Tin and selected inorganic tin compounds

Evaluation of the effects on reproduction, recommendation for classification

To: the Minister of Social Affairs and Employment
No. 2022/27, The Hague, November 8, 2022

Health Council of the Netherlands

contents

samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad voor tin en een aantal anorganische tinverbindingen beoordeeld of beroepsmatige blootstelling invloed kan hebben op de voortplanting. Op basis van deze beoordeling is een classificatievoorstel opgesteld.

Dit advies is tot stand gekomen in de Subcommissie Classificatie reproductietoxische stoffen, van de Commissie Gezondheid en beroepsmatige blootstelling (GBBS).
Op www.gezondheidsraad.nl staat informatie over de taken van deze vaste commissie van de Gezondheidsraad. De samenstelling van de commissie is te vinden achterin dit advies.

Gebruik van tin

Een belangrijke eigenschap van tin is dat het een mengsel kan vormen met andere metalen (legering). In die hoedanigheid wordt het veel gebruikt voor het solderen van elektrische en industriële apparaten (soldeertin). Ook wordt tin gebruikt als beschermlaag voor andere metalen, in het bijzonder in blik voor voedingsmiddelen.

Tin komt ook voor in allerlei verbindingen.
De commissie heeft tin en de volgende anorganische tinverbindingen beoordeeld: tinsulfide, tinoxide, ditinpyrofosfaat, tindichloride, tindifluoride, tinsulfaat, tindifluoroboraat, tindisulfide en tindioxide. Tindichloride is in commercieel opzicht de belangrijkste anorganische tinverbinding. Het wordt voornamelijk gebruikt als hulpstof bij allerlei chemische processen en bij de productie van glas, gemetalliseerd glas en pigmenten. Tindifluoride wordt gebruikt in de preventieve tandheelkunde.

Werknemers kunnen via de lucht blootgesteld worden aan stof en damp van tin en anorganische tinverbindingen bij het vullen en legen van verpakkingen van tinhoudende materialen in poedervorm, het smelten van tinhoudend materiaal (bijvoorbeeld tijdens het solderen) en bij schoonmaakwerkzaamheden.

Classificeren naar bewijskracht

Bij de beoordeling van effecten op de voortplanting, kijkt de commissie zowel naar effecten op de vruchtbaarheid van mannen en vrouwen als naar effecten op de ontwikkeling van het nageslacht. Daarnaast worden effecten op de lactatie (productie en afgifte van moedermelk) beoordeeld en effecten via de moedermelk op de zuigeling. Als er aanwijzingen bestaan dat de stof schadelijke effecten heeft, stelt de commissie voor om de stof in te delen in gevarencategorieën.

Deze categorieën zijn afgeleid van EU-verordening (EG) 1272/2008.

Geraadpleegde onderzoeken

Er zijn slechts enkele onderzoeken bij mensen beschikbaar over effecten van blootstelling aan tin op de vruchtbaarheid. Over effecten op de ontwikkeling zijn meer onderzoeken beschikbaar, maar zowel voor effecten op de vruchtbaarheid als ontwikkeling tonen deze onderzoeken geen of geen duidelijk verband aan met blootstelling aan tin. Er zijn ook dierstudies gedaan met tin en enkele geselecteerde anorganische tinverbindingen, zowel naar effecten op de vruchtbaarheid als naar effecten op de ontwikkeling. Deze laten ook geen duidelijke nadelige effecten zien, maar de diergevens zijn onvoldoende om conclusies uit te trekken.

Voor effecten van blootstelling aan tin op of via lactatie baseert de commissie zich op onderzoeken bij mensen. In die onderzoeken zijn concentraties van tin in de moedermelk gemeten waarvan de commissie het niet waarschijnlijk acht dat ze tot nadelige gevolgen leiden bij de baby na borstvoeding.

Advies aan de minister

Wegens onvoldoende wetenschappelijke gegevens adviseert de commissie om tin en alle beoordeelde anorganische tinverbindingen, zowel voor effecten op de vruchtbaarheid, als voor effecten op de ontwikkeling, niet in te delen in een gevarencategorie. Op basis van de beschikbare wetenschappelijke gegevens acht de commissie voor effecten op of via lactatie een indeling niet op zijn plaats.

Classificatievoorstel commissie:

- voor effecten op de fertiliteit: niet classificeren wegens onvoldoende geschikte gegevens;
- voor effecten op de ontwikkeling: niet classificeren wegens onvoldoende geschikte gegevens;
- voor effecten op of via lactatie: niet classificeren.

executive summary

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluated the effects of tin and selected inorganic tin compounds on reproduction. This advisory report was drafted by the Subcommittee on the Classification of Reproduction Toxic Substances of the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council, hereafter called the Committee. The Health Council has a permanent task in assessing the hazard of substances to which man can be occupationally exposed. More information about this task can be found at www.gezondheidsraad.nl.

Use of tin and inorganic tin compounds

An important property of tin is the ability to form alloys with other metals. As such, tin is frequently used for electrical/electronic and general industrial applications. Tin also finds extensive use as a protective coating for other metals, especially for food containers.

Various tin compounds exists. The committee has evaluated tin and the following inorganic tin compounds: tin sulphide, tin oxide, ditin pyrophosfate, tin dichloride, tin difluoride, tin sulphate, tin difluoroborate, tin disulphide and tin dioxide. Tin dichloride is commercially the most important inorganic compound and is mainly used as a reducing agent in organic and inorganic syntheses and in the manufacture of metallized glazing, glass, and pigments. Tin difluoride is broadly used in preventive dentistry.

Workers may be exposed to inorganic tin substances via air (dust and fumes) during bagging, smelting operations and cleaning.

Classification based on evidence

To assess effects on reproduction, the Committee evaluates the effects on male and female fertility and on the development of the offspring. Moreover, the Committee considers effects of a substance on lactation and on the offspring via lactation. If the data indicate hazardous properties, the Committee recommends classification in a hazard category. The classification is performed according to EU-regulation (EC) 1272/2008.

Research consulted

Only a few epidemiological studies are available both regarding effects of exposure to tin on fertility. Several studies are available on developmental effects. However, in both cases studies indicate no, or no clear association with exposure to tin. Also, animal studies have been performed with tin and some selected inorganic tin compounds, on effects on fertility as well as

on effects on development. These studies do not show clear adverse effects, however, the data available are insufficient to draw conclusions.

For effects of exposure to tin on or via lactation, the evaluation is based on research with humans. The Committee considers it unlikely that the concentrations of tin in breastmilk that have been measured in those studies will result in adverse effects for the infant after breastfeeding.

Recommendations to the Minister

Based on the scientific data available, the Committee recommends to not classify tin, and all evaluated inorganic tin compounds for effects on fertility, for effects on offspring development and for effects on or via lactation.

The Committee recommends:

- for effects on fertility: not to classify due to a lack of appropriate data;
- for effects on development: not to classify due to a lack of appropriate data;
- for effects during lactation: not to classify.

01 scope

1.1 Background

As a result of the Dutch regulation on registration of compounds toxic to reproduction that came into force on 1 April 1995, the Minister of Social Affairs and Employment requested the Health Council of the Netherlands to classify compounds toxic to reproduction. This classification is performed by the Health Council's Subcommittee on the Classification of reproduction toxic substances of the Dutch Expert Committee on Occupational Safety (DECOS). The classification is performed according to European Union Regulation (EC) 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. The CLP regulation is based on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). The subcommittee's advice on the classification will be applied by the Ministry of Social Affairs and Employment to extend the existing list of compounds classified as reproductive toxicant (category 1A and 1B and 2) or compound with effects on or via lactation.

1.2 Committee and procedure

This document contains the recommendations for classification of tin and tin compounds by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances, hereafter called the Committee.
The members of the Committee are listed on the last page of this report.
The classification is based on the evaluation of published human and animal studies concerning adverse effects with respect to fertility and offspring development as well as adverse effects on or via lactation.

Classifications and hazard statement codes

Classification for reproduction (fertility (F) and development (D)):

Category 1	Known or presumed human reproductive toxicant (H360(F/D))
Category 1A	Known human reproductive toxicant
Category 1B	Presumed human reproductive toxicant
Category 2	Suspected human reproductive toxicant (H361(f/d))

No classification for effects on fertility or development

Classification for lactation:

Effects on or via lactation (H362)
No labeling for lactation

Hazard statement codes:

H360F	May damage fertility.
H360D	May damage the unborn child.
H361f	Suspected of damaging fertility.
H361d	Suspected of damaging the unborn child.
H360FD	May damage fertility. May damage the unborn child.
H361fd	Suspected of damaging fertility. Suspected of damaging the unborn child.
H360Fd	May damage fertility. Suspected of damaging the unborn child.
H360Df	May damage the unborn child. Suspected of damaging fertility.
H362	May cause harm to breast-fed children.

The classification and labelling of substances is performed according to the guidelines of the European Union (Regulation (EC) 1272/2008).
The classification of compounds is the result of an integrated assessment of the nature of all parental and developmental effects observed, their

specificity and adversity, and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the committee has agreed upon a number of additional considerations.

Additional considerations to Regulation (EC) 1272/2008

If there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or subsequent developmental toxic effects in the offspring, the compound will be classified in category 1A, irrespective of the general toxic effects (see Regulation (EC) 1272/2008, 3.7.2.2.1.).

Adverse effects in a reproductive study, reported without information on the paternal or maternal toxicity, may lead to a classification other than category 1B, when the effects occur at dose levels which cause severe toxicity in general toxicity studies.

Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.

The committee does not only use guideline studies (studies performed according to OECD[a] standard protocols) for the classification of compounds, but non-guideline studies are taken into consideration as well.

[a] Organisation for Economic Cooperation and Development

Regarding fertility, the Committee takes into account data on parameters related to fertility, such as seminal fluid volume and spermatozoa concentration, that are related to male fertility. The Committee excludes publications containing only data on sex hormone levels from the assessment, because the relationship between these hormone levels and functional fertility (ability to conceive children) is too uncertain.

In 2022, the President of the Health Council released a draft of the report for public review. The Committee has taken the comments received into account in deciding on the final version of the report. These comments, and the replies by the Committee, can be found on the website of the Health Council.

1.3 Labelling for lactation

The recommendation for classifying substances for effects on or via lactation is also based on Regulation (EC) 1272/2008. The criteria define that substances that are absorbed by women and have been shown to interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled. Unlike the classification of substances for fertility and developmental effects, which is based on hazard identification only (largely independent of dosage), the labelling for effects on or via lactation is based on a risk characterization and

therefore, it also includes consideration of the level of exposure of the breastfed child.

Consequently, a substance should be labelled for effects on or via lactation when it is likely that the substance would be present in breast milk at potentially toxic levels. The Committee considers a concentration of a compound as potentially toxic to the breastfed child when this concentration leads to exceeding the exposure limit for children, or if that level is unknown, the exposure limit for the general population, e.g., the acceptable daily intake (ADI).

1.4 Data

A literature search for publications on reproductive toxicity of tin and inorganic tin compounds was performed using various databases up to March 2021. Additionally, the search strategy included publications on (toxico)kinetics and monitoring. The NIOSH suggested additional literature during public consultation which was included in the final version of the report.

Details on the literature search strategy can be found in Annex A.

02 identity of the compounds

2.1 Name and other identifiers of the substances

For the selection of tin and inorganic tin compounds, an overall list was compiled first based on data from the WHO[1], a report of the Health Council of the Netherlands[2], and the Handbook of chemistry and physics.[3] From this list, a selection of compounds was made, which were divided into five groups based on chemical properties:

- Group 1: Metallic tin;
- Group 2: Inorganic tin compounds; oxidation state 2+, insoluble (tin sulphide, tin oxide, and ditin pyrophosphate);
- Group 3: Inorganic tin compounds; oxidation state 2+, soluble (tin dichloride, tin difluoride, tin sulphate, and tin(II) difluoroborate);
- Group 4: Inorganic tin compounds; oxidation state 4+, insoluble (tin disulphide and tin dioxide).

For an explanation of the selection of compounds, the Committee refers to section 4.5 ‘Grouping’.

Table 1 Substance identity and information related to molecular and structural formula of tin (group 1).

Category	Value
Name(s) in the IUPAC nomenclature or other international chemical name(s)	Tin
Other names (usual name, trade name, abbreviation)	-
ISO common name (if available and appropriate)	N/A
EC/EINECS number (if available and appropriate)	231-141-8
EC name (if available and appropriate)	Tin
CAS number	7440-31-5
Other identity code (if available)	[Sn]
Molecular formula	Sn
Structural formula	Sn
Molecular weight or molecular weight range	118.7
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	N/A
Description of the manufacturing process and identity of the source (for UVBC substances only)	N/A
Degree of purity (%) (if relevant for the entry in Annex VI)	N/A

Table 2 Substance identity and information related to molecular and structural formula of tin sulphide, tin oxide, and ditin pyrophosphate (group 2).

