apart; sacrifice 6 hours after last treatment) at doses of 4, 40, 400mg/kg bw. The dose of 400mg/kg bw was reported to be the LD5. The test item was dissolved in 0.85% saline and given via gavage. Positive control animals received a single i.p. injection of triethylene amine. Following treatment, the males were sequentially mated to 2 females per week for 8 weeks (7 weeks in the subacute study). Two virgin female rats were housed with a male for 5 days. These two females were removed and housed in a cage until killed. The male was rested for two days and then two new females were introduced to the cage. Females were killed at 14 days after separating from the male, and at necropsy the uterus was examined for early deaths, late foetal deaths, and total implantations. Corpora lutea, early foetal deaths, late foetal deaths and total implantations per uterine horn were recorded. Results are not considered interpretable because either positive control data were not given or positive data were negative at some time point or all time point.

Due to the missing test item characterisation, the low number of metaphases scored per animal in the *in vitro* CA assay and the low number of animals used per dose group this study is considered reliable with restriction and should only be used in a weight of evidence approach.

In the two *in vivo* micronucleus studies performed with tin(II) bismethanesulphonate, some isolated increase in micronuclei were observed and are difficult to interpret as only one dose level was tested.

In addition, three negative micronucleus assays (Shelby *et al*., 1993; Gocke *et al.*, 1981; De Mattos *et al.*, 2012), two equivocal chromosomal aberration assays (Shelby *et al*., 1993; El-Makawy, 2008) and one positive comet assay (De Mattos *et al*., 2012) were assessed but were considered unreliable due to severe methodology deficiencies.

Therefore, during initial substance evaluation, **an *in vivo* rat chromosomal aberration assay was requested to clarify the positive *in vitro* clastogenic activity of divalent tin salts in the mammalian chromosome aberration assay**. The study was submitted by the registrants (Unpublished study report#15, 2019) and was performed according to OECD TG 475 in compliance with GLP. Han Wistar rats were exposed to tin (II) chloride (CAS no. 7772-99-8) by oral gavage as a single administration. Corn oil was used as a vehicle as tin dichloride is unstable in water. The positive control group consisted of 3 animals and were exposed to cyclophosphamide (CPA). In the range-finding study, tin dichloride was tested at 500, 1000 and 2000 mg/kg (n=1/sex/dose) and was well tolerated up to 2000 mg/kg. The same dose-levels were used in the main experiment. As no differences were noted between sexes, only males were used in the main experiment

(n=6/group). Animals were sampled at 16 hour (sub-group 1) and 42 hours (sub-group 2) after administration. Mitotic index was measured in 1000 cells per animals. Where possible, 200 metaphases from each animal were analysed for chromosome aberrations.

In the main study, no clinical signs of toxicity were observed in animals dosed up to 1000 mg/kg. At 2000 mg/kg, piloerection was noted in all animals. No notable effects were noted on body weight. Cytotoxicity, as shown by the increase in mitotic index, was observed at 500 mg/kg and in the positive control. The increase was mainly due to two animals at 500 mg/kg. Although the increase in mitotic index was not explained in these animals, the bioanalysis study did not suggest a non-monotonic dose-response in the exposed rats. In the bioanalysis study, whole blood was taken in satellite animals for bioanalysis. The results confirmed that animals dosed at 500, 1000 and 2000 mg/kg were systemically exposed to Tin dichloride, with a dose-related increase and a plateau noted at ≥1000 mg/kg. Controls were below the LOQ (5 ng/mL), concentration of tin in rat plasma was between 83.7 to 447ng/mL in animals exposed at 500 mg/kg, between 653 and 2550 ng/mL at 1000 mg/kg and between 807 and 2790 ng/mL at 2000 mg/kg.

The tables below summarised the results of the main experiment.

Table 31 Summary of the results of chromosomal aberration, 16 hours (Sub-group 1)

Treatment (mg/kg)	Mitotic index inhibition	Cells scored	Aberrant cells (excluding gaps)	Frequency of aberrant cells	% with numerical aberration[1]
Vehicle	-	1200	0	0.00	0.4
500	33%	902	1	0.11	0.3
1000	0	1200	1	0.08	0.3
2000	0	1200	0	0.00	0.2
CPA, 20	69%	555	76	13.69**	0.9

**p≤0.001; [1] statistical analysis not performed

Table 32 Summary of the results of chromosomal aberration, 42 hours (Sub-group 2)

Treatment (mg/kg)	Mitotic index inhibition	Cells scored	Aberrant cells (excluding gaps)	Frequency of aberrant cells	% with numerical aberration[1]
Vehicle	-	1200	2	0.17	0.2
2000	0	1199	5	0.42	0.2

[1] statistical analysis not performed

Based on mitotic index inhibition, there was **no evidence of bone marrow toxicity in the study up to 2000 mg/kg.**

There were no statistically significant increases in structural chromosome aberrations in the exposed groups compared to the vehicle group at the 16 hours or 48 hours sample time. The frequencies were inside the negative historical control range. An exception was noted in a single animal with 2% aberrant cells without gaps at the 42-hour sample time. As this increase was not observed in the remaining 5 animals in this dose group, the isolated increase was not considered of biological relevance. The positive control induced the expected increase in chromosomal aberration. The frequency of structural chromosomal aberration of the vehicle control group was within the negative historical control data range (mean=0.1%; 95% reference range: 0-0.5% at 16h and mean = 0.1%, 95% reference range: 0-1.03% at 42-hour time point). There was also no increase in numerical aberration in the exposed groups compared to the control group.

Conclusion

There was no evidence for mutagenic activity of divalent tin salts in bacterial reverse mutation assays or in a mouse lymphoma assay up to the maximum concentration limited

by cytotoxicity. There was evidence *in vitro* for clastogenic activity of divalent tin salts in the mammalian chromosome aberration assay.

Genotoxicity potential of tin(II) chloride has been assessed in many *in vivo* assays available in the registration dossiers and in literature. Based on some equivocal results in vivo, mainly with tin(II) bismethane sulphonate, an *in vivo* chromosomal aberration study was requested. Based on the negative results obtained with tin(II) chloride, **evaluating MSCA concluded that tin (II) sulphate is unlikely to be mutagenic**.

7.9.6. Carcinogenicity

Table 33 Summary of carcinogenicity data

<table>
<tr><th>Method</th><th>Type of effect</th><th>Remarks</th><th>Reference</th></tr>
<tr>
<td><u>Chronic toxicity study</u>
Similar to OECD 451, no data on GLP status

Oral, feed

rat: F344/N, mice: B6C3F1

105-week exposure

0, 1000 and 2000 ppm $SnCl_2$ nominal for diet in male and female rats (e.q., to around 32 and 63 mg Sn/kg bw in rats and 82 and 164 mg Sn/kg bw in mice, respectively)

50 rats or mice/sex/dose

Limitations: only 2 low dose tested, no haematological or biochemical parameters were measured</td>
<td><u>Rats</u>
- No effects on bw or food consumption
- No significant effect on survival

Neoplastic findings:
Thyroid C-cell effects in male rats (%):
<table>
<tr><th>Dose (ppm)</th><th>0</th><th>1000</th><th>2000</th><th>HC</th></tr>
<tr><td>Adenoma</td><td>4</td><td>48*</td><td>10</td><td>8.3</td></tr>
<tr><td>Adenoma + carcinoma</td><td>4</td><td>27*</td><td>16*</td><td>Max 20% moy 11.4%</td></tr>
<tr><td>Hyperplasia</td><td>2</td><td>2</td><td>4</td><td></td></tr>
</table>
*p<0.05, HC: historical controls

Thyroid C-cell adenomas and carcinomas (combined) occurred in male rats with a significant positive trend and the incidence in either dosed group was significantly higher than seen in the controls.

Adenomas of the lung in male rats occurred with a significant positive trend.
<table>
<tr><th>Dose (ppm)</th><th>0</th><th>1000</th><th>2000</th><th>HC</th></tr>
<tr><td>Lung adenoma</td><td>0</td><td>0</td><td>6%</td><td>0-6%</td></tr>
</table>
Tumours observed in female mice:
<table>
<tr><th>Dose (ppm)</th><th>0</th><th>1000</th><th>2000</th><th>HC</th></tr>
<tr><td>Liver: adenoma + carcinoma</td><td>6 %</td><td>8%</td><td>16%</td><td>4-18%</td></tr>
<tr><td>Hystiocytic lymphoma</td><td>0</td><td>0</td><td>8%</td><td>0-6%</td></tr>
</table>
LOAEL = 32 mg/kg Sn/kg based on thyroid C cells tumours

<u>Mice</u>
Increase histiocytic lymphomas were also seen in mice above historical control data.</td>
<td>2 (reliable with limitations)
Test material : Tin(II) chloride</td>
<td>NTP, 1982</td>
</tr>
</table>

<u>115-week chronic toxicity study</u> Similar to OECD 451, no data on GLP status Wistar rats 70ppm iron and 10 ppm copper Treatment of stannous chloride with casein in aqueous medium 30/group/sex 0, 200, 400, 800 ppm tin in diet (nominal), <4, 182, 379, 764 (mean actual level) e.q., to 5, 10, 19 mg/kg bw using default values for dose calculation of 40 (ECHA guidance chapter R8, table R.8-17). Limitations: - no certificate of analysis - no data on GLP status - only low dose levels tested - low number of animals (30 instead of 50 per groups) - no data on actual concentration - no general toxicity at the highest dose - haematocrit not investigated - no individual data reported in the report - no details on neoplastic findings - treatment of stannous chloride with casein in aqueous medium which allow tin to bind to protein or complex. This may reduce its biological activity.	No effects on mortality, bw and food intake. No carcinogenicity **800 ppm** Decreased haemoglobin after 4 and 13 weeks. No differences after 2 years increase tin content in bone **400ppm** Decreased haemoglobin after 4 and 13 weeks. No differences after 2 years Decreased serum iron content, saturation percentage at week 4 but not 115. **200 ppm** Decreased haemoglobin after 4 and 13 weeks. No differences after 2 years **NOAEL < 200 ppm based on haematological findings.**	2 (reliable with limitations) Test material: **Tin(II) chloride, dihydrate**	Unpublished study report #16, 1980 (Not in CSR but submitted by registrant during informal discussion)
Non-guideline life-time study in rats Rats, long-Evans Swiss Mice Oral, drinking water 5 ppm in rats (equivalent to 0.4 mg Sn/kg bw), 0.28 ppm in mice Limitations: - only one dose tested - low number of tissue examined for histopathology, - no access to the study, - the tested dose is too low	No tumorigenic effects. Fatty degenerative changes in liver and vacuolar changes in the renal tubules were observed. These effects were not observed in mice.	3 (unreliable) Test material: **tin(II) chloride**	Schroeder *et al*., 1968

non guideline, no data on GLP Rats, Long evans males and females oral, drinking water 0.34-0.38 mg Sn/kg bw/day Limits: few information available, secondary literature	No tumourigenic effect.	4 (not assignable) Test material: **Tin(II) chloride**	Kanisawa *et al.*, 1967

Summary and discussion of carcinogenicity

In the NTP study (1982), carcinogenicity of tin(II) chloride was carried out with F344 rats and B6C3F1 mice (50 per dose and per sex). Tin(II) chloride was administered for 105 weeks with the diet in **only two** concentrations of 32 and 63 mg/kg bw/d and to the mice 82 and 164 mg/kg bw/d for 105 weeks. Body weight development and food consumption were not affected in either species. At the end of the study, survival of the female mice was reduced in a dose-dependent manner (38/50 in controls, 33/50 at low dose, 28/50 at high dose), survival of the male rats was reduced (37/50 controls, 39/50 at low dose, 30/50 at high dose).