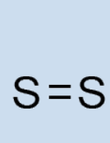
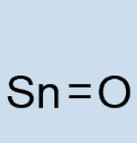
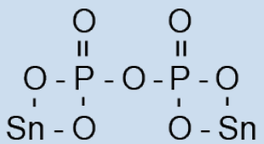
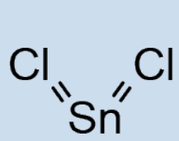
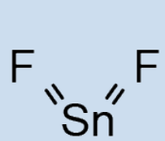
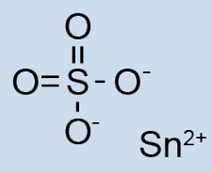
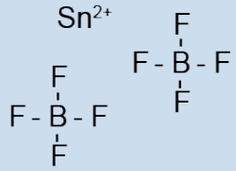
Category	Tin sulphide	Tin oxide	Ditin pyrophosphate
Name(s) in the IUPAC nomenclature or other international chemical name(s)	Stannanethione	Stannanone	ditin(2+) (phosphonooxy) phosphonate
Other names (usual name, trade name, abbreviation)	Tin sulphide, tin(2+) sulphide, tin(II) sulphide, tin sulphide, tin monosulphide	Tin(II) oxide, stannous oxide	Tin(II) pyrophosphate, stannous pyrophosphate
ISO common name (if available and appropriate)	N/A	N/A	N/A
EC/EINECS number (if available and appropriate)	215-248-7	244-499-5	239-635-5
EC name (if available and appropriate)	Tin sulphide	Tin monoxide	Ditin pyrophosphate
CAS number	1314-95-0	21651-19-4	15578-26-4
SMILES code (if available)	S=[Sn]	O=[Sn]	[O-]P(=O)([O-])OP(=O)([O-])[O-].[Sn+2].[Sn+2]
Molecular formula	SnS	SnO	$Sn_2P_2O_7$
Structural formula			
Molecular weight or molecular weight range	150.8	134.7	411.3
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	N/A	N/A	N/A
Description of the manufacturing process and identity of the source (for UVBC substances only)	N/A	N/A	N/A
Degree of purity (%) (if relevant for the entry in Annex VI)	N/A	N/A	N/A

Table 3 Substance identity and information related to molecular and structural formula of tin dichloride, tin difluoride, tin sulphate and tin(II) tetrafluoroborate (group 3).

Category	Tin dichloride	Tin difluoride	Tin sulphate	Tetrafluoroborate
Name(s) in the IUPAC nomenclature or other international chemical name(s)	Tin(2+) dichloride	Tin(2+) difluoride	Lambda2-tin(2+) sulphate	tin(2+); ditetrafluoroborate
Other names (usual name, trade name, abbreviation)	Tin dichloride; tin(II) chloride;	Tin difluoride, tin(II) fluoride, stannous fluoride	Tin(II) sulphate, stannous sulphate	Tin(II) tetrafluoroborate; Tin(II) fluoroborate; Tin fluoroborate; tin(2+); ditetrafluoroborate
ISO common name (if available and appropriate)	stannous chloride	N/A	N/A	N/A
EC/EINECS number (if available and appropriate)	231-868-0	231-999-3	231-302-2	237-487-6
EC name (if available and appropriate)	Tin dichloride	Tin difluoride	Tin sulphate	Tin bis(tetrafluoroborate)
CAS number	7772-99-8	7783-47-3	7488-55-3	13814-97-6
SMILES code (if available)	Cl[Sn]Cl	F[Sn]F	[O-]S(=O)(=O)[O-] .[Sn+2]	[B-](F)(F)(F)F.[B-](F)(F)(F)F.[Sn+2]
Molecular formula	$SnCl_2$	SnF_2	$SnSO_4$	B_2F_8Sn
Structural formula				
Molecular weight or molecular weight range	189.6	156.7	214.8	292.3

Category	Tin dichloride	Tin difluoride	Tin sulphate	Tetrafluoroborate
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	N/A	N/A	N/A	N/A
Description of the manufacturing process and identity of the source (for UVBC substances only)	N/A	N/A	N/A	N/A
Degree of purity (%) (if relevant for the entry in Annex VI)	N/A	N/A	N/A	N/A

Table 4 Substance identity and information related to molecular and structural formula of tin disulphide and tin dioxide, (group 4).

Catgory	Tin disulphide	Tin dioxide
Name(s) in the IUPAC nomenclature or other international chemical name(s)	Tin(4+) disulfanediide	Tin(4+) dioxidandiide
Other names (usual name, trade name, abbreviation)	Tin disulphide	Tin dioxide, stannic oxide
ISO common name (if available and appropriate)	N/A	N/A
EC/EINECS number (if available and appropriate)	215-252-9	242-159-0
EC name (if available and appropriate)	Tin disulphide	Tin dioxide
CAS number	1315-01-1; 12738-87-3	18282-10-5
SMILES code (if available)	S=[Sn]=S	O=[Sn]=O
Molecular formula	SnS_2	SnO_2
Structural formula	S=Sn=S	O=Sn=O
Molecular weight or molecular weight range	182.8	150.7
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	N/A	N/A
Description of the manufacturing process and identity of the source (for UVBC substances only)	N/A	N/A
Degree of purity (%) (if relevant for the entry in Annex VI)	N/A	N/A

2.2 Composition of the substances

Not applicable to mono-constituent substances.

2.3 Physico-chemical properties of the substances

The physicochemical properties of the selected tin compounds are presented in Tables 5, 6 and 7 below. The ECHA dissemination website and the Handbook of chemistry and physics were used as the primary sources.

In many cases, data were waived in the REACH registration dossier, because the data are considered scientifically not necessary or technically not feasible. This is indicated in the tables (i.e. N/A).

The 2+ (stannous) and 4+ (stannic) oxidation states are both reasonably stable and interconverted by moderately active reagents. In aqueous solutions tin(IV) is more stable than tin(II), which can be oxidized to tin(IV). The Sn^{2+}/Sn^{4+} potential is low (-0.15 V) and tin(II) can act as a mild reducing agent. Tin reacts with strong acids and strong bases but remains relatively resistant to neutral solutions. A thin protective oxide film forms on tin exposed to oxygen or dry air at room temperature; heat accelerates this reaction.

Table 5 Summary of physicochemical properties: state of the substance, melting/freezing point, boiling point, relative density, water solubility and partition coefficient.

Substance	State of the substance at normal temperature and pressure	Melting/freezing point (at 101325 Pa)	Boiling point (at 101325 Pa)	Relative density	Water solubility	Partition coefficient n-octanol/water
Tin	Solid, grey metallic powder	232°C	2,500-2,600°C	5.8-7.3 (20°C)	Insoluble: <0.1 mg/L at 20°C	N/A
Tin sulphide	Solid, dark grey powder	>650°C	1210°C	1.6 (20°C)[a]; 5.08[b]	Insoluble: 0.6 µg/L (20°C)	N/A
Tin oxide	Solid	1,080°C[c,d]	-[d]	6.3-6.45 (20°C)	Insoluble: <0.1 mg/L (25°C)	N/A
Ditin pyrophosphate	White inorganic solid	>400°C[d]	-	4 (25°C)	Insoluble	N/A
Tin bis(tetrafluoroborate)	White powder; registered as aquous solution	-	-	-	Soluble	-
Tin dichloride	Solid, white crystalline substance	247°C	623°C	3.9 (20°C)	Very soluble: 178 g/L (20°C)	Log Kow -2.15 (20°C)
Tin difluoride	Solid, white, monoclinic, crystalline, hygroscopic	215°C	850°C	4.6 (25°C)	Very soluble: 300-390 g/L (20°C)	N/A
Tin sulphate	Solid, white crystals	378°C[d]	-[d]	4.15 (20°C)	Very soluble[e]	Log Kow 3.28 (20°C)
Tin disulphide	Odourless gold yellow powder	515-600°C[d]	>515°C[d]	4.5 (20°C)	Insoluble: 0.67 µg/L (20°C)	N/A
Tin dioxide	Solid white powder	1,630°C[d]	-[d]	6.9 (20°C)	Insoluble: <0.1 mg/L at 20°C	N/A

N/A: Not applicable. Data was waived in the REACH registration dossier.

[a] Source: ECHA dissemination website

[b] Source: Handbook of chemistry and physics, 96th edition.

[c] At ca. 600 mmHg (= 80,000 Pa).

[d] Decomposes before melting.

[e] The REACH registration dossier mentions a solubility of 10 g/L at 20°C (source not provided) and a solubility of 188 g/L at 20°C (source: CRC Handbook of Chemistry and Physics).

Table 6 Summary of physicochemical properties: vapour pressure, surface tension, flammability, explosive properties and self-ignition.

Substance	Vapour pressure	Surface tension	Flash point	Flammability	Explosive properties	Self-ignition temperature
Tin	0 kPa (20°C)[a]	N/A	N/A	Not highly flammable	N/A	Not below 400°C
Tin sulphide	-	N/A	-	Not highly flammable	-	-
Tin oxide	N/A	N/A	N/A	N/A	N/A	N/A
Ditin pyrophosphate	N/A	N/A	N/A	Not flammable	N/A	N/A
Tin bis(tetrafluoroborate)	-	-	-	-	-	-
Tin dichloride	0 kPa (20°C)[a]	N/A	N/A	N/A	N/A	N/A
Tin difluoride	N/A	N/A	N/A	Not flammable	N/A	N/A
Tin iodide[b]	-	-	-	-	-	-
Tin sulphate	N/A	73 mN/m	N/A	Not flammable	Not explosive	No self-ignition
Tin disulphide	N/A	72.8 mN/m	N/A	Not flammable	Not explosive	348°C
Tin dioxide	N/A	N/A	N/A	N/A	Not explosive	N/A

N/A: Not applicable. Data was waived in the REACH registration dossier.

[a] 1 Pa at 1224°C

[b] No REACH registration dossier available.

Table 7 Summary of physicochemical properties: oxidising properties, granulometry, stability in organic solvents, dissociation constant and viscosity.

Substance	Oxidising properties	Granulometry	Stability in organic solvents and identity of relevant degradation products	Dissociation constant (pKa)	Viscosity
Tin	No oxidising properties	D25: 2.7 µm D50: 3.2 µm D75: 3.8 µm	N/A	N/A	N/A
Tin sulphide	No oxidising properties	D10: 5 µm, D50: 26 µm, D90: 78 µm	N/A	N/A	N/A
Tin oxide	N/A	D50: Approx. 15 µm	N/A	N/A	N/A
Ditin pyrophosphate	N/A	Mass median aerodynamic diameter: 18.2 µm D10: 11 µm D50: 27 µm D99: 47 µm[a]	-	-	-
Tin dichloride	No oxidising properties	Aerodynamic diameter >32.4 µm. The ratio of particle <10 µm is approximate 3.6%.	N/A	logK = 7.8	N/A
Tin difluoride	N/A	D10: 36.9 µm D50: 82.2 µm D90: 144.4 µm	N/A	N/A	N/A
Tin bis(tetrafluoroborate)	N/A	-	N/A	N/A	N/A
Tin sulphate	No oxidising properties	D50: 20 µm	N/A	N/A	N/A
Tin disulphide	No oxidising properties	D10: 0.59 µm D50: 1.58 µm D90: 6.22 µm	N/A	N/A	N/A
Tin dioxide	N/A	D10:0.115 µm D50: 0.691 µm D90: 1.979 µm	N/A	N/A	N/A

N/A: Not applicable. Data was waived in the registration dossier.

[a] Data from one of the two REACH registration dossiers.

03 manufacture and uses

The main use of tin, accounting for approximately a third of the annual global production, is for solder alloys for electrical/electronic and general industrial applications. Tin also finds extensive use (about 25-30% of production) as a protective coating for other metals, especially for food containers. Tin dichloride is commercially the most important inorganic compound and is mainly used as a reducing agent in organic and inorganic syntheses and in the manufacture of metallized glazing, glass, and pigments. Tin tetrachloride is used in organic synthesis, in plastics, as an intermediate in organotin compound manufacture, and in the production of tin tetraoxide films on glass. Tin difluoride is broadly used in preventive dentistry.[1]

An important property of tin is its ability to form alloys with other metals. Tin alloys cover a wide range of compositions and many applications.

People can be exposed to organic, inorganic and elemental tin through food, drinking water, consumer products and environmental media (air, soil and dust). Most of this tin exposure is in the form of inorganic tin from the consumption of canned food and beverages.[1,4]

Workers may be exposed to inorganic tin substances via air (dust and fumes) during bagging, smelting operations and cleaning.

04 toxicokinetics and grouping

In this section, a short summary is provided mainly based on the evaluation of the WHO[1], supplemented with information from ATSDR[4], SCOEL[5], and a report of the Health Council of the Netherlands.[2] Additional studies are referenced where appropriate. The overview of studies in humans and animals as presented here is not comprehensive.

4.1 Absorption

Generally, absorption of tin from the gastrointestinal tract is low in humans and laboratory animals, including rats, mice, rabbits, cats, and dogs, but it may be influenced by aqueous solubility, dose, anion, and the presence of other substances. Absorption seems to occur by passive diffusion. Adequate data on uptake following inhalation or dermal exposure appear to be lacking.

Eight healthy volunteers were given a diet containing 0.11 mg of tin per day for 20 days. Mean faecal excretion was 55% of the daily dose, suggesting a mean net absorption of 45% at this low dose (although the range was wide, varying from -4 to 71%). When the diet was supplemented (with tin dichloride) to provide an additional 50 mg of tin per day for 20 days, mean faecal excretion was 97% of the daily dose, suggesting a net absorption of 3% (range -7 to 9%) at this higher dose.

Four volunteers with tin blood levels of <2 ng/mL (<17 nmol/L) each consumed 60 mg of tin in the form of fruit juice from an unlacquered can, and blood samples were taken after 2, 5, and 24 h. The two women had detectable tin blood levels (3 ng/mL) only in the 5-h samples. The two men had peak blood tin concentrations of 4.7 ng/mL (40 nmol/L) after 2 hours and 3.9 ng/ml (33 nmol/L) after 24 hours, respectively.

A single administration of 20 mg/kg bw ^{113}Sn(II) or ^{113}Sn(IV) as the citrate or fluoride to rats by gavage resulted in an absorption of 2.85% (2+ oxidation state) and 0.64% (4+ oxidation state). This was based on 48-h recovery of radioactivity in the urine and tissues.

4.2 Distribution

Inorganic tin distributes mainly to bone, but also to the lungs, liver, kidneys, spleen, lymph nodes, tongue, and skin. In a survey of tin concentrations in post-mortem human tissues collected from several hundred subjects, the highest concentrations occurred in the kidney (0.2-0.78 mg/kg tissue), liver (0.35-1.0 mg/kg), lung (0.45-1.20 mg/kg), and bone (0.5-8.0 mg/kg). Certain data indicate that tin may have a higher affinity for the thymus than for other organs. Laboratory animal data suggest that inorganic tin does not readily cross the blood-brain barrier.

With increasing age, tin levels seem to increase in the human lung, possibly because of inhalation of tin from polluted air. The tin content in human tissues was high in the United States and low in Africa, and seldom present in newborn babies in the United States. In humans with no

occupational exposure to tin compounds, blood tin concentrations of 2-9 µg/L are reported. Others reported average tin concentrations in the general population of 11.6 ± 4.4 nmol/L (=1.4 µg/L) in plasma and 21.7 ± 6.7 nmol/L (=2.6 µg/L) in red blood cells in 12 humans (8 women, 4 men, mean age 77.8 years). Background tin concentrations of <1 µg/L in serum and urine have been reported, and a 95th upper percentile of 20 µg/L in urine was calculated for a group of 496 US residents.

The concentrations of a variety of heavy metals were measured in 25 amniotic fluid samples obtained from amniocentesis between 15 and 18 weeks of gestation. The aim of this study was to evaluate the presence of heavy metals in human amniotic fluid to investigate whether there is early foetal exposure. Eighteen metals were detected in measurable amounts in the amniotic fluid; the tin concentrations ranged from 0.001 to 1.279 µg/L. The study demonstrates that tin can pass into the foetal compartment from a very early stage in gestation, although it is noted that only trace amounts were found.[6]

In pregnant rats fed tin at 20 mg/kg bw/day as radioactive tin difluoride or tin tetrafluoride, no tin was found in foetal or placental tissues on day 10 of pregnancy. On day 21, foetuses of dams administered tin difluoride apparently contained approximately 0.2% of the cumulative dose.

In another study, pregnant female Sprague-Dawley rats received tin salts (tin difluoride, sodium pentachlorostannite, or sodium pentafluorostannite) at 125-625 mg/kg in the feed (about 10-50 mg of tin/kg bw/day). Foetal tin values were only slightly elevated (0.8-1.3 mg/kg bw) on day 20 of gestation, compared to foetuses of the control group (0.64 mg/kg bw).

Others have reported that “considerable” tin concentrations were noted in embryos of rats exposed to tin dichloride, without further specification. Data are very limited but suggest the possibility of a low level of tin transfer across the placenta.

Metal concentrations in liver, kidney, brain and testes were measured in rats exposed to miniature alloy pellets containing bismuth, tin and minor amounts of lead by implantation in muscle tissues of the hind legs. The tin concentrations during a 53-week period decreased in the kidney and liver, but increased in time in the testes and brain. The highest concentrations of tin in whole blood were observed three weeks after implantation, then declining to background levels 53 weeks after implantation.[7]

The profile of prenatal exposure to toxic elements and metals, including tin, was assessed using the maternal blood, cord blood and placenta in the Tohoku Study of Child Development of Japan of n=594-650 pregnant women. Tin was detected in 44% of the maternal blood samples (LOD =

0.20 ng/ml) and in 36% of the cord blood samples, with a maximum concentration measured of 8 ng/mL.[8]

4.3 Biotransformation

Few data on biotransformation are available. The difference in the relative affinity of the kidneys and liver for tin(II) and tin(IV) indicates a valence stability of the administered tin.[9] Similarly, the difference observed between tin dichloride and tin tetrachloride in their effects on the immune response in C57BL/6J mice also suggests that these two oxidation states are not readily interconverted in vivo.[10] Together, the available data suggest that tin cations are not rapidly oxidized or reduced during absorption and systemic transportation in mammals.

44 Excretion

Both faeces and urine are major routes of excretion of ingested tin in humans. Ingested tin is largely unabsorbed and excreted mainly in the faeces. Absorbed tin is mainly excreted via the kidneys.

In a mineral balance study, eight adult men ate food providing 0.11 mg or 50 mg of tin per day (as tin dichloride) for 20-day periods. Their urinary excretion was 29 ± 13 µg/day (mean ± SD) and 122 ± 52 µg/day, respectively, representing 36% and 2.4% of the dose, respectively. Mean faecal excretion accounted for 55% and 97% at the low and high daily dose, respectively. A review stated that, in humans, 20% of absorbed tin was cleared with a halftime of 4 days, a further 20% with a half-time of 25 days, and the remaining 60% with a longer half-time of 400 days. No further details were given. When nine healthy adults were given diets consisting of fresh foods (10 mg of tin per day), cold-stored canned foods (26 mg of tin per day), or warm-stored canned foods (163 mg of tin per day) for 24 days, faecal excretion accounted for the whole dose, and none was detected in the urine.

In laboratory animals, the small proportion of tin that is absorbed following ingestion is mainly excreted via the kidneys.

For rat liver and kidney, the biological half-life of tin(II) has been estimated to be 10-20 days. For bone, the half-life of tin(II) and tin(IV) is approximately 20-100 days. A biological half-life of approximately 30 days was estimated for inorganic tin in mice, using a whole-body counting method.

4.5 Grouping

The list of inorganic tin compounds is long and for most of the compounds specific toxicity data are lacking. Therefore, the Committee applies a grouping-approach.

For each compound, information on reproduction toxicity, water solubility and the existence of a REACH registration dossier was collected.[11]

Reproduction toxicity data were collected based on the literature search and from the REACH registration dossiers when available.

Second, criteria were set to be used for grouping of inorganic tin compounds. For grouping of metals, solubility and ionic state have been identified as the main parameters (Guidances such as ECHA's Read-Across Assessment Framework (RAAF)).[12]

A selection of tin compounds was made based on the following criteria:

1. Registration status. Only substances that are registered under REACH, implicating use of the substance within the EU, are included;
2. Oxidation state. Some studies suggest that effects of tin and inorganic tin compounds can differ depending on the oxidation state. In mice, tin tetrachloride caused suppression of both IgM and IgG antibody production in a plaque forming test with spleen cells, whereas tin dichloride caused suppression of IgM and stimulation of IgG antibody production.[10] Also, a differential toxicity between dichloride tin tetrachloride in fish has been observed.[1] Further, a difference in the relative affinity of the kidneys and liver for tin dichloride and tin tetrachloride is seen in rats.[9] These observations suggest a valence stability and that tin cations are not rapidly oxidized or reduced during absorption and distribution in mammals;
3. Water solubility. Inorganic tin compounds have low toxicity in general, partly due to their low solubility. The solubility of tin compounds (partly) determines the bioavailability of the compounds, and thus also the potential of inducing toxicity;
4. Reproductive toxicity data. For at least one of the grouped compounds, reproductive toxicity data are available for evaluation.

Applying the four criteria resulted in the selection of tin and 9 tin compounds and the following four groups:

1. Metallic tin;
2. Tin sulphide, tin oxide, and ditin pyrophosphate (oxidation state 2+, insoluble);
3. Tin dichloride, tin difluoride, tin sulphate, and tin(II) difluoroborate (oxidation state 2+, soluble);
4. Tin disulphide and tin dioxide (oxidation state 4+, insoluble).

The above grouping of tin compounds is only relevant for the evaluation of animal data. In the epidemiological studies, only elemental tin was measured and the oxidation status was not determined.

An overview of all inorganic tin compounds considered is presented in Table 8.

Table 8a List of all inorganic tin compounds considered for this overview: selected inorganic tin compounds

Chemical name	Synonyms	Chemical formula	CAS number	REACH registration dossier	Reproduction toxicity data	Oxidation state	Solubility in water
Tin		Sn	7440-31-5	+	+		Insoluble
Tin sulphide	Tin(II) sulphide, stannous sulphide; tin monosulphide	SnS	1314-95-0	+	+	2+	Insoluble
Tin monoxide	Tin(II) oxide, tin oxide; stannous oxide	SnO	21651-19-4	+	-	2+	Insoluble
Ditin pyrophosphate	Tin(II) pyrophosphate, stannous pyrophosphate	$Sn_2P_2O_7$	15578-26-4	+	-	2+	Insoluble
Tin dichloride	Tin(II) chloride, stannous chloride, stannous chloride dihydrate	$SnCl_2$	7772-99-8	+	+	2+	Soluble
Tin difluoride	Tin(II) fluoride, stannous fluoride	SnF_2	7783-47-3	+	-	2+	Soluble
Tin sulphate	Tin(II) sulphate, stannous sulphate	$SnSO_4$	7488-55-3	+	-	2+	Soluble
Tin(II) difluoroborate	Stannous fluoroborate	$Sn(BF_4)_2$	13814-97-6	+	-	2+	Soluble
Tin disulphide	Tin(IV) sulphide, stannic sulphide	SnS_2	1315-01-1; 12738-87-3	+	+	4+	Insoluble
Tin dioxide	Tin(IV) oxide; stannic oxide	SnO_2	18282-10-5	+	-	4+	Insoluble

Table 8b List of all inorganic tin compounds considered for this overview: compounds considered but not selected for grouping

Chemical name	Synonyms	Chemical formula	CAS number	REACH registration dossier	Reproduction toxicity data	Oxidation state	Solubility in water
Stannane		SnH_4	2406-52-2	-	-		Soluble / very soluble
Disodium tin trioxide	Sodium stannate	Na_2SnO_3	12058-66-1;	+	-	4+	Soluble
Disodium tin hexahydroxide	Sodium stannate trihydrate	$Na_2Sn(OH)_6$	12027-70-2;	+	-	4+	Soluble
Potassium stannate	Dipotassium tin trioxide	K_2SnO_3	12142-33-5	-	-	4+	Very soluble
Potassium stannate trihydrate	Potassium stannate trihydrate; dipotassium tin trioxide trihydrate	$K_2Sn(OH)_6$	12125-03-0	-	-	4+	Soluble/miscible
Sodium pentachlorostannite	Sodium chlorostannite	$NaSn_2Cl_5$	102696-35-5	-	-	2+	-
Sodium hexachlorostannate	Sodium chlorostannate	Na_2SnCl_6	Not found	-	-	4+	-
Sodium pentafluorostannite	Sodium fluorostannite	$NaSn_2F_5$	22578-17-2	-	-	2+	-
Sodium tin citrate	Sodium stannous citrate	$C_{12}H_{10}Na_2O_{14}Sn$	Not found	-	-	4+	-
Tin(II) bromide	Tin dibromide; stannous bromide	$SnBr_2$	10031-24-0	-	-	2+	-
Tin(IV) bromide	Tin tetrabromide; stannic bromide	$SnBr_4$	7789-67-5	-	-	4+	Soluble
Tin(IV) chloride	Tin tetrachloride; stannic chloride	$SnCl_4$	7646-78-8	-	-	4+	Soluble

Chemical name	Synonyms	Chemical formula	CAS number	REACH registration dossier	Reproduction toxicity data	Oxidation state	Solubility in water
Tin(IV) chloride iodide	Tin dichloride diiodide; stannic dichloride diiodide	$SnCl_2I_2$	13940-16-4	-	-	4+	Soluble
Tin(IV) chloride pentahydrate	Stannic chloride pentahydrate	$SnCl_4 \cdot 5H_2O$	10026-06-9	-	-	4+	Very soluble
Tin(IV) chromate	Stannic chromate	$Sn(CrO_4)_2$	38455-77-5	-	-	4+	Soluble
Tin(II) citrate	Stannous citrate; tritin dicitrate	$Sn_3((HO)C(COO)-(CH2COO))_2$	59178-29-9	-	-	2+	-
Tin(IV) citrate	Stannic citrate	$H_2N_4O_{12}Sn$	Not found	-	-	4+	-
Tin(IV) fluoride	Stannic fluoride, tin tetrafluoride	SnF_4	7783-62-2	-	-	4+	Soluble
Tin(II) hydroxide	Stannous hydroxide; tin dihydroxide	$Sn(OH)_2$	12026-24-3	-	-	2+	-
Tin(IV) hydroxide	Stannic hydroxide; tin tetrahydroxide	$Sn(OH)_4$	12054-72-7	-	-	4+	-
Tin(IV) iodide	Tin tetraiodide; stannic iodide	SnI_4	7790-47-8	-	-	4+	Soluble
Tin(II) nitrate	Stannous nitrate	$Sn(NO_3)_2$	Not found	-	-	2+	-
Tin(IV) nitrate	Stannic nitrate	$Sn(NO_3)_4$	13826-70-5	-	-	4+	-
Tin(II) orthophosphate	Tritin bis(orthophosphate); stannous phosphate	$Sn_3(PO_4)_2$	15578-32-2	-	-	2+	-
Tin(IV) orthophosphate	Stannic phosphate	$Sn_3(PO_4)_4$	Not found	-	-	4+	-
Tin monophosphide	Tin(IV) phosphide; stannic phosphide	SnP	25324-56-5	-	-	2+	-
Tin triphosphide	Tetratin triphosphide	Sn_4P_3	12286-33-8	-	-		-
Tin(II) phytate	Stannous phytate	Not found	Not found	-	-	2+	-
Tin(IV) sulphate	Stannic sulphate	$Sn(SO_4)_2$	19307-28-9	-	-	4+	-
Tin(II) telluride	Tin(II) telluride, stannous telluride	SnTe	12040-02-7	-	-	2+	-

05
adverse effects on sexual function and fertility

Adverse effects reported in animal studies are statistically significant ($p<0.05$), unless specified otherwise.