Thyroid: C-cell adenomas were significantly increased in low-dose male rats. C-cell carcinomas of the thyroid in male rats did not occur at a significant incidence; however, C-cell adenomas or carcinomas (combined) occurred in male rats with a significant positive trend (P = 0.027 for the life table test), and the incidence in either dosed group was significantly higher than that seen in the controls (control, 2/50, 4%; low-dose, 13/49, 27%; high-dose, 8/50, 16%). The incidence of C-cell carcinomas or the combined incidence of C-cell adenomas and carcinomas in previous control groups of male F344/N rats from this laboratory has been as high as 7% and 20%, respectively (historical incidence at this laboratory: C-cell adenomas, 24/288, 8.3%; C-cell carcinomas, 8/288, 2.8%; C-cell adenomas or carcinomas, 32/288, 11.1%). If the historical control rate is used as a basis of comparison, the low-dose effect remains significant ($p < 0.01$), but the high-dose does not (historical control data from about 300 animals; no information about period or laboratory in which the data were obtained). It was proposed by previous evaluation that since the incidences of these tumours in high-dose male rats were not significantly different from the historical control rate at this laboratory and since the incidence of C-cell hyperplasia in male rats (control, 1/ 50, 2%; low-dose, 1/49, 2%; high-dose, 2/50, 4%) was similar in dosed groups and controls, the increased incidence of thyroid tumours in dosed male rats is difficult to interpret. The evaluating MS would like to recall that historical controls are normally used to only identify aberrant values and should not be a substitute to the concurrent control. This latter is the one which has to be used to determine the statistically significance of an effect. Therefore, evaluating MSCA judged that these results had to be considered as a relevant alert to further investigate the effect through the request performed during Substance Evaluation.

Lung: Adenomas of the lung in male rats occurred with a significant ($P < 0.05$) positive trend, but the increased incidence in the high-dose group was not significant in a direct comparison with the control group (controls, *0/50, 0%;* low-dose, *0/50,* 0%; high-dose, 3/50, 6%). It should be noted that the historical incidence of control F344/N male rats with adenomas of the lung at this laboratory is 2.1% (6/289) with a range of 0%-6%. The incidence of male rats with either adenomas or carcinomas (combined) in the lung was not

statistically significant.

Liver: The incidence of female mice with either hepatocellular adenomas or carcinomas exhibited a significant (P < *0.05)* dose-related trend (controls, 3/49, 6%; low-dose, 4/49, 8%; high-dose, 8/49, 16%). However, it was proposed by the authors of the study that the incidence observed in the high-dose group falls within the historical range for female control mice at the laboratory (4%-18%; mean, 24/297, 8%), and is not statistically significant relative to the historical control rate; thus the increase was not considered to be related to administration of tin chloride. The evaluating MSCA would like to recall that historical controls are normally used to identify aberrant data and data should always be compared to the concurrent control. This latter is the one which has to be used to determine the statistically significance of an effect. In addition, homogeneous liver cell cytoplasm and oval cell type hyperplasia of bile ducts were observed in rats (De Groot, 1973). Histopathological examination of livers from tin-treated male rabbits showed marked changes in hepatocytes as well as proliferation of duct epithelium, dilatation, and congestion of blood vessels as well as mononuclear inflammatory infiltrate (El-Demerdash *et al.*, 2005). Evaluating MSCA would therefore prefer to say that the increase observed in one sex and in the range of the historical data is difficult to interpret and is not sufficient to warrant a classification.

Lymph: Histiocytic lymphomas in female mice occurred with a significant positive trend (P <0.05). The incidence of histiocytic lymphomas in the female controls (O/50, 0%) is lower than the historical incidence for mice of the same sex and strain at this laboratory (9/298, 3.0%; range, 0%-6%). The incidence of all lymphomas or leukaemias was not significantly elevated in groups of dosed female mice (control, 6/50, 12%; low-dose, 10/49, 20%; high-dose, 11/49, 22%). The authors justified that incidence of lymphomas or leukaemias in the dosed groups was similar to the historical incidence for control female B6C3Fl/N mice at this laboratory (67/298, 22%).

Under the conditions of this bioassay, tin(II) chloride was judged by the NTP "not to be carcinogenic for male or female F344/ N rats or M6C3F1 in mice, although C-cell tumours of the thyroid gland in male rats may have been associated with the administration of the test chemical.". EFSA, 2018 report also concluded that studies on carcinogenicity performed in rats and mice did not indicate concern for carcinogenicity of stannous chloride.

Evaluating MSCA notes that 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.

Following the initial evaluation, the eMSCA identified a concern for the possible effects of tin salts on thyroid and calcium homeostasis that could lead to potential carcinogenesis. On this basis the eMSCA requested sub-chronic toxicity and *in vivo* mammalian bone marrow chromosomal aberration studies to clarify this concern (ECHA decision, June 2018). These data did not confirm a concern on potential calcium homeostasis and genotoxicity. In the 90-day study there was no effect on thyroid hormone, thyroid weight, macroscopic or microscopic findings in the thyroid that would suggest that thyroid could be a potential target organ. Based on these new data the eMSCA concludes that due to the uncertainty on the treatment-relation for the thyroid tumours, occurring in one sex and one species only, the evidence for carcinogenicity is not sufficient to meet the classification criteria. Therefore the concern for this endpoint is refuted. However**, evaluating MSCA concludes that a concern remains on the possible effects of tin salts on thyroid and calcium homeostasis that could lead to potential carcinogenesis**. In the requested studies

(ECHA decision, June 2018), on mutagenicity and 90-day repeated-dose toxicity investigating potential effects of tin (II) sulphate on calcium homeostasis (C-Cell are involved in calcium homeostasis) did not confirm a concern on potential calcium homeostasis and genotoxicity. In addition, in the 90-day study there were **no effect on thyroid hormone, thyroid weight, macroscopic or microscopic findings in the thyroid that would suggest that thyroid could be a potential target organ.** Due to the uncertainty on the treatment-relation for the thyroid tumours, occurring in one sex and one species only, the evidence for carcinogenicity are not sufficient to meet the classification criteria. However, as a worst case, the LOAEL of 32 mg/kg, has been considered for risk assessment as C-cell thyroid tumours may have been possibly treatment-related.

In the 115-week toxicity study performed in 1980, as only low dose of tin(II) chloride were tested, the study is not considered as appropriate to identify potential carcinogenicity of tin compounds.

The other two published studies were not considered as reliable (Schroeder *et al.*, 1967, Kanisawa *et al.,* 1969) due to lack of information on study method and as only very low dose were tested.

Conclusion:

No data is available for Tin(II) sulphate.

In a NTP study (1982) in was concluded that Tin(II) chloride was not carcinogenic for male or female rats or mice, although C-cell tumours of the thyroid gland in male rats may have been associated with the administration of the test chemical. Based on the available data (90d study, 2021) the thyroid is not a target tissue. Nevertheless, **a concern remains on the possible effects of tin salts on thyroid and calcium homeostasis that could lead to potential carcinogenesis.**

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Table 34: Effects on fertility

EFFECTS ON FERTILITY_ORAL			
Method	**Results**	**Remarks**	**Reference**
Three-Generation Reproduction Toxicity rat (CPB:WU randomly bred) male/female oral: diet 10 males and 20 females/group 0, 200, 400, 800 ppm tin in diet (<4, 182, 379, 764 mg/kg diet), eq. to 10, 20, 40 mg tin/kg The iron content of the diets was maintained at 70 ppm (0.007%), but for the F2 generation onwards was	• Reproduction study Parental toxicity: **800ppm** - F3: poor nursing behaviour - F2: slight decreased Hb in females not receiving additional iron Developmental toxicity **800 ppm** - F2: ♂ pup bw gain during lactation - F2: ♀ pup mortality during the first 10-d of treatment not prevented by additional dietary iron - ♂ Hg, Ht in weanling rats reversible after weanling Decreased iron serum level F3: ♀ relative weight of spleen (extramedullary haematopoietic	2 (reliable with restriction) Experimental result Test material (EC name): Tin(II)chloride, dihydrate Purity: no data Vehicle: water	Unpublished study report#19, 1979

increased to 140 ppm (0.014%). Limitations: - The stannous chloride was allowed to react in aqueous medium with the case in component of the diet, in order to simulate the form of tin likely to be found in canned food. Treatment of stannous chloride with casein in aqueous medium which allow tin to bind to pt or complex. This may reduce its biological activity. - no certification of analysis - only low dose levels tested - no data on actual concentration - no data on GLP status - no general toxicity at the highest dose.	activity) F3: histopathological findings in liver and spleen (reversible) **400 ppm** ↷ Hg, ht in weanling rats reversible after weanling **200 ppm** ↷ Hg, ht in weanling rats reversible after weanling upon increasing the level of iron in the diets from 70 to 140 ppm the pups of all groups showed considerably higher values for hb, serum iron and saturation. Considered by the author secondary to the known effects of tin on the iron status. <u>Reproductive toxicity</u> There was no effect on fertility of females, number of young born per litter and body weight. NOAEL (P): > 800 ppm NOAEL (F1): > 800 ppm NOAEL (D): < 200 ppm, anaemia, mortality, decrease iron serum level, recovery after weanling • Teratogenicity study A visceral and skeletal examination of the F2b generation rats did not show any tin-related teratogenic effects. One unilateral anophtalmia was observed in one foetus at 800 ppm.		
Non-guideline male fertility study New Zealand rabbits Oral: gavage 12-week exposure Age: 7-month old N=6 male/group 0, 40 mg/kg ascorbic acid, 20 mg/kg SnCl2.2H2O, or their combination Semen collection: weekly over the 12 weeks Limitations: - only one dose tested - low dose tested only - low number of	- No effect on bw or food consumption compared to control - ↓ testes and epididymis relative weight (by 20%) ($p<0.05$) in tin(II) chloride exposed group compare to control. Ascorbic acid caused a significant increase in these weight. No difference with combination of treatment compared to control. - ↓ semen ejaculate volume ($p<0.05$), sperm concentration, sperm motility, total motile sperm per ejaculate, total functional sperm fraction, normal sperm, initial fructose, and decreased reaction time to ejaculation compared to control. Ascorbic acid caused an increase in these parameters. No effect compared to control following combination of treatment.	Published study Test material: tin(II) chloride, dehydrate Purity: 97%	Youssef *et al.*, 2005