5.1 Animal data

Table 9a Summary table of animal studies on adverse effects on sexual function and fertility. Group 1: Metallic tin

Reference	Species	Experimental period and design	Dose and route	General toxicity	Effects on reproductive organs or reproduction	Remark
ECHA Registration dossier[13]	Wistar rats, males and females, 10/ sex/group Control group: ten males and ten females, dosed with vehicle alone (1% (w/v) aqueous carboxy methylcellulose (sodium salt))	Reproduction / developmental toxicity screening test according to OECD Guideline 421 Daily treatment: Females: 14 days pre-mating, mating (days not specified), gestation and 5 days postpartum Males: 43 days (starting at pre-mating) Duration of exposure: 56 days Effect parameters: maternal examinations, ovarine and uterine content including gravid uterus weight, number of corpora lutea, number of implantations and pre- and post-implantation loss indices Statistical analysis: not reported	Test material: tin metal powder (2-11 µm) Purity: not reported Route of exposure: oral, gavage Exposure levels: 0 (vehicle), 100, 300 and 1,000 mg/kg bw/ day	No treatment-related adverse effects on parental animals Males treated with 1,000 mg/kg/day showed a statistically significant increase in bodyweight gain during Week 3	No effects on mating performance, conception rates, gestation length or parturition Group mean corpora lutea, implantation counts, and implantation losses all indicated no effect of maternal exposure	Study is reported to comply with GLP Only a study summary is available for evaluation
Naser et al., 2020[14]	Wistar rats, males, 6 animals/group Control: deionized water only	30-day exposure of rats to nanoparticles of silver, copper, zinc oxide, cadmium oxide or tin Parameters: luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone, measured in blood Statistical analysis: ANOVA one-way	Test material: tin nanoparticles. Average diameter is 67.34 nm Route of exposure: oral gavage Exposure level: 0.3 mL per day for 30 days, concentration is 53.45 ppm (corresponding to 53-64 µg/kg bw/day) Total experiment includes 6 groups: 1 control group and 5 groups for each of the metals tested	No data reported	Increased concentrations of LH, FSH and testosterone compared to control levels	No guideline study. No information on GLP. No method described on hormone analysis in the blood. Limited number of animals

Table 9b Summary table of animal studies on adverse effects on sexual function and fertility. Group 2: Inorganic tin compounds; oxidation state 2+, insoluble

Reference	Species	Experimental period and design	Dose and route	General toxicity	Effects on reproductive organs or reproduction	Remark
Study report[15, 26]	Wistar rats, males and females, 12 animals/sex/dose Control: concurrent vehicle (0.5% methylcellulose in water)	Reproduction / Developmental Toxicity Screening Test (OECD 421) Daily administration for the following periods: • males and females: 2 weeks prior to the mating period and during the mating period • pregnant females: during pregnancy and till the 3rd day of lactation • males: after mating period; totally for 42 days • non-pregnant females (mated females without parturition): for 25 days after the confirmed mating Parameters: observations and examinations parental animals, phases of the oestrous cycle (recorded during histopathological examination), sperm motility and sperm morphology, litter observations (behaviour, number and sex of pups, stillbirths, live births and presence of gross anomalies), post-mortem examinations parental animals and offspring Statistical analysis: the ANOVA test	Test material: tin sulphide Analytical purity: ca. 97.6% (77.5% Sn, 20.1% S) Route of exposure: oral gavage Exposure levels: 0, 100, 300 and 1,000 mg/kg bw/day	Parental males: increased absolute weight of pituitary gland in males at the dose level of 1,000 mg/kg bw/day No changes of microscopic structure of the pituitary gland Parental females: no significant treatment-related effects	Parental males: microscopical changes in structure of the testes (sporadic degeneration and/or atrophy of germ epithelium, residual bodies in germ epithelium and vacuolation of cytoplasm of spermiogonia) at 1,000 mg/kg bw/day No effect on sperm parameters were observed. Parental females: no significant treatment-related effects Reproductive performance: no effect on the ability of male and female animals to successfully mate and produce viable offspring No effect on sex ratio and development of pups F1 generation: decreased number of corpora lutea, implantations and number of pups (not statistically significant), most notably at dose levels 300 and 1,000 mg/kg/day). No effect on sex ratio	Study in compliance with GLP.

Table 9c Summary table of animal studies on adverse effects on sexual function and fertility. Group 3: Inorganic tin compounds; oxidation state 2+, soluble

Reference	Species	Experimental period and design	Dose and route	General toxicity	Effects on reproductive organs or reproduction	Remark
EFSA, 2018[16]; WHO, 2005[1]; ECHA Registration dossier[17]	CPB:WU rats, 10 males/group 20 females/group	Multigeneration study Daily administration via diet Mating after 12 and 20 weeks (1 male/2 females) leading to F1A and F1B generation F1B generation was used to produce F2A and F2B generation	Test material: tin dichloride, reacting in aqueous medium with the casein content of the diet to simulate exposure through canned food Exposure levels: 0, 200, 400, or 800 ppm in diet, equivalent to 0, 10, 20, or 40 mg tin/kg	No maternal effects were noted	No effect on mating (14-16 of 20 females in each group successful) and pregnancy (14-15/20 in all groups) Increased mortality in F2 generation during lactation (iron deficiency of maternal animals)	Not according to current guidelines. Based on abstracts only; original study by Sinkeldam et al. (1979) not available
NTP, 1982[18]	F344/N rats, males and females, 10/ sex/group Control group: diet only	13-week toxicity study Duration of exposure: 13 weeks Parameters: mortality, clinical examination, body weight, feed consumption, necropsy, histopathology Microscopy included mammary gland, seminal vesicles, prostate, testes, ovaries and uterus	Test material: tin dichloride, CAS 7772-99-8 Purity: not specified Route of exposure: oral, feed Exposure levels[a]: 0, 500, 1000, 1,900, 3,800 and 7,500 ppm, equivalent to 0, 20, 40, 76, 152 and 316 mg/kg bw/day for males and 0, 25, 50, 95, 190 and 395 mg/kg bw/ day for females	No treatment related mortality Mean body weight gain >10% lower in the rats receiving the highest dose, compared to controls Gross distention of the cecum and reddened gastric mucosa in 70%-100% of all rats receiving 3800 or 7500 ppm, but no compound-related histopathologic effects in the cecum or stomach or in any other tissues examined	No effects on reproductive organs	Dose range finding study
NTP, 1982[18]	F344/N rats, males and females, 50/ sex/group Control group: diet only	Carcinogenesis bioassay Duration of exposure: 105 weeks Parameters: mortality, clinical examination, body weight, feed consumption, necropsy, histopathology. Microscopy included mammary gland, seminal vesicles, prostate, testes, ovaries and uterus	Test material: tin dichloride, CAS 7772-99-8 Purity: not specified Route of exposure: oral, feed Exposure levels: 0, 1,000 and 2,000 ppm, equivalent to 0, 40 and 80 mg/ kg bw/day for males and 0, 50 and 100 mg/kg bw/day for females	Survival of high-dose male rats was somewhat lower than that of the control and low-dose groups (37/50, control; 39/50, low-dose; 30/50, high-dose)	No effects on reproductive organs were observed	Study aimed at determining carcinogenicity

[a] 1 ppm is equivalent to 0.04 mg/kg bw/day for male rats and 0.05 mg/kg bw/day for female rats, based on the default values as reported in ECHA guidance R.8, version 2.1, Table 8-17.

Reference	Species	Experimental period and design	Dose and route	General toxicity	Effects on reproductive organs or reproduction	Remark
NTP, 1982[18]	B6C3F1/N mice, males and females, 10/sex/group. Control group: diet only	13-week toxicity study Duration of exposure: 13 weeks Parameters: mortality, clinical examination, body weight, feed consumption, necropsy, histopathology. Microscopy included mammary gland, seminal vesicles, prostate, testes, ovaries and uterus	Test material: tin dichloride, CAS 7772-99-8 Purity: not specified Route of exposure: oral, feed Exposure levels[a]: 0, 1,900, 3,800, 7,500, 15,000 and 30,000 ppm, equivalent to 0, 228, 456, 900, 1,800 and 3,600 mg/kg bw/day for males and 0, 247, 494, 975, 1,950 and 3,900 mg/kg bw/day for females	No mortality observed A pronounced reduced relative weight gain in the highest dose group (56% in males; 32% in females) A dose-dependent increase in incidence of mice with distended cecum from 3,800 ppm and higher No compound-related histopathological effects detected in the cecum	No effects on reproductive organs	Dose range finding study
NTP, 1982[18]	B6C3F1/N mice, males and females, 50/sex/group. Control group: diet only	Carcinogenesis bioassay Duration of exposure: 105 weeks Parameters: mortality, clinical examination, body weight, feed consumption, necropsy, histopathology. Microscopy included mammary gland, seminal vesicles, prostate, testes, ovaries and uterus	Test material: tin dichloride, CAS 7772-99-8 Purity: not specified Route of exposure: oral, feed Exposure levels: 0, 1,000 and 2,000 ppm, equivalent to 0, 120 and 240 mg/kg bw/day for males and 0, 130 and 260 mg/kg bw/day for females	No effects on body weight Survival of the control group was lower compared to the treatment groups in males	No effects on reproductive organs	Study aimed at determining carcinogenicity

[a] 1 ppm is equivalent to 0.04 mg/kg bw/day for male rats and 0.05 mg/kg bw/day for female rats, based on the default values as reported in ECHA guidance R.8, version 2.1, Table 8-17.