males per groups - no data on absolute weight of testis or epididymis			

7.9.7.2 Developmental toxicity

Table 35 Summary of developmental toxicity studies

DEVELOPMENTAL_ORAL			
Method	**Type of effect**	**Remarks**	**Reference**
Developmental prenatal toxicity study in rats, mice, and hamster Similar to OECD 414, prior to GLP **Mice** CD-1 female albino mice 0, 0.5, 2.3, 11, 50 mg/kg oral, gavage GD 6-15 Limitations: - no data on controlled temperature and humidity, detailed on food content is not available, - food consumption or clinical findings have been observed but not reported - age of the animals is not available - no historical control data - no statistical analysis **Hamster** Female adult golden hamsters GD 6-10 oral, gavage 0, 0.5, 2.3, 11, 50 mg/kg limitations: - no data on controlled temperature and humidity, detailed on food content is not available, - food consumption or clinical findings have been observed but not reported - age of the animals is not available - no historical control data - no statistical analysis **Rats** Wistar derived rats GD6-15 Dose: 0, 0.5, 2.3, 11, 50 mg/kg as stannous chloride oral, gavage limitations: - GD6-15 instead of GD6-19 recommended in the guideline	Maternal toxicity None reported in mice, hamsters and rats Developmental toxicity • **Mice** ✂ dead foetuses (no dose-relation); ✂ litter with incomplete ossification or variation of sternebrae (no clear dose-relation); ✂ foetuses and litter with reduced hyoid at all dose tested ; 1/189 meningoencephalocele at 2.3 mg/kg and 1/167 at 50 mg/kg; • **Hamster** ✂ Resorption and dead-foetuses but absence of dose-response ✂ missing hyoid ✂ missing sternebrae one fetus (1/174) with meningo-encephalocele at 0.5 mg/kg • **Rat** ✂ wavy ribs at the highest dose test (no dose-related); ✂ missing hyoid (4.9, 9.5, 3.1, 6.1, 7.8% foetuses in 30, 41, 23, 26, 38 % of litters examined at 0, 0.5, 2, 11 and 50 mg/kg , respectively	Study report K2, WOE Test material: stannous chloride Vehicle: water	Unpublished study report# 21, 1972

- no data on controlled temperature and humidity, detailed on food content is not available, - food consumption or clinical findings have been observed but not reported - age of the animals is not available - no historical control data - only one-third of the foetuses examined for visceral examination instead of one-half in the guideline - page 28 and 29 of the report missing - no statistical analysis			
Prenatal developmental toxicity study in rabbit Similar to OECD 414, prior to GLP Dutch-belted female rabbits oral, gavage GD6-18 0, 0.42, 1.90, 8.90, and 41.5 mg/kg as stannous chloride administered as a water solution (nominal) Treatment groups: 15 - 17 mated females (11 - 12 pregnant females) Control group: 14 mated females (10 pregnant females) Limitations: - no data on controlled temperature and humidity, detailed on food content is not available, - food consumption or clinical findings have been observed but not reported - no mating procedure, instead does were inseminated artificially - Age of the animals is not available - low only 10-12 pregnant females instead of at least 20 females - GD6-18 instead of GD6-28 - no data on external examination - the live fetuses were placed in an incubator for 24-h for the examination of the neonatal survival. These pups were also observed for visceral abnormalities but it is not clear from the protocol if they were also observed for skeletal abnormalities. - No certificate of analysis was provided in the report - No statistical analysis was performed - Individual data for weight was not provided - The highest did not induce clinical signs or decrease in bw. - No historical control data available.	<u>Maternal toxicity</u> No reported effects <u>Developmental toxicity</u> No effect on resorptions, foetal survival or bw ✂ incomplete ossification ✂skeletal variation in sternebrae (no dose-response) ✂ incidence of rotation of hindlimbs (malformation according to dev tox) : 0, 0, 1, 1 at 0, 0.42, 1.9, 8.9, 41.2 mg/kg respectively. 1 (1/49) meningoencephalocele at 1.9 mg/kg	Study report K2, WOE Test material: stannous chloride Vehicle: water	Unpublished study report# 22, 1974

Prenatal developmental toxicity study in mice non guideline, non GLP Swiss albino mice oral, gavage 10 pregnant mice/group 5 males/group 0, 2, 10, 20 mg/kg bw of $SnCl_2$ 3-w premating till gestation day 18 Investigation: implantations sites, resorptions, late fetal deaths, live fetuses, weight, gross external, visceral and skeletal abnormalities of fetuses Limitations: - no justification on species selection (mice) - age and individual weights of the animals at the start of the test were missing - number of pregnant females was too low - test item administration started already before mating and was too long - administration volume was not stated - clinical observations, body weights, and food consumption of the dams were not recorded - no pathological examination of the dams, except for examination of uterine contents - gravid uteri weights and number of corpora lutea were not recorded - sex of foetuses was not recorded - individual data was missing - number and percent of pre-implantation losses were not recorded	Maternal toxicity No data Developmental toxicity **At 2 mg/kg bw** ✂ post-implantation losses (not statistically significant) foetal bw (significant) delayed ossification **At 10 mg/kg bw** foetal bw (significant) (significant) number of live foetuses ✂ post implantation losses (P≤0.01). delayed ossification **At 20 mg/kg bw** - complete post-implantation losses. Data not shown: Reduction in the rate of successful pregnancies in females that had a positive mating outcome.	Published data K2, WOE test material: tin chloride dehydrate purity > 99% Vehicle: water	El-Makawy *et al.* (2008)

Summary and discussion of developmental toxicity

Prenatal developmental toxicity studies are available in rats, hamster, mice, and rabbits (Unpublished study report#21, 1972). In none of these studies, maternal toxicity was observed up to the highest tested dose. Although not dose-related, embryotoxicity was observed in hamster and mice, delayed development in mice and rabbits and skeletal variations were observed in rat, hamster, and rabbits. It is not clear if these effects are related to treatment due to the absence the absence of dose-relation and lack of historical control data to appreciate the severity of the effects according to the authors. **The evaluating MSCA would like to recall that historical controls are normally used to**

identify aberrant data and data should always be compared to the concurrent control. This latter is the one which has to be used to determine the statistically significance of an effect.

Malformations were also observed in three species (meningoencephalocele in mice, rabbits and hamsters and rotation of hindlimbs in rabbits), however the low incidence (one animal at one or 2 dose levels) and the absence of historical control data does not permit to conclude on the biological relevance of these findings. The authors of these studies and EFSA (2018) concluded that no developmental toxicity was observed with the test material. However, the study is not adequate for human health risk assessment and classification and labelling as only low doses without toxicity were tested.

In a non-guideline study published by El-Makawy in 2008 (Klimisch 3), dose-related developmental toxicity (post-implantation losses, delayed development) was also observed in mice at ≥ 2 mg/kg bw. However, the number of animals per group in this study impaired a proper assessment of dose-relation characterisation. No data are reported on maternal toxicity in this study.

Two other studies were available in the registration dossiers for tin (II) sulphate. Although these studies raised a concern on potential developmental effects observed with tin compounds such as tin (II) sulphate or chloride, the studies were not available in English and it was not possible to check their reliability.

- Grin *et al.* (1988) [article in Russian], female rats were exposed to an aerosol of tin (II) sulphate ad libitum at concentrations of 0.290, 0.130 and 0.045 mg/m³ throughout pregnancy. The following parameters were investigated on day 21 of pregnancy. The number of corpora lutea in the ovaries, of implantation sites in the uterus, and of live and dead embryos; the size characteristics of the ovary and the foetal placenta; internal and external developmental anomalies; and the extent of intrauterine death served as the criteria for assessing the embryotoxic effect of tin sulphate. The somatic functional state of the mother and foetus and the quantitative and qualitative composition of the amniotic fluid were also studied. According to the authors, the, **inhalation loading of pregnant rats with 0.290 mg/m³ tin (II) sulphate causes an increase in foetal death,** an imbalance of biochemical processes in the bodies of the experimental animals, and a change in the quantitative and qualitative composition of their amniotic fluid. Furthermore, they stated that less severe reactions were observed with exposure to 0.130 mg/m³, a dosage below the threshold for an embryotoxic effect.

- Wu *et al*., 1990 [article in Chinese] also reported developmental effects with tin(II) chloride. Rats were exposed to 0, 20, 100 or 500 mg/kg tin(II) chloride by oral gavage during GD7 to 12. According to the abstract, the experimental results showed that the placenta not only retains some stannous chloride but also diverts parts of the stannous chloride to the foetus. **Tin chloride showed teratogenic effects on the early growing embryos and protruding tongue of foetus**.

A data gap has been identified on developmental toxicity and a concern has been identified as effects have been observed even at low dose levels. In addition, copper deficiency observed with tin chloride also increase the concern on potential developmental toxicity. Therefore, **evaluating MSCA concluded that a compliance check should be initiated by ECHA in order to fill this data gap and to be able to clarify this concern**.

Summary and discussion of effects on fertility

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 (1973a) or 0.2% tin(II) bismethanesulphonate in presence of marked general toxicity. 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 (ECHA disseminated website).

In a 3-generation toxicity study (Unpublished study report#19, 1979), no effects on fertility, reproductive organs or on parental toxicity was observed up to the highest tested dose of 800 ppm (e.q., to 40 mg Sn/kg). However, as only low doses were tested in this 3-generation toxicity study, this may explain the absence of effects. Developmental effects in this study (anaemia, mortality) were considered secondary to the decrease serum iron content and were observed already at 200 ppm (equivalent to 10 mg/kg bw using default conversion factor).

Male New Zealand White rabbits (n = 6/group) were administered by gavage 20 mg /kg bw tin(II) chloride, dihydrate for 12 weeks (Yousef, 2005). Body weight and food intake of the animals treated with tin(II) chloride were comparable to the controls. At necropsy, relative weights of epididymis and testes were decreased. Treatment with tin(II) chloride caused an increase of the reaction time, a decrease in ejaculate volume, sperm concentration, total sperm output, sperm motility (%), total motile sperm per ejaculate, packed sperm volume, total functional sperm fraction, normal and live sperm and semen initial fructose. Dead sperm and initial hydrogen ion concentration (pH) were increased. Two extra groups (n = 6/group) were included; one group administered with ascorbic acid (AA; 40 mg/kg bw every other day) and another group administered with tin (II) chloride and AA. Treatment with AA alone caused significant increase in body weight, food intake, relative weights of epididymis and testes, and semen characteristics compared to control group. In presence of AA in the animals administered stannous tin(II) chloride, the sperm parameters were comparable to controls. However, in this study only one dose was tested and there were no data on reproductive outcome.

On the basis of this study, **a potential concern was identified on potential effects of tin salts on both testis and spermatogenesis** that could be partially overcome in the presence of ascorbic acid.

During the discussion on the initial draft decision on tin(II) sulphate, the registrant proposed to perform an Extended One Generation Reproductive Toxicity Study (EOGRTS) according to OECD TG 443 for animal welfare reasons instead of a 90-day study. It was considered that a sub-chronic toxicity study (90-day) in rats and the *in vivo* mammalian bone marrow chromosomal aberration test shall be conducted before the EOGRTS. Indeed, the results from these studies could be used, among other relevant information, to decide on the relevant study design of the EOGRTS.

The use of the results of the 90-day toxicity study and the genotoxicity study to decide on the need to conduct an EOGRTS and to trigger the appropriate study design of this study was considered as the most proportionate option for compliance with the 3'Rs implemented mid-2017 ECHA policy: "*The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts)".*

As a result, specific investigation of spermatogenesis were requested in the 90-day 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 sperms. Indeed, these parameters were not investigated in any studies already performed with tin(II) sulphate or tin(II) chloride. ECHA recommends to follow the latest draft version of OECD TG 408 (points 39-41) for spermatogenesis investigations*".

Conclusion:

Overall, no effects on reproductive organs or spermatogenesis were noted in the most recent 90-day study. Nevertheless, **a data gap is identified in the dossier for reproductive toxicity (fertility and sexual function)** and further investigation of tin(II) sulphate is considered necessary as only low dose assessment is available. Therefore, **evaluating MSCA concluded that a compliance check should be initiated by ECHA in order to fill this data gap and to be able to clarify the concern for testis and spermatogenesis**.

7.9.8. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

No data are available on oral and dermal absorption provided by the registrant. By default, 10% is considered relevant (based on oral absorption of tin chloride). 100% is considered for inhalation absorption.

The following critical effects and point of departure were identified for tin(II) chloride.

Table 36: Descriptors for critical health effects

CRITICAL DNELS/DMELS				
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**Corrected dose as tin(II) sulphate***
Repeated dose toxicity in rats (Unpublished study report #5, 2021)	Systemic	Repeated-dose toxicity, 13 weeks, oral Bw changes, locomotor activity, copper deficiency	NOAEL= 57.3 mg tin(II) chloride/kg	NOAEL = 54. 5 mg/kg
Repeated dose toxicity in rats (de Groot, 1973)	Systemic	Repeated-dose toxicity, 13 weeks, oral Haematological findings	NOAEL = 32 mg tin/kg	NOAEL = 57.9 mg/kg
Repeated-dose toxicity in rats (Unpublished study report #4, 2007)	Systemic	Repeat dose toxicity, inhalation Local lymph node and kidney findings	NOAEC = 9.19 mg tin(II) oxide/m^3	NOAEC= 14.65 mg/m^3
Reproductive toxicity in rats (Unpublished study report #19, 1979)	Systemic	3-generation, oral No effects at the maximum dose tested	NOAEL = 40 mg tin/kg	NOAEL= 72 mg/kg
Repeated dose toxicity in rats (Unpublished study #4, 2007)	Local	Repeated dose toxicity, inhalation (lung local effects)	LOAEC = 2.3 mg tin(II) oxide/m^3	LOAEC= 3.7mg/m^3
Carcinogenicity in rats (NTP, 1982)	Systemic	Carcinogenicity, oral (C-cell tumours)	LOAEL= 32 mg tin/kg	LOAEL= 57.9 mg/kg
Repeated dose toxicity in rats (Pekelharing et al., 1994)	Inhibition of trace elements (Zn, Cu, Ca^{++}, iron)	Repeated dose toxicity, oral, 4 weeks	LOAEL= 10 ppm	
Repeated-dose toxicity in rats (Yamagushi et al., 1980)	Inhibition of Ca^{++} in serum and femur	Repeated-dose toxicity, 13 weeks, oral	NOAEL = 0.6 mg Sn/kg bw	

Repeated dose toxicity, human data (Johnson et al., 1982)	Inhibition of trace elements (Zn)	Oral administration, cross-over design study	LOAEC= 0.7 mg Sn/kg bw per day	

*based on LOAEC of 32 mg/kg tin converted to tin (II) sulphate (conversion factor=MW tin (II) sulphate/MW tin oxide/chloride or tin; MW tin (II) sulphate= 214.8, MW tin chloride = 225.65 and MW tin= 118.7, MW tin oxide = 134.7))

For systemic effect, the NOAEL of 54.5 mg tin (II) sulphate/kg bw per day is the lowest point of departure for systemic toxicity in oral toxicity studies based on the most reliable studies (having in mind that this study did not reproduce expected tin effects). The effect of tin(II) chloride on thyroid tumours was of borderline significance and it is uncertain if the effect was treatment-related. For the sake of consistency between hazard characterisation and risk assessment, this was not considered as a good basis for DNEL derivation. Effect of tin (II) sulphate on essential elements disturbance is considered as potential precursor effects of tin (II) sulphate toxicity and were not used for risk assessment. Evaluating MSCA notes that foetus may be particularly sensitive to copper deficiency and that a revised risk assessment may be needed following receipt of the reproductive toxicity studies.

a. DNEL derivation for workers

- DNEL long-term, inhalation, systemic effect

Table 37: DNEL long-term, inhalation, systemic effect

Study	Point of departure	Correction	Assessment factor	DNEL
Repeated-dose toxicity, oral	NOAEL=54.5 mg/kg tin(II) sulphate	- Standard respiratory factor of 1/0.38 m³/kg/day - Absorption rates (oral 50 %, inhalation 100%) - Standard respiratory volume in humans/ worker respiratory volume (6.7 m³ (8 h) / 10 m³ (8 h)) - Correction factor between human and experimental exposure conditions of workers (5 working days vs. 7 days continuous exposure) of 1.4. NOAEC corrected = 34 mg/m³	AF= 2 (sub-chronic to chronic)*2.5 (interspecies)*5 (intraspecies)=25	DNEL=1.4 mg/m³

It may be noted that the use of the LOAEC at 32 mg Sn/kg based on the carcinogenicity studies would result in a similar DNEL (1.9 mg/m³). Acknowledging the uncertainties on the effect of tin(II) chloride on thyroid tumours, the use of a DNEL of 1.4 mg/m³ is retained for risk assessment for systemic effects.

- DNEL long-term inhalation, local effect

Table 38: DNEL long-term inhalation, local effect

Study	Point of departure	Correction	Assessment factor	DNEL
Repeated-dose toxicity (28-d), inhalation	LOAEC = 2.3 mg/m³ tin(II) oxide	- exposure duration (6h/8h), - respiratory volume under light activity (6.7/10 m³). LOAEC corrected = 1.2 mg/m³	AF=2 (sub chronic to chronic)*3 (LOAEC to NOAEC)*2.5 (interspecies)*5 (intraspecies)=75	DNEL=0.0002 mg/m³

Evaluating MSCA notes that for long-term inhalation, local effects, there are uncertainties on the proposed read-across. The DNEL may be considered appropriate as a pragmatic way forward in the absence of specific data on the substance. However, a default generic DNEL of 1 mg/m³ may be considered as an indicative value in case of corrosive substances

(Messinger, 2014). The value of **0.0002 mg/m³** based on tin(II) oxide may be overly conservative. Tin(II) sulphate was stated to be poorly inhalable, therefore, lung exposure may be low. Based on the lead registrant proposed default STOT RE 1 (although of questionable relevance for tin (II) sulphate), **a qualitative risk assessment for local effects by inhalation, based on high hazard is recommended.**

- DNEL acute inhalation, systemic and local effect

There are no specific data with tin(II) sulphate to derive a relevant value.
For the DNEL systemic acute by inhalation, the registrant derived a value of 3.241 mg/m³ based on tin oxide preliminary 5-day study (NOAEC corrected = 81 mg/m³ and AF 25). Evaluating MSCA notes that the read-across may not be relevant. **Evaluating MSCA also notes the substance should be classified as corrosive and that an appropriate risk assessment related to this hazard should be performed.**

- Dermal Systemic effects - Long-term

Table 39: Dermal Systemic effects - Long-term

Study	Point of departure	Correction	Assessment factor	DNEL
Repeated-dose toxicity, oral (Unpublished study report #5, 2021)	NOAEL=54.5 mg/kg tin(II) sulphate	- absorption rates (oral 100%, dermal 100%) - correction factor between human and experimental exposure conditions of workers (5 working days vs. 7 days continuous exposure) of 1.4. NOAEC corrected = 75.6 mg/kg	AF= 2 (sub-chronic to chronic)*4 (allometric scaling)*2.5 (interspecies)*5 (intraspecies)=100	DNEL=0.76 mg/kg

Based on the worst-case critical effect in animals, a DNEL of 0.39 mg/kg, is proposed for dermal systemic effects.

- Dermal local effects- acute or long-term, systemic acute effects

Qualitative assessment has been performed for these effects. Based on the classification Skin Sens. 1, high hazard class is set according to ECHA guidance.

b. DNEL derivation for the general population

- DNEL long-term, inhalation, systemic effect

Table 40: DNEL long-term, inhalation, systemic effect

Study	Point of departure	Correction	Assessment factor	DNEL
Repeated-dose toxicity, oral	NOAEL=54.5 mg/kg tin(II) sulphate	- standard respiratory factor of 1/1.15 m³/kg/day, - absorption rates (oral 50 %, inhalation 100 %) NOAEC corrected = 19.9 mg/m3	AF= 2 (sub-chronic to chronic)*2.5 (interspecies)*10(intraspecies) =50	DNEL=0.34 mg/m³

The use of a DNEL of 0.34 mg/m³ is retained for risk assessment.

- DNEL acute or long-term, inhalation or dermal, local effect

Only a qualitative assessment was considered. Based on STOT SE 3, H335, a low hazard was set for inhalation and based on Skin Sens. 1 classification, a high hazard was set for dermal route.