Reference	Species	Experimental period and design	Dose and route	General toxicity	Effects on reproductive organs or reproduction	Remark
Yousef, 2005[19]	New Zealand White rabbits, males, 7 months old, 6/ group Control group: 6 animals, not further specified	Treatment: every other day for 12 weeks Parameters: volume of ejaculate, sperm concentration, fructose concentration in seminal plasma. Assessment of live and normal spermatozoa and weight of testes and epididymis. Statistical analysis: General Linear Model (GLM) procedure using SAS statistical package. Variations between means were compared by Duncan's Multiple Range Test	Test material: tin dichloride ($SnCl_2$). Purity: 97.0% Animals treated with or without ascorbic acid (Vitamin C) Exposure route: oral, inserted directly into the oesopharyngeal region Exposure level: 20 mg/kg bw	No effect on body weight	Decreased relative testes weight (control 0.187 g/100g bw; treated 0.149 g/100g bw) and relative epididymis weight (control 0.069 g/100g bw; treated 0.055 g/100g bw) Decrease in the overall means of sperm parameters (ejaculate volume (EV), sperm concentration, total sperm output (TSO), sperm motility (%), total motile sperm per ejaculate (TMS), packed sperm volume (PSV), total functional sperm fraction (TFSF), normal sperm, initial fructose), and a decrease in the reaction time during mating Increase in dead sperm and initial hydrogen ion concentration (pH)	No measurement of tissues other than testes and epididymis No clinical observations, clinical biochemistry or (histo)pathology Only one dose tested No data on reproductive outcome Not according to GLP; limited number of animals

Table 9d Summary table of animal studies on adverse effects on sexual function and fertility. Group 4: Inorganic tin compounds; oxidation state 4+, insoluble

Reference	Species	Experimental period and design	Dose and route	General toxicity	Effects on reproductive organs or reproduction	Remark
Bai et al, 2018[20]	ICR mice, males, 10/group Total: 70 males (7 groups) Control group: de-ionized water without tin disulphide flowers	Treatment: 4 weeks Animals were exposed by gavage 6 times a week, for 4 weeks The content of tin was determined in liver, kidney, spleen, heart, brain, testicle and whole blood The sperm count and survival rate were measured Analysis of the testes: morphological analysis, TUNEL assay and Caspase-3 staining for determining apoptotic rates, ultrastructure observation by transmission electron microscopy (TEM), measurement of malondialdehyde level and superoxide dismutase activity to evaluate oxidative stress, immunohistochemistry, Q-PCR and Western blotting Statistical analysis: The chi-squared test for sperm survival rates data, and one-way analysis of variance (ANOVA) test for other data	Test material: Three different sizes of tin disulphide (SnS_2) nanoflowers (diameters of 50, 80, and 200 nm) with high purity (not specified) Route of exposure: intraperitoneal injection Exposure levels: variations in size and in dose level: • 38 mg/kg, 50 nm • 38 mg/kg, 80 nm • 38 mg/kg, 200 nm • 0.38 mg/kg, 50 nm • 3.8 mg/kg, 50 nm • 38 mg/kg, 50 nm • control group	No apparent changes in growth, activity, or performance of the mice Gradual increase in body weight in the 4 groups with varying sizes (control, 50 nm, 80 nm, 200 nm), but without statistical significance	Morphology testes: no changes in the 200 nm group but a moderate intertubular oedema and a mild interstitial infiltration of inflammatory cells in testes of mice treated with 50 and 80nm tin disulphide nanoflowers A dose-dependent increase in tin levels were observed in all examined tissues Sperm count and sperm survival mildly decreased in mice in the 50 and 80 nm groups Sperm count and sperm survival percentages mildly decreased in the 38 mg/kg group (50 nm), but not in the 0.38 and 3.8 mg/kg groups Blood testes barrier (BTB) relevant gene expression: changes in expression of several genes and expression of TGF-β3 protein in the 38 mg/kg group with 50 and 80 nm tin disulphide nanoflowers, but not in the other groups TEM analysis: vacuolation of the seminiferous epithelium in affected tubules, especially near the rete, revealing a breakdown in Sertoli-germ cell junctions in the 50 nm and 80 nm groups (dose: 38 mg/kg) Oxidative stress: elevated malondialdehyde level and decreased superoxide dismutase activity in the tin disulphide NFs (dose: 38 mg/kg; size: 50 and 80nm) treated groups Apoptosis: apoptosis was induced in the 50 and 80 nm groups (dose: 38 mg/kg) Testicular inflammation: signs of inflammation in the 50 and 80 nm groups (dose: 38 mg/kg) by immunohistochemistry and expression of key inflammatory cytokine and enzymes	

OECD 421 study with tin powder (only abstract available)

Tin metal powder (2-11 µm) was administered by gavage to male and female Wistar rats (10 animals/group) in compliance with OECD guideline 421 (Reproduction/developmental toxicity screening test).[13] Rats were exposed for up to 56 consecutive days (including a two-week maturation phase, pairing, gestation and early lactation for females) to 100, 300 and 1,000 mg/kg bw/day tin metal powder. A control group was dosed with vehicle alone (1% (w/v) aqueous carboxy methylcellulose (sodium salt)). Clinical signs, bodyweight development, dietary intake and water consumption were monitored during the study. The parental rats were paired one to one from day 15 of treatment and females were allowed to litter and rear young to day 5 post-partum. During the lactation phase, daily clinical observations were performed on all surviving offspring, together with litter size and offspring weights and assessment of surface righting reflex. Adult males were euthanised on Day 43, and all females and surviving offspring on Day 5 post-partum. All animals were subjected to a gross necropsy examination and histopathological evaluation of reproductive tissues was performed.

There were no deaths and no significant clinical signs of toxicity.

Males treated with 1,000 mg/kg bw/day showed a statistically significant increase in bodyweight gain during Week 3 (results not presented quantitatively). Female body weight (gain) was unaffected. There were no effects on food consumption. No effects of tin metal powder exposure on mating performance, conception rates, gestational length, or parturition were observed.

30-day study with tin nanoparticles (Naser et al., 2020)

The effect of nanoparticles of tin on sexual hormones was investigated in rats (6 animals/group).[14] Male Wistar rats were exposed for 30 days to low levels of tin nanoparticles (average diameter: 67.34 nm) at 0.3 mL per day, with a concentration of 53.45 ppm (corresponding to 53-64 µg/kg bw/day). At the end of the experimental period, blood was collected and the concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone were measured. The concentrations of LH, FSH and testosterone were significantly increased compared to levels ($P<0.05$) in the control group. Results were given in figures; no absolute number were presented.

OECD 421 study with tin sulphide

A reproduction/developmental toxicity screening test, according to OECD 421, was performed with male and female Wistar rats (12 animals/group).[15,26] The animals were treated with 0, 100, 300 and 1,000 mg/kg bw/day tin sulphide via oral gavage at daily basis.

No relevant clinical changes were observed in males at all dose levels. A slight reduction of weight (one male at the dose level of

100 mg/kg bw/day in the 6th week) and thinner excrements (one male at the dose of 1,000 mg/kg bw/day in the first week) were observed sporadically in treated males. Slight decreases in body weights were sporadically (in 1 or 2 females from the group) recorded in the 3rd week at all groups including control. In treated females at all dose levels, no signs of disease were found during the check-in, acclimatization and application period. Treatment-related effects were not detected during health condition control and clinical observation of females (except of vocalization in one female at the dose level of 1,000 mg/kg/day in the 5th week). There were no unscheduled deaths during the study and no treatment-related effects on body weight and food consumption.

Effects were observed in the pituitary gland of males and in the testes. A statistically significant increase in absolute pituitary weight was detected in males at 1,000 mg/kg bw/day. No changes of microscopic structure of the pituitary gland were found. Histopathological examination of testes of parental males showed increased incidence of degenerations and/or atrophies of germ epithelium and vacuolations of cytoplasm of spermatogonia in males of the dose level 1,000 mg/kg bw/day.
No effect on sperm parameters were observed.

Reproduction parameters – number of females achieving pregnancy, number of females bearing live pups and number of females with live pups at day 4 after parturition – in treated groups were similar to the control or higher than the control groups. Duration of mating and pregnancy were similar in the control and treated females. Pre-implantation, post-implantation and postnatal losses were relatively well balanced at the treated groups and control group.

Average numbers of pups per litter were well-balanced at the control and the dose level 100 mg/kg bw/day. At the dose levels 300 and 1,000 mg/kg bw/day, the average number of pups per litter was decreased compared to the control, however they fell within the normal range of historical control data.

Multigeneration study with tin dichloride (only abstracts available)

In a multigeneration reproduction study including 3 generations, rats (20 females and 10 males/group/generation) were exposed to levels of 0 (control), 200, 400 or 800 ppm (0, 10, 20 or 40 mg/kg bw/day) tin in the diet (WHO, 2005[1]; EFSA 2018[16]; ECHA 2022[17]). To simulate tin exposure from canned food, tin chloride was allowed to react in aqueous medium. The iron content in the diet was increased for the F2 generation onwards (from initially 70 mg Fe/kg diet to 140 mg Fe/kg diet). In this study, no maternal effects were noted and no differences in the percentages of mated males and females and subsequent pregnancies were observed between the groups.

13-week study and carcinogenesis bioassay with tin dichloride (NTP, 1982)

The carcinogenicity of tin dichloride was examined in an NTP carcinogenesis bioassay, preceded by a 13-week toxicity study.[18] Both studies were performed with male and female F344/N rats and male and female B6C3F1/N mice (10 animals/group in the 13-week studies, 50 animals/group in the carcinogenicity bioassays).

Rats were exposed to 0, 20/25, 40/50, 76/95, 152/190 and 300/375 mg/kg bw/day (males/females) tin dichloride for 13 weeks via diet. Mortality, clinical signs, body weight, feed consumption, necropsy and histopathology were examined. Microscopy included examination of the mammary gland, seminal vesicles, prostate, testes, ovaries and uterus. No treatment-related adverse effects were reported on the reproductive organs. In the chronic study, the rats were exposed to 0, 40/50 and 80/100 mg/kg bw/day (males/females) tin dichloride for 105 weeks. Examination of organs included the mammary gland, seminal vesicles, prostate, testes, ovaries and uterus. No neoplastic or non-neoplastic adverse effects were found in these organs upon treatment with tin dichloride.

Mice were treated with tin dichloride for 13 weeks at a dose level of 0, 228/247, 456/494, 900/975, 1,800/1,950 and 3,600/3,900 mg/kg bw/day (males/females), via diet. In the chronic study, the dose levels were 0, 120 and 240 mg/kg bw/day for males and 0, 130 and 260 mg/kg bw/day for females. In both the 13-week study and the carcinogenicity bioassay, no adverse effects were observed in the reproductive organs upon treatment with tin dichloride.

12-week study with tin dichloride (Yousef, 2005)

The protective role of ascorbic acid on reproductive performance of male New Zealand White rabbits treated with tin dichloride was studied by Yousef (2005).[19] Rabbits (6 animals/group) were treated with 20 mg/kg bw tin dichloride, 40 mg/kg bw ascorbic acid or a combination of both treatments. A control group (6 animals) was included but not specified. Treatment was performed every other day for 12 weeks, by gavage. Daily feed intake and body weight were recorded weekly. Sperm collection occurred weekly over the 12 weeks of the study and was used to measure the volume of each ejaculate, the sperm concentration, fructose concentration in seminal plasma, and assessment of live and normal spermatozoa. The weight of the testes and epididymis was recorded. Only results from the control group and the tin dichloride exposure group are described here.

Exposure to tin dichloride did not change the body weight or feed intake. The relative weight of testes and epididymis was statistically significantly decreased in rabbits treated with tin dichloride compared to control animals. Most sperm parameters (volume, concentration, output, motility, functional fraction) were decreased compared to the control group.

The percentage of dead sperm was increased in the treated group. Overall, effects were observed on testes and epididymis weight and on sperm parameters. It is noted that only the testes and epididymis were assessed (no other organs) and that no other clinical observations, clinical biochemistry or (histo)pathology was performed. Only one dose was tested in this study.

4-week study with tin disulphide (Bai et al., 2018)

In a 4-week study, ICR mice (10 animals/group) were exposed via intraperitoneal injection to three different sized tin disulphide (SnS_2) nanoflowers and to different dose levels to investigate the effect on the testes.[20] Three groups were exposed to 38 mg/kg bw of 50, 80, or 200 nm tin disulphide nanoflowers, and three groups were exposed to 0.38, 3.8, or 38 mg/kg bw tin disulphide nanoflowers (50 nm). The animals were exposed by injection 6 times a week, continued for 4 weeks. Nanoflowers are a newly developed class of nanoparticles showing a structure similar to flower.

No apparent changes in growth, activity, or performance of the mice were seen upon treatment. The results of sperm count and survival analysis, histopathological evaluation, and qRT-PCR analysis showed that apparently size-dependent, moderate toxicity was induced in the group of 50 and 80 nm tin disulphide nanoflowers (dose: 38 mg/kg bw) in testicle tissues. Furthermore, signs of oxidative stress, apoptosis and inflammation responses were seen in the same treatment groups. Also ultrastructural abnormalities were more severe than those formed by the large-sized tin disulphide particles in testes. It is noted that results were presented in figures; no quantitative data were available.

5.2 Human data

An overview of the human studies on adverse effects on sexual function and fertility is provided in Table 10. These studies include cross-sectional studies only.

Table 10 Summary table of human data on adverse effects on sexual function and fertility.