- Dermal or oral, Systemic effects - Long-term

Table 41: Dermal or oral, Systemic effects - Long-term

Study	Point of departure	Correction	Assessment factor	DNEL
Repeated-dose toxicity, oral	NOAEL=54.5 mg/kg tin(II) chloride	None	AF= 2 (sub-chronic to chronic)*4 (allometric scaling)*2.5 (interspecies)*10 (intraspecies) =200	DNEL=0.27 mg/kg

Evaluating MSCA notes that for the use of tin(II) chloride as food additive, a PMTDI of 2 mg/kg bw per day, based on gastric irritancy was set by JECFA (latest update, 2006). In addition EFSA notes that in human, zinc status may be affected by continuous exposure to 50 mg Sn per day, corresponding to 0.7 mg Sn/kg bw per day, equivalent to **1.3 mg/kg tin(II) sulphate**. Therefore, although a lower DNEL is calculated based on REACH default assessment factor, the value set by EFSA (2018) is considered conservative and used for risk assessment.

7.9.9. Conclusions of the human health hazard assessment and related classification and labelling

Tin(II) sulphate has no current Annex VI entry in the CLP regulation (EC 1272/2008).

The main hazards identified following exposure to Tin(II) sulphate are: corrosion, sensitisation and effects via inhalation route.

Based on the effects seen in the studies evaluating MSCA consider that the substance should be classified as:

- **Acute Tox. 4, H332 «Harmful if inhaled»**
- **Skin Corr. 1B, H314 « Causes severe skin burns and eye damage »** and not Skin Irrit. 2, H315 « Causes skin irritation » as proposed in the registration dossier ;
- **Eye damage 1, H318 "Causes serious eye damage"**;
- **Skin Sens. 1, H317 "May cause an allergic reaction"**;
- **STOT RE 1, H372 "Causes damage to organs <lung> through prolonged or repeated exposure"**;

Additional classification may be needed when the data for reproduction and development will become available.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

A systematic review of the literature was done and did not raise any alert on the endocrine activity of tin(II) sulphate or any adverse effect for the environmental organisms. The targeted literature search into potential endocrine properties was conducted on SCOPUS (https://www.scopus.com/) on 24 March 2022. The search was conducted without any temporal limits. A search has been performed using search terms and combinations proposed in Annex F of the ECHA/EFSA ED guidance related to the substance ("Tin sulphate," "7488-55-3", "231-302-2") and an endocrine disrupting mode of action on non-mammalian organisms.

From this literature review no relevant publication for the potential endocrine disrupting properties of the tin sulphate against non-mammalian organisms (fish, invertebrate and amphibian) has been identified. No study assessed the potential endocrine activity of the tin sulphate (EATS and non-EATS modalities) and none assessed the potential sub-lethal adverse effects on non-mammalian organisms.

7.10.2. Endocrine disruption - Human health

Due to missing information on reproductive toxicity (developmental, fertility and sexual function), eMSCA cannot conclude on the ED properties of tin (II) sulphate. It is noted that although some decrease in calcium levels have been found following repeated exposure to tin chloride, this was not confirmed in the recent 90-day study.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

No particular concern based on the data currently available.

7.11. PBT and vPvB assessment

According to Annex XIII in REACH Regulation, PBT and vPvB criteria are not applicable to inorganic substances, therefore no assessment was performed.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

The registrant describes exposure scenario concerning the manufacture and industrial use in three sectors (electroplating, chemical industry, and cement industry) and service-life contributing scenario (electroplating).

Table 42 Worker exposure scenarios

ES n°	Exposure Scenario (ES) name	PROC	Product category/Sector of end-use
Manufacture			
1	Manufacture of tin(II) sulphate	1, 2, 3, 4, 8a, 8b, 15, 28	/
Formulation			
2	Formulation into mixture up to 7% solid) or up to 60% of tin(II) sulphate (liquid)	1, 2, 3, 4, 5, 8a, 8b, 9, 14, 15, 28	Product category formulated: PC14: Metal surface treatment products; PC20: products such as pH regulators, flocculants, precipitants, neutralisation agents No technical function
Use at industrial sites			
3	Industrial use electroplating	1, 2, 3, 4, 5, 8a, 8b, 9, 15, 21, 28	Sector of end use: SU15: manufacture of fabricated metal products, except machinery and equipment Function: plating agent Subsequent service life: yes (ES5, ES8, ES10)
4	Industrial use in cement for the reduction of Cr6+	1, 2, 3, 4, 5, 8a, 8b, 9, 15, 21, 28	Product category use: PC 9: Fillers, putties, plasters, modelling clay Function: reducing agent Sector of end use: SU 13: Manufacture of other non-metallic mineral products, e.g. plasters, cement ; SU 19: Building and construction work
Use by professional workers			

5	Widespread use by professional workers – professional use electroplating	1, 2, 3, 4, 5, 8a, 8b, 9, 13, 15, 28	Product Category used: PC 14: Metal surface treatment products Sector of end use: SU 15: Manufacture of fabricated metal products, except machinery and equipment Technical function of the substance: plating agent
6	Widespread use by professional workers – professional use in cement for the reduction of Cr6+	1, 3, 4, 5, 8a, 8b, 28	Product Category used: PC 9: Fillers, putties, plasters, modelling clay Sector of end use: SU 13: Manufacture of other non-metallic mineral products, e.g. plasters, cement ; SU 19: Building and construction work Technical function of the substance: reducing agent
Service life			
8	Industrial service life of articles with electroplated metal	21	Article category related to subsequent service life (AC): AC7a: Metal articles: Large surface area articles ; AC7d: Metal articles: Articles intended for food contact Function: corrosion inhibitor
9	Professional service life of articles with electroplated metals	21	Article category related to subsequent service life (AC): AC7a: Metal articles: Large surface area articles ; AC7d: Metal articles: Articles intended for food contact Function: corrosion inhibitor

For all the exposure scenario, modelling with either ECETOC TRA Workers v3.0 as Tier I or ART v1.5 was used as Tier II. Exposure assessment has been conducted for both physical state of the substance, solid and liquid. No measured data were provided to support the modelling values. No worker exposure data were found in the literature.

The range of exposure values provided by the registrant for the proposed exposure scenarios are available in the confidential document associated to the present document (not publicly available).

7.12.1.2. Consumer

The registrant describes consumer use and service-life contributing scenario for consumers (electroplating). For consumer article service life, the registrant considered that there will be no release from article. Evaluating MSCA acknowledge that tin (II) sulphate used as food contact material is not expected to migrate. The current maximum limit for inorganic tin is between 50 and 200 mg/kg according to regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs and the maximum specific limit for tin intended for food contact is recommended to be 100 mg/kg (Council of Europe, 2014).

Table 43: Consumer exposure scenarios

ES n°	Exposure Scenario (ES) name	AC	Sector of end-use
Consumer use			
7	Consumer use in cement for reduction of Cr6+	/	PC9b: use in cement Function: reducing agent
Service life			
10	Consumer service life of articles with electroplated metals	AC7a, AC7d	Substance not intended to be release from article Article category related to subsequent service life (AC): AC7a: Metal articles: Large surface area articles ; AC7d: Metal articles: Articles intended for food contact Technical function: corrosion inhibitor

AC7a: metal article: large surface area articles, AC7d: metal articles, articles intended for food contact

For consumer uses and for consumer service life contributing scenario, TRA consumers v3.1 was used for estimation of consumer exposure. The values can be found in the associated confidential document.

7.12.2. Environment

7.12.2.1. Introduction to the assessment for the environment

Exposure Scenario n°	Exposure Scenario name
Life Cycle Stage (LCS) IS: Manufacture	
ES 1	**Manufacture of the substance , ERC1**
Relevant information The releases have been estimated on the basis of SPERC Eurometaux SPERC 1.2h.v3: Manufacture of metal compounds (Kd 250000-400000 L/kg) Annual tonnage (t/yr) = 300 Annual use amount at site (t/yr) = 300 Emission days (d/yr) = 182[2] Daily tonnage "per site" (t/d) = 1.648 **Release fraction to air** = 0.03% Justification: SPERC Eurometaux SPERC 1.2h.v3 **Release fraction to wastewater** = 0.001 % Justification: SPERC Eurometaux SPERC 1.2h.v3 **Release fraction to non agricultural soil** = 0.01 % Justification: ERC default $Elocal_{wastewater}$ = 1.65E-02 kg/d **Application of the STP sludge on agricultural soil:** No	
Life Cycle Stage (LCS) F: Formulation	
ES 2	**Formulation into mixture, ERC 2**
Relevant information The releases have been estimated on the basis of SPERC FEICA / EFCC SPERC 2.3a.v1: Non-volatile Substances for the Formulation of Cementitious Construction Chemical Products and Tile Adhesives Annual tonnage (t/yr) = 800 Annual use amount at site (t/yr) = 800 Emission days (d/yr) = 300 Daily tonnage "per site" (t/d) = 2.667 **Release fraction to air** = 5E-3 % Justification: SPERC FEICA / EFCC SPERC 2.3a.v1 **Release fraction to wastewater** = 0 % Justification: SPERC FEICA / EFCC SPERC 2.3a.v1 **Release fraction to non agricultural soil** = 0 % Justification: SPERC FEICA / EFCC SPERC 2.3a.v1 $Elocal_{wastewater}$ = 0.00 kg/d **Application of the STP sludge on agricultural soil:** Yes	

[2] Default number of emission days are derived from a multi-metal background database of measured site-specific release factors collected under the former Directive of New and Existing Substances and REACH 2010 registration dossiers. 182 days/year is the 10th percentile of reported site-specific number of emission days for 168 sites from production of metal compounds.

Life Cycle Stage (LCS) IS : Industrial use	
ES 3	**Industrial use electroplating, ERC 5**
Relevant information The releases have been estimated on the basis of SPERC Eurometaux SPERC 5.1.v3: Industrial use of metals and metal compounds in metallic coating Annual tonnage (t/yr) = 950 Annual use amount at site (t/yr) = 99 Emission days (d/yr) = 220[3] Daily tonnage "per site" (t/d) = 0.45 **Release fraction to air** = 0.2 % Justification: SPERC Eurometaux SPERC 5.1.v3 **Release fraction to wastewater** = 0.5 % Justification: SPERC Eurometaux SPERC 5.1.v3 **Release fraction to non agricultural soil** = 1% Justification: ERC default $Elocal_{wastewater}$ = 2.25 kg/d **Application of the STP sludge on agricultural soil:** No	
Life Cycle Stage (LCS) IS : Industrial use	
ES 4	**Industrial use in cement for the reduction of Cr6+, ERC 5**
Annual tonnage (t/yr) = 235 Annual use amount at site (t/yr) = 5 Emission days (d/yr) = 20 Daily tonnage "per site" (t/d) = 0.25 **Release fraction to air** = 0.5 % Justification: For the use of Tin (II) sulphate in cement, cement containing Tin (II) sulphate is mixed with water and gravel or sand. Due to the low volatility the substance is not likely to be introduced to the air in gaseous form from the prepared cement. Moreover, it is also not likely that particles will be released to the air from the prepared cement matrix. Hence, as a worst-case assumption the release factor is set to 0.5 % to account for a potential release to air during transfer/filling processes of the powder prior to mixing with water and gravel/sand. **Release fraction to wastewater** = 0.001 % Justification: Water is used for preparing the cement mixture to be used. Due to the mixing with water a hydration reaction takes place whereby the water will get chemically bond. Hence, the used water will not be released to the environment. Only the water used for cleaning will introduce small amounts of cement to the environment. As a worst-case assumption the release factor is set to 1E-3 %. **Release fraction to non agricultural soil** = 1 % Justification: ERC default $Elocal_{wastewater}$ = 2.50E-03 kg/d **Application of the STP sludge on agricultural soil:** Yes	
Life Cycle Stage (LCS) P: Professional use	

[3] The 10th percentile of reported site-specific number of emission days for 97 sites. Default number of emission days (220 d/y) are derived from a multi-metal background database of measured site-specific release factors collected under the former Directive of New and Existing Substances and REACH 2010 registration dossiers.

ES 5	Professional use electroplating, ERC 8c

Relevant information
The industrial electroplating use describes the electrolytic colouring of anodized aluminium with Tin (II) sulphate solutions. Thereby the colouring occurs with an alternating current. During the cathode phase, the metal ion (Tin) precipitates into the depth of the oxide pore. The anodic layers are so-called "conversion layers" which means that parts of the base material are included in the layer, which leads to an enormous adhesive strength of the anodic layers. After the electrolytic colouring process the surface of the produced articles including the anodic layers is sealed.
Following the Integrated Pollution Prevention and Control – BAT Reference note document, the treatment methods are very much dependent on the specific processes and the metals involved. More information can be found in the BAT Reference Document for the Non-Ferrous Metals Industry (2017).

Annual tonnage (t/yr) = 180
Annual use amount at site (t/yr) = -
Emission days (d/yr) = 365
Daily tonnage "per site" (t/d) = 9.9E-05

Release fraction to air = 0.2%
Justification: As a reasonable worst case assumption the release to air was set to 0.2 % in accordance with Eurometaux SpERC 5.1v.3.

In general metals and metal compounds do not volatilize. Additionally, during use there is no dust formation that can become air-borne.

Release fraction to wastewater = 0.5 %
Justification: The SnSO4 baths are only replaced very rarely, meaning once in several years. The actual electrolyte can continue to be used almost indefinitely. However, if the solution is no longer suitable it is completely disposed of or recycled. Thereby some companies will even recover the Tin residues.

During cleaning operations the bath is usually transferred to another tank. Then the plating tank is cleaned and the SnSO4 solution is transferred back afterwards. It was indicated that the contaminated rinsing water is stored in IBC and disposed of as well. Furthermore, it was emphasized that rinsing water is reused and not discharged.

As a reasonable worst case assumption the release to water was set to 0.5 % in accordance with Eurometaux SpERC 5.1v.3.

Release fraction to non agricultural soil = 0.00%
Justification: ERC default

$Elocal_{wastewater}$ = 4.93E-04 kg/d

Application of the STP sludge on agricultural soil: Yes

Life Cycle Stage (LCS) P: Professional use	
ES 6	**Professional use in cement for the reduction of Cr6+ (indoor/outdoor), ERC 8c/8f**

Relevant information
The releases have been estimated on the basis of SPERC EFCC SPERC 8c.1a.v2: Widespread use of non-volatile substances in construction chemical products - indoor
The releases have been estimated on the basis of SPERC EFCC SPERC 8f.1a.v2: Widespread use of non-volatile substances in construction chemical products - outdoor

Annual tonnage (t/yr) = 300
Annual use amount at site (t/yr) = -
Emission days (d/yr) = 365
Daily tonnage "per site" (t/d) = 1.65E-04

Release fraction to air =0 %
Justification: SPERC EFCC SPERC 8c.1a.v2 / SPERC EFCC SPERC 8f.1a.v2

Release fraction to wastewater =1.5 %
Justification: SPERC EFCC SPERC 8c.1a.v2 / SPERC EFCC SPERC 8f.1a.v2

Release fraction to non agricultural soil = 0 %
Justification: SPERC EFCC SPERC 8c.1a.v2 / SPERC EFCC SPERC 8f.1a.v2

$Elocal_{wastewater}$ = 2.43E-03 kg/d

Application of the STP sludge on agricultural soil: Yes

Life Cycle Stage (LCS) C: Consumer use	
ES 7	**Consumer use in cement for the reduction of Cr6+ (indoor/outdoor), ERC 8c/8f**

Relevant information
The releases have been estimated on the basis of SPERC EFCC SPERC 8c.1a.v2: Widespread use of non-volatile substances in construction chemical products - indoor
The releases have been estimated on the basis of SPERC EFCC SPERC 8f.1a.v2: Widespread use of non-volatile substances in construction chemical products - outdoor

Annual tonnage (t/yr) = 125
Annual use amount at site (t/yr) = -
Emission days (d/yr) = 365
Daily tonnage "per site" (t/d) = 6.85E-05

Release fraction to air =0 %
Justification: SPERC EFCC SPERC 8c.1a.v2 / SPERC EFCC SPERC 8f.1a.v2

Release fraction to wastewater =1.5 %
Justification: SPERC EFCC SPERC 8c.1a.v2 / SPERC EFCC SPERC 8f.1a.v2

Release fraction to non agricultural soil = 0 %
Justification: SPERC EFCC SPERC 8c.1a.v2 / SPERC EFCC SPERC 8f.1a.v2

$Elocal_{wastewater}$ = 1.03E-03 kg/d

Application of the STP sludge on agricultural soil: Yes

Life Cycle Stage (LCS) SL: Service Life	
ES 8	**Industrial Service Life of articles with electroplated metal, ERC 12a**

Relevant information
The releases have been estimated on the basis of SPERC Eurometaux SPERC 12a.1.v2.1: Industrial use of massive metal in shaping

Annual tonnage (t/yr) = 675
Annual use amount at site (t/yr) = 15
Emission days (d/yr) = 216
Daily tonnage "per site" (t/d) = 6.94E-02

Release fraction to air = 0.02 %
Justification: SPERC Eurometaux SPERC 12a.1.v2.1

Release fraction to wastewater = 0.003 %
Justification: SPERC Eurometaux SPERC 12a.1.v2.1

Release fraction to non agricultural soil = 2.5 %
Justification: ERC default

$Elocal_{wastewater}$ = 2.08E-03 kg/d

Application of the STP sludge on agricultural soil: Yes

Life Cycle Stage (LCS) SL: Service Life

ES 9	Industrial Service Life of cement, ERC 12a

Relevant information
Supporting document: "Heavy Metals in Cement and Concrete resulting from the Co-incineration of Wastes in Cement Kilns with Regard to the Legitimacy of Waste Utilisation" published in 2003 by Forschungszentrum Karlsruhe (Karlsruhe Institute of Technology; KIT) and the Umweltbundesamt (UBA).

Annual tonnage (t/yr) = 240
Annual use amount at site (t/yr) = 12
Emission days (d/yr) =
Daily tonnage "per site" (t/d) =240

Release fraction to air = 0 %
Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the supporting document.

Release fraction to wastewater = 0 %
Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the supporting document.

Release fraction to non agricultural soil = 0 %
Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the supporting document.

$Elocal_{wastewater}$ = 0 kg/d

Application of the STP sludge on agricultural soil: Yes

Life Cycle Stage (LCS) SL: Service Life	
ES 10	**Professional Service Life of articles with electroplated metal, ERC 10a**

Annual tonnage (t/yr) = 425
Annual use amount at site (t/yr) = -
Emission days (d/yr) = 365
Daily tonnage "per site" (t/d) = 2.33E-04

Release fraction to air = 0 %
Justification: During the industrial electroplating use electrolytic colouring of anodized aluminium is conducted with Tin (II) sulphate solutions. Thereby the colouring occurs with an alternating current. During the cathode phase, the metal ion (Tin) precipitates into the depth of the oxide

pore. The anodic layers are so-called "conversion layers" which means that parts of the base material are included in the layer, which leads to an enormous adhesive strength of the anodic layers. After the electrolytic colouring process the surface of the produced articles including the anodic layers is sealed. Hence, a release of Tin is very unlikely. Moreover, metals and metal compounds do not volatilise. Due to the massive physical state of the articles in service life as well as the incorporation of the metal onto the article's surface, there is no dust formation that can become air-borne. As a reasonable worst case assumption the release factor is set to the release factor which is indicated by Eurometaux SPERC 10A.1.v2.

Release fraction to wastewater = 0.1 %
Justification: During the industrial electroplating use electrolytic colouring of anodized aluminium is conducted with Tin (II) sulphate solutions. Thereby the colouring occurs with an alternating current. During the cathode phase, the metal ion (Tin) precipitates into the depth of the oxide pore. The anodic layers are so-called "conversion layers" which means that parts of the base material are included in the layer, which leads to an enormous adhesive strength of the anodic layers. After the electrolytic colouring process the surface of the produced articles including the anodic layers is sealed. Hence, a release of Tin is very unlikely. As a reasonable worst case assumption the release factor is set to 0.1 %.

Release fraction to non agricultural soil = 1.25%
Justification: During the industrial electroplating use electrolytic colouring of anodized aluminium is conducted with Tin (II) sulphate solutions. Thereby the colouring occurs with an alternating current. During the cathode phase, the metal ion (Tin) precipitates into the depth of the oxide pore. The anodic layers are so-called "conversion layers" which means that parts of the base material are included in the layer, which leads to an enormous adhesive strength of the anodic layers. After the electrolytic colouring process the surface of the produced articles including the anodic layers is sealed. Hence, a release of Tin is very unlikely. As a reasonable worst case assumption the release factor is set to the release factor which is indicated by Eurometaux SPERC 10A.1.v2. However, the indicated release factor of 1.25 % is regarded as an overestimation of the actual emission.

$Elocal_{wastewater}$ = 2.33E-04 kg/d

Application of the STP sludge on agricultural soil: Yes

Life Cycle Stage (LCS) SL: Service Life	
ES 11	**Professional Service Life of cement articles, ERC 10a**

Relevant information
Background document: "Heavy Metals in Cement and Concrete resulting from the Co-incineration of Wastes in Cement Kilns with Regard to the Legitimacy of Waste Utilisation" published in 2003 by Forschungszentrum Karlsruhe (Karlsruhe Institute of Technology; KIT) and the Umweltbundesamt (UBA).