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on sexual function and fertility	Bias and confounding	Remarks
Wang, et al (2017)[21]	Design: cross-sectional study Study location: subjects recruited at reproductive medicine centre in Wuhan, China Study period: 2013 Population: 1247 men, aged 18-55 yrs, from subfertile couples visiting fertility centre Exclusion criteria: azoospermia (n=58), occupational exposure to metals (n=16), self-reported disease with possible adverse effect on the reproductive system or urinary excretion of chemicals (n=121). Among the remaining 1052 subjects, semen volumes were inadequate in n=306. Final population: n=746	Exposure assessment: • Tin and 17 other metals in seminal plasma; • Semen specimen produced at clinic visit, after 2-7 days abstinence; • Measured by ICP-MS, reported in micrograms per litre semen, µg/L; • Limit of quantification (LOQ) for tin: 0.020 µg/L; % > LOQ: 57%. Statistical analysis: • Multivariable: linear and logistic regression to estimate associations between metals and outcomes; Tin in three equally-sized categories: <LOQ, middle, and high exposure; • Logistic regression to estimate associations between metal levels and dichotomized outcomes (sperm quality using WHO reference values as cut-off); • Covariables (obtained by questionnaire during centre visit): age, BMI, abstinence duration, time between semen ejaculation and analysis, daily number of cigarettes smoked, smoking (current, former, never), having ever fathered a pregnancy, education category, and alcohol consumption; • Models with multiple metals were constructed on the basis of statistical significance in single metal models; • Benjamini-Hochberg method (with false discovery Rate (FDR)) used to account for multiple testing.	Semen quality tested in fresh semen (using computer-aided semen analyser): • Volume, progressive sperm motility, non-progressive sperm motility, total motility, total sperm count, sperm concentration, sperm morphology ; • Quality measures were dichotomized based on WHO reference values; • Sperm apoptosis reported as % necrotic, % apoptotic and % viable spermatozoa; • Sperm DNA-damage, reported as tail DNA %, tail length, and tail distributed moment. Not all measurements done in all subjects: for spermatozoa apoptosis n=331, for DNA integrity n=404.	Group with at least one sperm quality abnormality versus group without abnormalities: • No difference in tin geometric mean concentration in seminal plasma Association between tin level in semen (<60 (<LOQ), 60-80, >80 percentiles, and % necrotic spermatozoa; p-trend = 0.03, adjusted for FDR and adjustment for multiple metals and covariables. Chosen percentiles (<60, 60-80, >80) were different than for the other metals, indicating that cut-offs were data-based.	For tin concentration in semen, approximately one third of samples below LOQ (risk of exposure misclassification) Number of days of abstinence in 3 categories: <3; 3-5; >5, but might be too crude Smoking included both as continuous variable (cigarette consumption) and categorical (current or former/never). Sperm quality measurement in same sample as tin measurement: an *ex vivo* direct effect of tin on sperm (in contrast to the effect on spermatogenesis due to chronic exposure) cannot be excluded	The study population is the same as in Wang, et al (2016), but a lower number of participants was included due to extra exclusion criteria (semen volume)

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on sexual function and fertility	Bias and confounding	Remarks
Wang et al. (2016a)[22]	Design: cross-sectional study Study location: Subjects recruited at reproductive medicine centre in Wuhan, China Study period: 2013 Population: 1247 men, aged 18-55 yrs, from subfertile couples visiting fertility centre Exclusion criteria: Azoospermia (n=58), occupational exposure to metals (n=16), self-reported disease with possible adverse effect on the reproductive system or urinary excretion of chemicals/ (n=121). Final population: n=1052	Exposure assessment: • Tin and 17 other metals in two spot-urine samples collected a few hours apart (mean interval 4.4 h (SD 3.7 h; range 2.0-11 h), measured by ICP-MS, reported in µg/L; • Lower limit of quantification (LOQ) 0.020 µg/L. Percentages below LOQ: first urine sample 17%, second urine sample 24%. Statistical analysis: • Multivariable linear regression to estimate associations between tin and outcomes, with ln-transformed tin concentrations in quartiles (as ordinal variable); • *Covariables* (obtained by questionnaires during centre visit): age, BMI, abstinence duration, daily number of cigarettes smoked, smoking status (current, formed, never), education, alcohol consumption, income, and creatinine levels (average over the two samples); • Models with multiple metals were constructed on the basis of statistical significance in single metal models ; • Dose-response relations were modeled using cubic splines, with reference values set to median; • Benjamini-Hochberg method used to account for multiple testing.	Sperm quality characteristics in semen sample, after 2-7 days abstination: • Progressive motility; • Total motility; • Sperm concentration; • Total sperm count; • Morphology.	No associations between semen quality parameters and a 10-fold increase in average urine metal levels (ln-transformed).	The two urine samples taken within a few hours, so variability of exposure over longer period not known Selected population (male partners from infertile couples)	The study population overlaps partly with Wang et al. (2017), see above.

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on sexual function and fertility	Bias and confounding	Remarks
Wang, et al (2016b)[23]	See Wang, 2016a	See Wang, 2016a	Sperm characteristics in semen sample, after 2-7 days abstination • Spermatozoa apoptosis, reported as % necrotic, % apoptotic, % viable; • Sperm DNA-damage, reported as tail DNA %, tail length, and tail distributed moment. Serum hormones, in blood samples collected in the morning, same day as semen sample: total testosterone (T), luteinizing hormone (LH), oestradiol, follicle-stimulating hormone, sex-hormone-binding globulin; and derived measures: total T/LH ratio, free androgen index, free T Not all measurements done in all subjects: for hormones n=511, for spermatozoa apoptosis n=460, for DNA integrity n=516. N=171 measured for all three	No associations were found for tin with any of the sperm characteristics tested Median, interquartile range (IQR) tin concentrations 0.38 (0.26-0.54) µg/L in first urine sample, 0.35 (0.24-0.53) µg/L in second urine sample Urinary tin quartiles negatively associated with total testosterone (T) 4th quartile versus 1st quartile, mean (95%CI): -20% (-32%, -7.3%) Median value of T for whole study population: 389 ng/dL Urinary tin quartiles associated with Total T/LH ratio 4th quartile versus 1st quartile: -25% (-43%, -8.3%) Median value of Total T/LH ratio for whole study population: 3.5	The two urine samples taken within a few hours, so variability of exposure over longer period not known Not all outcomes were measured in all subjects because of limitations due to need to analyse sperm within 1 hr Selected population (male partners from infertile couples)	The study population overlaps partly with Wang et al. (2017), see above. Intraclass correlation coefficients (ICC) between tin concentrations in the two samples was 0.66, i.e. fair to good (i.e 0.40 <ICC <0.75)

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on sexual function and fertility	Bias and confounding	Remarks
Guzikowski, et al (2015)[24]	Design: cross-sectional study Study location: hospital in Opole, Poland Study period: first half of 2009 Population: 34 men, aged 26-42 (mean 28.9) yrs, from primary infertile couples visiting fertility centre Exclusion criteria: all other potential causes of subfertility, such as previous pelvic surgery, alcohol consumption, thyroid disturbances	Exposure assessment: • Tin and 8 other metals in seminal plasma; • Semen specimen produced by masturbation after 5 days of abstinence measured by ICP-MS with time-of-flight analyser (ICP-ToF-MS); • Units not reported, nor other details of measurement results. Statistical analysis: • Group comparisons: at least one of the sperm quality criteria not meeting WHO reference values (abnormal group: n=23) versus the reference group (meeting all three criteria: n=11); • Correlations (Pearson) between metal concentrations and sperm quality parameters.	Semen quality according to WHO criteria: • Semen volume • Semen pH (not reported) • Sperm count (per ml) • Sperm motility (% motile) • Sperm morphology (% abnormal) Quality measures were dichotomized based on WHO reference values: count >20×10^6 sperm/ml, >50% of sperm motile, <15% abnormal forms	Pearson correlation between tin level and sperm count: 0.34 (p-value not reported, but flagged as significant) Difference in tin levels between group with abnormal sperm quality parameters (n=23) and reference group (n=11): p=0.04 (group concentrations and difference between groups not reported)	No results of measurements provided No information on potential exposure to metals or potential confounders Being men from subfertile couples for which no fertility abnormalities were found in the women, sperm parameters of reference group may be suboptimal. This might have resulted in a lower power to detect associations.	Statistical analysis and reporting are poor; description results section does not match tables; some conclusions are not supported by data.

Associations between environmental exposure to metals and semen quality were investigated by Wang et al. (2017).[21] They analysed 18 metals, including tin, in seminal plasma of 764 men (subgroup of 1052 men from a previous investigation using metal concentrations in spot urine samples, see Wang et al (2016) below), recruited from a reproductive medicine centre in Wuhan, China. Semen quality parameters, including volume, sperm count, sperm concentration, sperm motility and sperm morphology, were dichotomized according to WHO reference values. Also, sperm apoptosis and sperm DNA-damage were analysed in subgroups (n=331 and n=404, respectively). Tin geometric mean concentrations (SDs not reported) did not differ between the group with sperm abnormalities (n=264) and the reference group (n=482): 0.17 µg/L versus 0.16 µg/L, p=0.15. However, an association was found between tin levels across percentiles (<60, 60-80, >80 percentiles, cut-off choice data-driven) and the percentage of necrotic spermatozoa, with a p_{trend} of 0.03, after adjustment for multiple metals and a range of other covariables.

Wang et al. (2016a) analysed 18 metals (including tin) in two spot urine samples (collected a few hours apart) of 1052 men from subfertile couples.[22] Semen quality parameters (motility, sperm concentration and count, and morphology) were determined and associated with urinary levels of tin using confounder adjusted linear and logistic regression analyses. No associations were observed for urinary tin levels and any of the semen quality parameters.

In an earlier investigation within the same setting, Wang et al (2016b) analysed 18 metals (including tin) in two spot urine samples (collected a few hours apart) of 1052 men from subfertile couples.[23] Measurements were related to spermatozoa apoptosis (n=460) and sperm DNA-damage (n=516) and to sex hormones in serum (n=511). No associations were found for tin with any of the sperm characteristics under study. Urinary tin quartile concentrations were found to be associated with total testosterone (median 389 ng/dL), with adjusted mean percentage difference (95% CI) of -20% (-32%, -7.3%) of 4th quartile versus 1st quartile, and with total testosterone/luteinising hormone ratio (median 3.5), with a corresponding difference of -25% (-43%, -8.3%). These associations were maintained when tin was modelled as continuous variable in a cubic spline analysis (p<0.01), allowing for possibly non-linear associations.

Guzikowski et al. (2015) studied associations between exposure to 9 metals, including tin, and semen quality in a cross-sectional study conducted in 2009 in Poland.[24] Metals were measured in semen samples from 34 primary infertile couples, in which the women had no fertility abnormalities. A Pearson's correlation coefficient of 0.34 was found between tin level and sperm count, but no p-value was provided.
In addition, a difference in tin levels was observed between men with at

least one abnormal sperm quality parameter (n=23) and the remaining men (p=0.04), but group concentrations and difference between the groups were not reported. These results were not adjusted for other covariables.

5.3 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Animal studies

Several animal studies are available that provide information on the potential effects on fertility or reproductive organs of tin and selected inorganic tin compounds.

Group 1: Metallic tin

Tin metal powder was tested in a reproduction/developmental toxicity screening test in rats (only a study summary was available for evaluation).[13] After oral exposure to 0, 100, 300 and 1,000 mg/kg bw/day, no effects on fertility and developmental parameters were observed.

Naser et al. (2020) studied the effect of nanoparticles of tin, administered to male rats by gavage at a dose of 60 µg/kg bw/day for 30 days.[14] Concentrations of LH, FSH and testosterone were increased compared to levels in the control group.

Group 2: Inorganic tin compounds; oxidation state 2+, insoluble

In a reproduction/developmental toxicity screening test in rats, oral administration of tin sulphide (0, 100, 300 and 1,000 mg/kg bw/day) resulted in microscopical changes in structure of the testes.[26] No effects on sperm parameters were noted. The ability of male and female animals to successfully mate and produce viable offspring was unaffected.

Group 3: Inorganic tin compounds; oxidation state 2+, soluble

No effects were observed on mating and pregnancy in a multigeneration study of rats exposed up to 40 mg/kg bw/day.[1,16,17]

As part of an assessment for carcinogenicity, the NTP evaluated the effects of tin dichloride (administered via the diet, up to 395 mg/kg bw/day) on the organs of both rats and mice (males and females).[18] Both in a 13-w toxicity study and a chronic carcinogenicity assay, no effects were observed on mammary gland, seminal vesicles, prostate, testes, ovaries, and uterus.

Yousef (2005) administered 20 mg/kg bw/day tin dichloride to male rabbits for 12 weeks and studied the effects on testes and several sperm quality parameters.[19] A decreased relative testes weight was observed, and several sperm quality parameters were affected.

Group 4: Inorganic tin compounds; oxidation state 4+, insoluble

Bai et al. (2018) administered tin disulphide nanoparticles (0, 0.38, 3.8, or 38 mg/kg bw/day; 50, 80, or 200 nm) to male mice intraperitoneally.[20] Moderate effects in testicular tissue (reduced sperm count and sperm survival) were induced in the groups with 50 and 80 nm tin disulphide nanoflowers (dose: 38 mg/kg bw/day).

Epidemiological studies

A few epidemiological studies investigated the effects on sexual function and fertility. Wang et al (2016a/b and 2017) wrote three publications on a cross-sectional study within the same study setting (fertility centre in Wuhan, China) and largely the same study population (subfertile couples).[21-23] They found an association between quartiles of tin concentrations in urine and total testosterone levels (Wang, 2016b) and an association between tin levels in semen and percentage of necrotic spermatozoa (Wang, 2017). The analyses were adjusted for multiple testing, other metals, and a range of covariables, but an effect of co-exposure could not be excluded. As the small cross-sectional study by Guzikowski et al (2015) had several limitations and issues in presentation, the results are considered questionable.[24]

5.4 Comparison with the CLP criteria

Animal data on the effects of tin and inorganic tin compounds are very limited.

Group 1: For metallic tin, a reproduction/developmental toxicity screen showed no effects on fertility or reproductive organs. Naser et al. (2020) reported increases in hormone levels in male rats treated with nanoparticles of tin.[14] This study, however, included only 6 animals per group and showed limitations in reporting. The Committee also notes that is it not clear whether these effects can be attributed to intrinsic properties of tin or to nano-specific properties. Moreover, effects on hormone levels are not considered a basis for classification by the Committee.