Annual tonnage (t/yr) = 230
Annual use amount at site (t/yr) = -
Emission days (d/yr) = 365
Daily tonnage "per site" (t/d) = 1.26E-04

Release fraction to air = 0 %
Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the background document.

Release fraction to wastewater = 0 %
Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are

fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the background document.

Release fraction to non-agricultural soil = 0 %

Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the background document.

$Elocal_{wastewater}$ = 0kg/d

Application of the STP sludge on agricultural soil: Yes

Life Cycle Stage (LCS) SL: Service Life	
ES 12	**Consumer Service Life of articles with electroplated metal, ERC 10a**

Annual tonnage (t/yr) = 275
Annual use amount at site (t/yr) = -
Emission days (d/yr) = 365
Daily tonnage "per site" (t/d) = 1.51E-04

Release fraction to air = 0 %
Justification: Metals and metal compounds do not volatilise. Due to the massive physical state in service life, there is no dust formation that can become air borne.

Release fraction to wastewater = 0.1 %
Justification: During the industrial electroplating use electrolytic colouring of anodized aluminium is conducted with Tin (II) sulphate solutions. Thereby the colouring occurs with an alternating current. During the cathode phase, the metal ion (Tin) precipitates into the depth of the oxide pore. The anodic layers are so-called "conversion layers" which means that parts of the base material are included in the layer, which leads to an enormous adhesive strength of the anodic layers. After the electrolytic colouring process the surface of the produced articles including the anodic layers is sealed. Hence, a release of Tin is very unlikely. As a reasonable worst case assumption the release factor is set to 0.1 %.

Release fraction to non agricultural soil = 1.25 %
Justification: Realistic worst-case value based a literature study with runoff data and emission rates from metallic roofs of Cu, Zn, Pb, Cr, Al, Ni (in steel). A service life of 25 years was assumed.

$Elocal_{wastewater}$ = 1.51E-04 kg/d

Application of the STP sludge on agricultural soil: Yes

Life Cycle Stage (LCS) SL: Service Life	
ES 13	**Consumer Service life of cement articles, ERC 10a**

Relevant information
Background document: "Heavy Metals in Cement and Concrete resulting from the Co-incineration of Wastes in Cement Kilns with Regard to the Legitimacy of Waste Utilisation" published in 2003 by Forschungszentrum Karlsruhe (Karlsruhe Institute of Technology; KIT) and the Umweltbundesamt (UBA).

Annual tonnage (t/yr) = 225
Annual use amount at site (t/yr) = -
Emission days (d/yr) = 365
Daily tonnage "per site" (t/d) = 1.23E-04

Release fraction to air = 0 %
Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the background document.

Release fraction to wastewater = 0 %
Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the background document.

Release fraction to non agricultural soil = 0 %
Justification: During the preparation of cement, Sn(II) cations react rapidly with OH- to Sn(OH)2. Besides this Sn(II) reduces Cr(VI). In cement articles SnSO4 is not present but Tin. Thereby Tin is regarded as trace element. A few hours after concrete mixing already all trace elements are fixed in the highly alkaline cement paste. The cement paste is buffered strongly in the pH range of 12 - 12.5. As long as the buffer remains effective, it forms a stable sink for trace elements. This generally holds over the entire service life of the cement article. It can be concluded that the high buffer capacity of Ca(OH)2 prevents trace elements from being mobilised. Although some trace elements are mobilised (e.g., selenium, thallium), Tin is largely insoluble. Hence the mobilisation of Tin in cement during service life is negligible small. Consequently, no release of Tin is expected. For further information please refer to the background document.

$Elocal_{wastewater}$ = 0 kg/d

Application of the STP sludge on agricultural soil: Yes

7.12.2.2. PNEC derivation

PNECs derivation used in the environmental risk assessment*	
Environmental compartment	**Hazard conclusion (see section 7.8.4)**
Fresh water	PNEC freshwater = 2.71E-03 $mg.l^{-1}$
Sediment (freshwater)	Not relevant
Sewage Treatment Plant	PNEC STP = 6.51 $mg.l^{-1}$
Agricultural soil	PNEC soil = 2.66 $mg.kg_{soil\ dwt}^{-1}$

*PNEC Sn covering PNEC $SnSO_4$

7.12.2.3. Fate and distribution parameters

The substance properties reported in section 7.7 (Table 10) are used in the fate estimation done by the Guidance on information requirements and chemical safety assessment, chapter R.16.

Calculated fate and distribution in the STP – SimpleTreat v4.0	
Compartment	**Percentage [%]**
Air	0.00
Water	8.93
Sludge	91.07
Degraded in STP	0.00

7.13. Risk characterisation

7.13.1. Human Health

Based on Tier I modelling, no risk have been identified by inhalation (all RCR<0.01) based on the information from the CSR which has been further assessed by eMSCA.

However, a risk has been identified via dermal exposure for the following PROC (table below):

Table 44: Dermal exposure

Processes	PROC	OC & RMM	Risk characterisation ratio (RCR), dermal, systemic, long-term	Remark
Manufacture	PROC 2	No dermal protection, with LEV (90-95% effectiveness)	1.8	Tier I, likely to be overestimated*
	PROC 8a PROC 8b PROC 28	Dermal chemical gloves (assumed effectiveness 90-95%), with LEV (assumed effectiveness 90-95%)	1.8 for all PROC	Tier I
Formulation of mixture	PROC 2	No dermal protection, with LEV (90-95% effectiveness)	1.1	Tier I, likely to be overestimated*
	PROC 5 PROC 8a PROC 8b PROC 28	Dermal chemical gloves (assumed effectiveness 90%), with LEV (assumed effectiveness 90-95%)	1.1 1.1 1.8 1.8	Tier I
Industrial use, electroplating	PROC 5 PROC 8a PROC 8b PROC 13 PROC 28	Dermal chemical gloves (assumed effectiveness 90%), with LEV (assumed effectiveness 90-95%) except for PROC 28	1.8 for all PROC	Tier I
Professional use, electroplating	PROC 5 PROC 8a PROC 8b PROC 13 PROC 28	Dermal chemical gloves (assumed effectiveness 90%), with LEV (assumed effectiveness 90-95%) except for PROC 28	1.8 1.1 1.1 1.1	Tier I
Industrial use in cement for the reduction of Cr6+	PROC 8a, PROC 8b, PROC 28	Dermal chemical gloves (assumed effectiveness 90%), with LEV (assumed effectiveness 90-95%)	1.1 for all PROC	Tier I
Professional use in cement for the reduction of Cr6+	PROC 8a, PROC 8b, PROC 28	Dermal chemical gloves (assumed effectiveness 90%), with LEV (assumed effectiveness 90-95%) except for PROC 28	1.1 for all PROC	Tier I

* For dermal exposure, the validation results from Schlueter and Tischer (2002) and Marquart *et al*. (2107) indicate that the TIER I model overestimates dermal exposure for situations where contact with the substance is expected to be limited (PROC 1-3).

For PROC 2, used in close process, Tier I tool may overestimate the risk. As the RCR are only slightly above 1, no risk is identified.

Manufacturing processes (PROC 8a, 8b and 28) can lead to exposures above the DNELs resulting in calculating RCR of 1.8 for activities. It should be noted that ECETOC TRA may overestimate the efficiency of LEV in actual workplaces for PROC8a contributing scenarios (Schlueter & Tischer, 2020). Therefore, a risk may not be controlled for these scenarios. Refinement with Tier II modelling tool would be needed.

The use of tin(II) sulphate for formulation of mixture (PROC 5, 8a, 8b, 28) can lead to exposure above the DNELs, resulting in calculated RCR of 1.1 for PROC 5 and 8a to 1.8 for dermal exposure for PROC 8b and 28. As RR above 1 is calculated, as risk is identified. Therefore, refinement with Tier II modelling tool would be needed.

For industrial and professional use of tin (II) sulphate for electroplating (PROC 5, 8a, 8b, 13 and 28), RCR above 1 have been identified (between 1.1 and 1.8). Refinement with Tier II modelling tool would be needed to exclude the risk.

For industrial and professional use of tin (II) sulphate in cement (PROC 8a, 8b, 28), RCR only slightly above 1 have also been identified. However, it is expected that using a refinement tool, RCR below 1 is expected. Therefore, no risk is identified.

In addition, for scenario with RCR= 1.1, considering effectiveness of gloves having a reduction of >95% instead of 90% would lead to an acceptable risk.

Based on the actual DNELs set up and using the scenarios available, some risks are identified due to the conservativeness of the modelling approach (Tier I only). Evaluating MSCA believes that registrants should recalculate their scenarios and propose additional RMM if necessary.

7.13.2. Environment

LOCAL ASSESSMENT

Evaluating MSCA's conclusion of the environmental risk assessment for each exposure scenario:

ENV compartment	Exposure concentration	RCR value	Conclusion
ES 1	**Manufacture of the substance, ERC1**		
Sewage Treatment Plant	7.36E-04 mg.l^{-1}	1.13E-04	Acceptable
Fresh water	1.12E-05 mg.l^{-1}	4.13E-03	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	1.86E-01 mg.kg$^{-1}_{dwt}$	6.98E-02	Acceptable
Groundwater	**1.08E-01** µg.l^{-1}	Above the parametric drinking water limit of 0.1 µg/L[1]	
ES 2	**Formulation into mixture, ERC 2**		
Sewage Treatment Plant	0.00 mg.l^{-1}	0.00	Acceptable
Fresh water	0.00 mg.l^{-1}	0.00	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	0.00 mg.kg$^{-1}_{dwt}$	0.00	Acceptable

Groundwater	0.00 µg.l^{-1}	Under the parametric drinking water limit of 0.1 µg/L[1]	
ES 3	**Industrial use electroplating, ERC 5**		
Sewage Treatment Plant	1.00E-01 mg.l^{-1}	1.54E-02	Acceptable
Fresh water	1.53E-03 mg.l^{-1}	5.64E-01	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	2.53E+01 mg.kg$^{-1}_{dwt}$	**9.52E+00**	Unacceptable
Groundwater	**1.48E+01** µg.l^{-1}	Above the parametric drinking water limit of 0.1 µg/L[1]	
ES 4	**Industrial use in cement for the reduction of Cr6+, ERC 5**		
Sewage Treatment Plant	1.12E-04 mg.l^{-1}	1.71E-05	Acceptable
Fresh water	1.70E-06 mg.l^{-1}	6.27E-04	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	2.81E-02 mg.kg$^{-1}_{dwt}$	1.06E-02	Acceptable
Groundwater	1.64E-02 µg.l^{-1}	Under the parametric drinking water limit of 0.1 µg/L[1]	
ES 5	**Professional use electroplating, ERC 8c**		
Sewage Treatment Plant	2.20E-05 mg.l^{-1}	3.38E-06	Acceptable
Fresh water	3.35E-07 mg.l^{-1}	1.24E-04	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	5.55E-03 mg.kg$^{-1}_{dwt}$	2.09E-03	Acceptable
Groundwater	3.24E-03 µg.l^{-1}	Under the parametric drinking water limit of 0.1 µg/L[1]	
ES 6	**Professional use in cement for the reduction of Cr6+ (indoor/outdoor), ERC 8c/8f**		
Sewage Treatment Plant	1.10E-04 mg.l^{-1}	1.69E-05	Acceptable
Fresh water	1.67E-06 mg.l^{-1}	6.18E-04	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	2.78E-02 mg.kg$^{-1}_{dwt}$	1.04E-02	Acceptable
Groundwater	1.62E-02 µg.l^{-1}	Under the parametric drinking water limit of 0.1 µg/L[1]	
ES 7	**Consumer use in cement for the reduction of Cr6+ (indoor/outdoor), ERC 8c/8f**		
Sewage Treatment Plant	4.59E-05 mg.l^{-1}	7.05E-06	Acceptable
Fresh water	6.98E-08 mg.l^{-1}	2.58E-04	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	1.16E-02 mg.kg$^{-1}_{dwt}$	4.35E-03	Acceptable
Groundwater	6.74E-03 µg.l^{-1}	Under the parametric drinking water limit of 0.1 µg/L[1]	

ES 8	**Industrial Service Life of articles with electroplated metal, ERC 12a**		
Sewage Treatment Plant	9.30E-05 $mg.l^{-1}$	1.43E-05	Acceptable
Fresh water	1.42E-06 $mg.l^{-1}$	5.22E-04	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	2.35E-02 $mg.kg^{-1}_{dwt}$	4.35E-03	Acceptable
Groundwater	1.37E-02 $\mu g.l^{-1}$	Under the parametric drinking water limit of 0.1 $\mu g/L^1$	
ES 9	**Industrial Service Life of cement, ERC 12a**		
Sewage Treatment Plant	0.00 $mg.l^{-1}$	0.00	Acceptable
Fresh water	0.00 $mg.l^{-1}$	0.00	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	0.00 $mg.kg^{-1}_{dwt}$	0.00	Acceptable
Groundwater	0.00 $\mu g.l^{-1}$	Under the parametric drinking water limit of 0.1 $\mu g/L^1$	
ES 10	**Professional Service Life of articles with electroplated metal, ERC 10a**		
Sewage Treatment Plant	1.04E-05 $mg.l^{-1}$	1.60E-06	Acceptable
Fresh water	1.58E-07 $mg.l^{-1}$	5.84E-05	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	2.62E-03 $mg.kg^{-1}_{dwt}$	9.86E-04	Acceptable
Groundwater	1.53E-03 $\mu g.l^{-1}$	Under the parametric drinking water limit of 0.1 $\mu g/L^1$	
ES 11	**Professional Service Life of cement articles, ERC 10a**		
Sewage Treatment Plant	0.00 $mg.l^{-1}$	0.00	Acceptable
Fresh water	0.00 $mg.l^{-1}$	0.00	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	0.00 $mg.kg^{-1}_{dwt}$	0.00	Acceptable
Groundwater	0.00 $\mu g.l^{-1}$	Under the parametric drinking water limit of 0.1 $\mu g/L^1$	
ES 12	**Consumer Service Life of articles with electroplated metal, ERC 10a**		
Sewage Treatment Plant	6.76E-06 $mg.l^{-1}$	1.03E-06	Acceptable
Fresh water	1.02E-07 $mg.l^{-1}$	3.78E-05	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	1.70E-03 $mg.kg^{-1}_{dwt}$	6.38E-04	Acceptable
Groundwater	9.89E-04 $\mu g.l^{-1}$	Under the parametric drinking water limit of 0.1 $\mu g/L^1$	
ES 13	**Consumer Service life of cement articles, ERC 10a**		

Sewage Treatment Plant	0.00 $mg.l^{-1}$	0.00	Acceptable
Fresh water	0.00 $mg.l^{-1}$	0.00	Acceptable
Sediment (fresh water)	NR	NR	NR
Agricultural soil	0.00 $mg.kg^{-1}_{dwt}$	0.00	Acceptable
Groundwater	0.00 $\mu g.l^{-1}$	Under the parametric drinking water limit of 0.1 $\mu g/L$[1]	

[1] Maximum allowable concentration for pesticides by the revised Drinking Water Directive 2020/2184.
NR: not relevant

All the RCR are under the threshold limit of 1, except for the Manufacture of the substance (ES1) and Industrial use in electroplating (ES3) in groundwater and terrestrial compartment, respectively. For these two uses, the registrants proposed a risk management measure consisting of not applying STP sludge on agricultural soil. In parallel, calculating the risk ratio with the $PNEC_{soil}$ derived from the terrestrial microorganism literature study (Lighthart *et al.*, 1983) which is 20-fold time lower than the one derived from Unpublished study report #24 (2016), although this study is considered as not reliable, shows that the final conclusions remain unchanged: no risks are identified for the claimed uses, except for ES1 and ES3 where a risk management measure is already proposed by the registrants.

REGIONAL ASSESSMENT

The evaluating MSCA agrees with the conclusions of the registrants to consider the impact of the regional scale as negligible on environmental assessment.

CONCLUSION FOR ENVIRONMENT

Environmental risk assessment shows acceptable risks for the following uses:

- **Formulation into mixture** (ES2)
- **Industrial use in cement for the reduction of Cr6+** (ES4)
- **Professional use electroplating** (ES5)
- **Professional use in cement for the reduction of Cr6+ (indoor/outdoor)** (ES6)
- **Consumer use in cement for the reduction of Cr6+ (indoor/outdoor)** (ES7)
- **Industrial Service Life of articles with electroplated metal** (ES8)
- **Industrial Service Life of cement** (ES9)
- **Professional Service Life of articles with electroplated metal** (ES10)
- **Professional Service Life of cement articles** (ES11)
- **Consumer Service Life of articles with electroplated metal** (ES12)
- **Consumer Service life of cement articles** (ES13)

Environmental risk assessment shows acceptable risk for the **Manufacture of the substance** (ES1) and **Industrial use in electroplating** (ES3) considering the **Risk management measures** listed below:

- **No application of the STP sludge on agricultural soil (incineration)**

7.13.3. Overall risk characterization

Human health (combined for all exposure routes)

Worker contributing scenarios leading to RCR=1.1 were identified for some PROC (2, 5, 8a, 8b, 13, 28) in some exposure scenarios. **For some of these exposure scenarios,**

due to the conservativeness of the modelling approach (Tier I only) and remaining options for additional RMMs to be applied, no human health concern is expected even if the DNELs proposed by eMSCA are lower than the ones used by registrants.

For exposure scenario where RCR were =1.8, only a Tier I assessment tool was used and refinement with Tier II tools (e.g. Riskofderm) would be necessary to conclude on potential risk (using DNELs proposed by eMSCA). In case refinement with a Tier II tool would not be sufficient, further refinement of RMM would be necessary but the feasibility is unknown.

The human health risk assessment presented in this document is provisional pending the reception of the data on reproductive toxicity.

Environment (combined for all exposure routes)

Local risk due to all widespread uses

The local risk for environment is summarized in the following table.

Protection target	RCR
Freshwater (including sediment)	1.62E-03
Agricultural soil	2.73E-02

Local exposure due to combined uses at a site

The local risk for environment is summarized in the following table considering all industrial uses in the same site (manufacture, formulation, industrial use electroplating and industrial use cement).

Protection target	RCR
Freshwater (including sediment)	5.69E-01
Agricultural soil	NR, RMM proposed

7.14. References

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7.15. Abbreviations

ANSES:	*Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail* [French Agency for Food, Environmental and Occupational Health & Safety]
ATSDR:	Agency for Toxic Substances and Disease Registry
BCF:	Bioconcentration Factor
BMI:	Body Mass Index
BW:	Body weight
CLP:	Classification, Labelling, Packaging
CMR:	Carcinogen, mutagen and reprotoxic
CNS:	Central Nervous system
CoRAP:	Community rolling action plan
DNEL:	Derived no effect level
DMEL:	Derived minimum effect Level
ECETOC:	European Center for Chemical Safety Assessment
ECHA:	European Chemical Agency
ED:	Endocrine disruption
ELoC:	Equivalent Level of Concern
EOGRTS:	Extended one generation reproductive toxicity study
ER:	Estrogen Receptor
ES:	Exposure scenario
EU:	European Union
EUSES:	European Union System for the Evaluation of Substances
FR-MSCA:	France-Member State Competent Authority
GD:	Gestation day
GLP:	Good Laboratory Practice
HCD:	Historical control data
IPCS:	International Programme on Chemical Safety-
LD:	Lactation day
LC50:	Lethal concentration 50%
LD50:	Lethal Dose 50%
LEV:	Local Exhaust Ventilation
LLNA:	Local Lymph Node Assay
LOAEC:	Lowest observed adverse effect concentration
LOAEL:	Lowest observed adverse effect level
LOD:	Limit of Detection
MoA:	Mode of Action
MSCA:	Member State Competent Authority
NIS:	Sodium Iodide Symporter
NOAEC:	No observed Adverse Effect concentration
NOAEL:	No observed adverse effect level
NTP:	National Toxicology Program
OC:	Operating condition
OECD:	Organisation for Economic Co-operation and Development
OEL:	Occupational Exposure Limit
OR:	Odd ratio
PBT:	Persistent, bioaccumulative and Toxic
PND:	Postnatal Day
PNEC:	Predicted no effect concentration
PROC:	Process category
QSAR:	Quantitative structure-activity relationship
RCR:	Risk Characterisation Ratio
REACH:	Regulation (EC) No 1907/206 of 18/12/06 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACh)
RI:	Reliability Index
RMM:	Risk Management Measures
RR:	Risk ratio
SCL:	Specific Concentration Limit

SCOEL:	Scientific Committee on Occupational Exposure Limits
SD:	Standard Deviation
STOT RE:	Specific target organ toxicity – repeated exposure
STP:	Sewage treatment Plant
SVHC:	Substance of Very High Concern
T:	Testosterone
TG:	Technical Guidance
TGD:	Technical guidance document
TH:	Thyroid Hormone
TK:	Toxicokinetics
TRA:	Targeted Risk Assessment
TWA:	Time Weight Average
US EPA:	United State Environmental Protection Agency
WHO:	World Health organisation