Group 2: In a reproduction/developmental toxicity screening test in rats with tin sulphide, microscopical changes in structure of the testes were observed, but no effects on spermatogenesis were noted and the ability to produce viable offspring was unaffected.[25] Therefore, the results of this screening study do not provide sufficient indication for classification.

Group 3: In a multigeneration study with rats, no maternal toxicity after exposure to tin dichloride was noted and no differences with the control group were observed in the percentages of mated females and subsequent pregnancies. However, only limited summaries of this study are available for evaluation.[1,16,17] In repeated dose studies and carcinogenicity studies of the NTP with tin dichloride (oxidation state 2+, insoluble) in rats and mice (males and females), no histopathological changes in the reproductive organs were observed.[18] In a study with male rabbits, Youssef (2005) reported effects on testes and several sperm quality parameters.[19]

However, this study has several limitations in study design (e.g. only 6 animals/group) and reporting, and provides no information on functional effects.

Group 4: Bai et al. (2018) treated mice with different sizes of tin disulphide nanoflowers and observed effects on sperm count and survival and morphological changes in the testis.[20] As only one dose was tested, particle-specific effects cannot be excluded.

Four epidemiological studies were available on exposure to tin and effects on fertility. One study had substantial limitations[24], whereas the other three were performed well and used appropriate statistical analyses.[21-23] One of these studies showed an association between percentage necrotic spermatozoa and exposure to tin, but a role of co-exposure could not be excluded.[21]

As a result, no conclusions can be drawn regarding an association between exposure to tin and adverse effects on fertility in humans.

Conclusion

The Committee concludes that a lack of appropriate data precludes the assessment of tin and inorganic tin compounds for effects on fertility.

06 adverse effects on development

6.1 Animal studies

Table 11a Summary table of animal studies on adverse effects on development. Group 1: Metallic tin

Reference	Species	Experimental period and design	Dose and route	General toxicity	Developmental toxicity	Remark
ECHA Registration dossier[13]	Wistar rats, males and females, 10/sex/ group Control group: ten males and ten females, dosed with vehicle alone (1% (w/v) aqueous carboxy methylcellulose (sodium salt))	Reproduction / developmental toxicity screening test according to OECD Guideline 421 Daily treatment: Females: 14 days pre-mating, mating (days not specified), gestation and 5 days postpartum Males: 43 days (starting at pre-mating) Duration of exposure: 56 days Effect parameters: maternal examinations, external examinations (all per litter), soft tissue examinations (all per litter) Statistics: not reported	Test material: tin metal powder (2-11 µm) Purity: not reported Route of exposure: oral, gavage Exposure levels: 0 (vehicle), 100, 300 and 1,000 mg/kg bw/day	No treatment-related adverse effects on parental animals Increase in bodyweight gain in males treated with 1,000 mg/kg bw/day during Week 3	Non-statistically significant effects in high dose group: Decreased offspring weight at day 4 post-partum (14-15%) Increased number of implants per dam and live offspring per dam Decreased sex ratio (i.e. % male offspring) in the high dose group at day 4 post-partum as compared with the control group, from 54% to 44%	Only study summary available Study is reported to be in compliance with GLP
ECHA Registration dossier[13]	Crl:WI(Han) rats, females, 20/ group Control group: carboxymethyl cellulose	Prenatal developmental toxicity study according to OECD Guideline 414 Duration of exposure: daily from day 6 to 20 of gestation Effect parameters: • Maternal examinations (clinical observations, body weight, food consumption, post-mortem examinations); • Ovaries and uterine content -(gravid uterus weight, number of corpora lutea, implantations, early resorptions and late resorptions); • Foetal examinations (external, soft tissue and skeletal examinations. Statistics: • ANOVA (body weight, body weight gains, food consumption, gravid uterine weights and corrected body weights) ; • ANCOVA (mean foetal weight, litter size as covariate); • Kruskal-Wallis and Wilcoxon rank sum test (number of corpora lutea, implantation sites, early and late resorptions, dead foetuses, live foetuses and percent pre- and post-implantation loss, percent male foetuses and percentage of foetuses affected); • 1–sided upper tail Fishers exact test (proportion of litters affected).	Test material: tin powder (2-11 µm) Purity: not reported Route of exposure: oral, gavage Exposure levels: 0 (vehicle), 30, 300 and 1,000 mg/kg bw/day	No maternal toxicity Clinical observations consistent across groups and unaffected by treatment No mortality and no treatment-related effects on body weight or food consumption No macroscopic observations associated with treatment	No effects on development observed; foetal external, skeletal and visceral parameters consistent across all groups	Only study summary available Fifteen females with implantations in the control group, while sixteen females with implantations per group considered optimal for statistical analysis of data according to OECD 414 Study reported to be in compliance with GLP

Table 11b Summary table of animal studies on adverse effects on development. Group 2: Inorganic tin compounds; oxidation state 2+, insoluble

Reference	Species	Experimental period and design	Dose and route	General toxicity	Developmental toxicity	Remark
Study report[15, 26]	Wistar rats, males and females, 12 animals/sex/dose Control: concurrent vehicle (0.5% methylcellulose in water)	Reproduction / Developmental Toxicity Screening Test (OECD 421) Daily administration for the following periods: • males and females: 2 weeks prior to the mating period and during the mating period; • pregnant females: during pregnancy and till the 3rd day of lactation; • males: after mating period; totally for 42 days; • non-pregnant females (mated females without parturition): for 25 days after the confirmed mating. Parameters: observations and examinations parental animals, litter observations (behaviour, number and sex of pups, stillbirths, live births and presence of gross anomalies), post-mortem examinations parental animals and offspring Offspring viability: pre-implantation loss, post-implantation loss, postnatal loss, mating index, fertility index, conception index, gestation index, percentage of postnatal loss days 0-4 post-partum and viability index were calculated. Statistics: The ANOVA test	Test material: tin sulphide Analytical purity: ca. 97.6% (77.5% Sn, 20.1% S) Route of exposure: oral gavage Exposure levels: 0 (vehicle), 100, 300 and 1,000 mg/kg bw/day	Parental males: Absolute weight of pituitary gland increased in males at the dose level of 1,000 mg/kg bw/day No changes of microscopic structure of the pituitary gland Parental females: slight non-significant decrease in body weights at 300 and 1000 mg/kg bw/day; no other significant treatment-related effects	F1 generation No statistically significant effect on number of pups and accompanied weight of litter (decrease noted most notably at dose levels 300 and 1,000 mg/kg bw/day, within historical controls) Average weight of pups and postnatal development of pups unaffected. Macroscopic abnormalities described sporadically in pups of all treated and the control groups	Study in compliance with GLP

Table 11c Summary table of animal studies on adverse effects on development. Group 3: Inorganic tin compounds; oxidation state 2+, soluble

Reference	Species	Experimental period and design	Dose and route	General toxicity	Developmental toxicity	Remark
Theuer et al., 1971[27]	Sprague-Dawley rats, females 9-10 pregnant females	Rats were fed a diet containing tin fluoride from day 0 of pregnancy until gestation day 20 Body weight of dams, food/water intake, number of implantation sites, number of resorptions, number of live foetuses, number of litters, placental weight, foetal weight as well as tin levels in foetuses and placentas were recorded Note: significant methodological deficiencies Statistics: two-way analysis of variance; Duncan's multiple range test	Test material: tin difluoride (SnF_2), sodium pentafluorostannite ($NaSn_2F_5$), sodium pentachlorostannite ($NaSn_2Cl_5$) and a mixture of sodium fluoride and tin fluoride Route of exposure: oral, feed Exposure levels: • tin fluoride: 156, 312 and 625 ppm (as tin), equivalent to 7.8, 15.6 and 31.3 mg/kg bw/day[a]. • sodium pentafluorostannite, sodium pentachlorostannite, sodium fluoride + tin fluoride: 125, 250 and 500 ppm (as tin), equivalent to 6.3, 12.5 and 25 mg/kg bw/day	No data	No effects on the numbers of litters, live foetuses per litter, mean placental and foetal weights Increased number of resorptions in the 125 ppm and 500 ppm sodium pentafluorostannite group	Verly low number of pregnant females Gravid uterus weight (including cervix), number of corpora lutea, number of dead foetuses, foetal sex as well as on external, skeletal and soft alterations of foetuses not measured Clinical observation and macroscopic examination of dams not measured; intervals of recording body weight and food consumption not stated; individual animal data not given

[a] 1 ppm is equivalent to 0.05 mg/kg bw/day, based on an assumed body weight of 350 g and assumed food consumption of 17.5 g per day. See ECHA guidance R.8, version 2.1, Table 8-17.

Reference	Species	Experimental period and design	Dose and route	General toxicity	Developmental toxicity	Remark
ECHA Registration dossier[17]	Wistar rats, 24 mated females (22-24 pregnant) Control group: 24 mated females (20 pregnant females)	Prenatal developmental toxicity study equivalent or similar to OECD 414, with several deviations, including: • Purity of the test substance not stated • Body weight and food consumption was not recorded according to guidelines • Gross pathological examination of the females consisted only of the examination of the urogenital tract • Deviations of guidelines for organ and litter analyses • Data on clinical signs not provided • Age and individual weight of the animals not reported • Data on number and percent of pre- and post-implantation losses lacking • Daily treatment, from day 6 through day 15 of gestation • Test duration: 20 days Effect parameters: appearance and behaviour, food/water consumption and intake, post-mortem examinations, ovaries and uterine content, foetal examination	Test material: tin dichloride. Purity: not reported Route of exposure: oral, gavage Exposure levels: 0.5, 2.3, 11.0, and 50.0 mg/kg bw/day	No maternal toxicity was observed	No clearly discernible effect on nidation or on maternal or foetal survival. No differences were observed between the number of abnormalities seen in either soft or skeletal tissues of the exposed groups and the control group.	Only abstract available
ECHA Registration dossier[17]	CD-1 mice, 22-26 mated females (20-23 pregnant) Control group: 29 mated females (21 pregnant females)	Prenatal developmental toxicity study equivalent or similar to OECD 414, with several deviations, including: • Purity of the test substance not stated • Body weight and food consumption not recorded according to guidelines • Gross pathological examination of the females consisted only of the examination of the urogenital tract • Deviations of guidelines for organ and litter analyses • Data on clinical signs not provided. • Age and individual weight of the animals not reported • Data on number and percent of pre- and post-implantation losses lacking • Daily treatment, from day 6 through day 15 of gestation. • Test duration: 17 days Effect parameters: appearance and behaviour, food/water consumption and intake, post-mortem examinations, ovaries and uterine content, foetal examination	Test material: tin dichloride. Purity: not reported Route of exposure: oral, gavage Exposure levels: 0.5, 2.3, 11.0, and 50.0 mg/kg bw/day	No maternal toxicity observed	No clearly discernible effect on nidation or on maternal or foetal survival No differences observed between the number of abnormalities seen in either soft or skeletal tissues of the exposed groups and the control group	Only abstract available

Reference	Species	Experimental period and design	Dose and route	General toxicity	Developmental toxicity	Remark
ECHA Registration dossier[17]	Golden hamster, 22 mated females (20-21 pregnant) Control group: 22 mated females (21 pregnant females)	Prenatal developmental toxicity study equivalent or similar to OECD 414, with several deviations, including: • Purity of the test substance not stated • Body weight and food consumption not recorded according to guidelines • Gross pathological examination of the females consisted only of the examination of the urogenital tract • Deviations of guidelines for organ and litter analyses • Data on clinical signs not provided • Age and individual weight of the animals not reported • Data on number and percent of pre- and post-implantation losses lacking • Daily treatment, from day 6 through day 10 of gestation. Test duration: 14 days Effect parameters: appearance and behaviour, food/water consumption and intake, post-mortem examinations, ovaries and uterine content, foetal examination	Test material: tin dichloride. Purity: not reported Route of exposure: oral, gavage Exposure levels: 0.5, 2.3, 11.0, and 50.0 mg/kg bw/day	No maternal toxicity observed	No clearly discernible effect on nidation or on maternal or foetal survival No differences observed between the number of abnormalities seen in either soft or skeletal tissues of the exposed groups and the control group	Only abstract available
ECHA Registration dossier[17]	Rabbit, 15-17 mated females (11-12 pregnant) Control group: 14 mated females (10 pregnant females)	Prenatal developmental toxicity study equivalent or similar to OECD 414, with several deviations, including: • Purity of the test substance not stated. • Body weight and food consumption not recorded according to guidelines • Gross pathological examination of the females consisted only of the examination of the urogenital tract • Deviations of guidelines for organ and litter analyses • Data on clinical signs not provided. • Age and individual weight of the animals not reported • Data on number and percent of pre- and post-implantation losses lacking • Daily treatment, from day 6 through day 18 of gestation. • Test duration: 29 days Effect parameters: appearance and behaviour, food/water consumption and intake, post-mortem examinations, ovaries and uterine content, foetal examination	Test material: tin dichloride. Purity: not reported Route of exposure: oral, gavage Exposure levels: 0.42, 1.90, 8.90, and 41.5 mg/kg bw/day	No maternal toxicity was observed	No clearly discernible effect on nidation or on maternal or foetal survival. No differences were observed between the number of abnormalities seen in either soft or skeletal tissues of the exposed groups and the control group.	Only abstract available

Reference	Species	Experimental period and design	Dose and route	General toxicity	Developmental toxicity	Remark
WHO, 2005[1]; EFSA 2018[16]; ECHA registration dossier[17]	CPB:WU rats, 10 males/group 20 females/ group	Multigeneration study Daily administration via diet 20 mated F2b females included in the developmental toxicity study (including visceral and skeletal examination of the foetuses). Other F2 animals were allowed to mate and litter, and clinical and pathological examinations of their offspring (F3) were performed	Test material: tin dichloride, reacting in aqueous medium with the casein content of the diet to simulate exposure through canned food Exposure levels: 0, 200, 400, or 800 ppm in diet, equivalent to 0, 10, 20, or 40 mg/kg bw/day	No effects observed on maternal growth	No effects observed on the number of offspring per litter, or birth weight Decrease in body weight gain during lactation Increased mortality and decreased Hb at weaning in F1 generation off-spring (Fe-deficiency of maternal animals) No teratogenic effects in F2B offspring Microscopic changes were observed in the liver and spleen in the F3 pups	Only abstracts of this study available
El-Makawy et al., 2008[28]	Swiss albino mice, males and females, 15/ group (10 females and 5 males) Control group: distilled water by gavage.	32-39 days of treatment Females paired with males during week 3 of the treatment. Females sacrificed at GD18 Effect parameters: gravid uterine contents (numbers of implantation sites, resorptions, late foetal deaths and live foetuses) Examination: foetus weight, gross external malformation, viability of the foetuses, evaluation for weight, external, visceral, and skeletal abnormalities Statistics: one-way analysis of variance (ANOVA). Multiple comparisons were performed by Duncan's Test	Test material: tin dichloride. Purity: >99.0% Exposure route: oral gavage Exposure levels: 0, 2, 10 and 20 mg/kg bw/day	No information available on general toxicity of maternal animals	No effect on the number of implantations Increased post-implantation loss at 10 and 20 mg/kg bw/day Decreased number of live foetuses per litter at 10 mg/kg bw/day No live foetuses at 20 mg/kg bw/day Decreased foetal body weight at 2 and 10 mg/kg bw/day (no live foetuses at 20 mg/kg bw/day) Treatment-related reduction in the ossification of the foetal skeleton at 2 and 10 mg/kg bw (described as 'some evidence', no details available) Decrease in the size of the skeletons at 2 and 10 mg/kg bw/day, due to reduced ossification	No reporting of the condition of maternal animals or examination of maternal animals Not clear if reported developmental effects are (partially) caused by maternal toxicity or not Not clear if values were compared with the control group, or with the number of implantations of the treatment group itself

Table 11d Summary table of animal studies on adverse effects on development. Group 4: Inorganic tin compounds; oxidation state 2+, soluble

Reference	Species	Experimental period and design	Dose and route	General toxicity	Developmental toxicity	Remark
N/A	N/A	N/A	N/A	N/A	N/A	N/A

OECD 421 study with tin powder (ECHA registration dossier, only abstract available)

Tin metal powder (2-11 µm) was administered by gavage to male and female Wistar rats in compliance with OECD guideline 421 (Reproduction/developmental toxicity screening test).[13] Rats were exposed for up to 56 consecutive days (including a two-week maturation phase, pairing, gestation and early lactation for females) to 100, 300 and 1,000 mg/kg bw/day tin metal powder. A control group was dosed with vehicle alone (1% (w/v) aqueous carboxy methylcellulose (sodium salt)). It should be noted that only a summary of results is available.

Clinical signs, bodyweight development, dietary intake and water consumption were monitored during the study. The parental rats were paired one to one from day 15 of treatment and females were allowed to litter and rear young to day 5 post-partum. During the lactation phase, daily clinical observations were performed on all surviving offspring, together with litter size and offspring weights and assessment of surface righting reflex. Adult males were euthanised on Day 43, and all females and surviving offspring on Day 5 post-partum. All animals were subjected to a gross necropsy examination and histopathological evaluation of reproductive tissues was performed.

There were no deaths and no clinical signs of toxicity. Males treated with 1,000 mg/kg bw/day showed a statistically significant increase in bodyweight gain during week 3 (results not presented quantitatively). Female body weight (gain) was unaffected. No effects on food consumption were observed.

The offspring weight at day 4 post-partum was 14-15% decreased in the high dose group as compared to the control group. The number of implants per dam and live offspring per dam was increased at the high dose level. The sex ratio (i.e., % male offspring) was decreased in the high dose group at day 4 post-partum from 54% to 44%. None of the observations showed a statistically significant effect. There were no treatment-related effects on loss of offspring reported.

OECD 414 study with tin powder (ECHA registration dossier, only abstract available)

In a prenatal developmental toxicity study according to OECD guideline 414, female Crl:WI(Han) rats were exposed to tin powder (2-11 µm) by oral gavage.[13] The animals were treated from day 6-20 of gestation with 0, 30, 300 or 1,000 mg/kg bw/day tin powder. Control animals were given the vehicle alone (1% w/v aqueous carboxy methylcellulose).

Maternal examinations were performed, ovaries and uterine content were examined and foetal external, soft tissue and skeletal examinations were done.

Clinical observations were consistent across the groups. There were no treatment-related effects on body weight and food consumption and there were no treatment-related macroscopic observations in the dams. Effects on development were consistent across all groups and also no effects of the treatment were observed on external, skeletal and visceral malformations in the foetuses.

Developmental toxicity study with tin fluoride (Theuer et al., 1971)

Sprague-Dawley pregnant rats (7-10/group) were given a diet containing tin fluoride (SnF_2) at 156, 312 or 625 ppm as tin (equivalent to 7.8, 15.6 and 31.3 mg/kg bw/day), or with sodium pentafluorostannite ($NaSn_2F_5$), sodium pentachlorostannite ($NaSn_2Cl_5$) or a mixture of sodium fluoride + tin fluoride at 125, 250 or 500 ppm as tin (equivalent to 6.3, 12.5 and 25 mg/kg bw/day)[a].[27] Also sodium fluoride and sodium chloride were tested. On day 20 of gestation, foetuses and placentas were obtained for analyses on development and tin levels. Data on clinical and macroscopic observations of the dams, number of dead foetuses, foetal sex, external alterations, skeletal alterations or soft alterations are missing.

No treatment-related effects on the number of live foetuses, foetal weight or placental weight were observed. The number of resorptions was higher in the 50 ppm and 500 ppm sodium pentafluorostannite group, compared with the other treatment groups and the control group.

Foetal tin values were elevated when the maternal diet contained tin salts, but without apparent relation to dietary tin level. Placental levels of tin showed no correlation with the tin levels in the diet.

Multigeneration study with rats (WHO 2005; EFSA 2018, ECHA registration dossier; only abstracts available)

In a multigeration study with rats, the third generation was used to study the effect of tin dichloride (0, 10, 20, and 40 mg tin/kg bw) on developmental parameters.[1,16,17] Microscopic changes were observed in the liver and spleen in the F3 pups at weaning but were not observed in young at 4 weeks of age. Visceral and skeletal examination of the F2 generation rats did not show any tin-related teratogenic effects.
No abortions or litter resorptions were reported, all pregnant animals delivered live foetuses, the number of corpora lutea and implantation sites were higher in the treatment groups, and no gross changes were visible in pregnant animals. The growth of the parent rats was not adversely affected in any generation. In the abstract of the WHO, it was noted that increased mortality occurred in the F2 generation litters during the first 10

[a] Ppm conversion to mg/kg bw/day was based on ECHA guidance R.8, version 2.1, Table 8-17.

days of lactation, but this effect was negated following an increase in iron in the diet.

Developmental toxicity study in rats, mice, hamsters and rabbits (ECHA registration dossier, only abstracts available)

Two study reports (1972, 1974)[17], summarised in the REACH registration dossier[17], describe prenatal developmental studies with rats, mice hamsters and rabbits. These studies are reported to be equivalent or similar to OECD 414, with several deviations. For each species, 15-29 females were allowed to mate with males and were subsequently exposed to tin dichloride from gestational day (GD)6 through GD15 (rats and mice), GD6 through GD10 (hamsters) or GD6-GD18 (rabbits). It was noted that 'no clearly discernible effect on implantation or on maternal or foetal survival' was observed. Furthermore, no differences were observed between the number of abnormalities seen in either soft or skeletal tissues of the exposed groups and the control group.

OECD 421 study with tin sulphide (Study report, 2010)

A reproduction/developmental toxicity screening test, according to OECD 421, was performed with male and female Wistar rats.[26] The animals were treated with 0, 100, 300 or 1,000 mg/kg bw/day tin sulphide via oral gavage at daily basis.

No relevant clinical changes were observed in males at all dose levels after application of the test substance. A slight reduction in body weight was observed sporadically in treated males and females in different treatment groups. There were no unscheduled deaths observed during the study.

The average weights of the litters and pups at the dose level 100 mg/kg bw/day were slightly increased against control. At the dose levels of 300 and 1,000 mg/kg bw/day, the average weight of the litter was lower compared to control, but the average body weights of pups were slightly higher compared to pups in the control group. No statistically significant changes were found, and all observations were within historical control values.

Statistical evaluation was performed on the number of live pups. The total numbers of live pups (on the day of parturition/1st day after parturition and the 4th day after parturition) were similar in the controls and at the dose level 1,000 mg/kg bw/day. The number was higher at the dose level 100 mg/kg bw/day, and vice versa at the dose level 300 mg/kg bw/day, at which the number was slightly lower.

One pup of the control group and one pup in the 300 mg/kg bw/day group died after birth – in the period 0/1st day-4th day. No treatment related differences in external malformations were observed between the control

group and at all treated groups. Macroscopical examination was performed in all pups. Sporadic pathologic findings were recorded in pups of the treated and control groups. The number of pups with macroscopic changes was comparable in the control and 100 and 300 mg/kg bw/day dosed groups; an increase in livers with marked structure was noted in two litters in the 1,000 mg/kg bw/day dose group. This finding was attributed to physiological extramedullary haematopoiesis.

Developmental toxicity study with tin dichloride (El-Makawy et al., 2008)

A study with male and female Swiss mice treated with tin dichloride during pairing and gestation was performed by El-Makawy et al.(2008).[28]

Males and females were treated with 0, 2, 10 or 20 mg/kg bw/day and paired during week 3 of treatment. Females were sacrificed at gestational day 18, after 32-39 days of treatment in total. Effects were observed on post-implantation loss, number of live foetuses, foetal body weight and ossification of the foetal skeleton. The high dose (20 mg/kg bw/day) induced complete post-implantation loss. Treatment with 10 mg/kg bw/day induced a significant decrease in the number of live foetuses and a significant increase in the number of post-implantation losses. Further, the foetal body weight at 2 and 10 mg/kg bw/day was significantly decreased compared with the control group. It is noted that it is not clear if statistical analysis was performed by relating results to the control group (as suggested in the text above) or by relating results to the number of implantations of the corresponding treatment group.

There was some evidence of treatment-related reduction in the ossification of the foetal skeleton. The weight of foetuses in the 2 and 10 mg/kg bw/day group was statistically significantly decreased compared to those in the control group. All bones of the axial (skull and vertebrae) and appendicular (bones of pelvic girdle, fore and hind limbs, bones of digits) skeletons of foetuses in the treated groups showed less ossification than the controls. No (quantitative) details were provided on the results on ossification.

6.2 Human data

An overview of the human studies on adverse effects on development is provided in Table 12. These studies include prospective cohort studies, case-control studies, and one cross-sectional study.

Table 12a Human studies on adverse effects on development: cohort studies

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Howe, et al (2020a)[29]	Design: prospective cohort study Study location: Los Angeles, CA, USA Study period: 2015-2019 Population: participants in the MADRES (Maternal and Developmental Risks from Environmental and Social Stressors) study, i.e., pregnant women recruited at one of four prenatal care providers in LA, mainly lower-income Hispanic populations Exclusion criteria: pregnancy ≥20 wks of gestation at recruitment, <18 years of age, HIV positive, physical, mental or cognitive disability, multiple gestation, incarceration, no urine sample at first visit Urine analysis restricted to 262 participants (enrolled prior to urine metals analysis (fall 2019), not withdrawn from the study and complete covariable information present Other publications in the same cohort: Howe et al. (2020b), other health outcome	Exposure assessment: • Spot urine samples collected by participant during first study visit (median gestational age 13.1 weeks) • Tin and 9 other metals measured by ICP-MS in urine, expressed as µg/L 13.7% of samples <LOD • Urinary concentrations of tin (urine specific gravity corrected), median (IQR): 0.49 (0.27-0.97) µg/L Statistical analysis: • Tin was not included in the primary analysis with 7 metals, but was added to the secondary explorative analysis with 10 metals • Relation between mixture of metals and outcome analysed with Bayesian kernel machine regression • Directed acyclic graphs (DAG) were used to identify potential confounders: recruitment site; self-reported (questionnaire) variables: maternal age, pre-pregnancy BMI, race by ethnicity and birthplace, smoke exposure; measured variables: pregnancy anaemia (Hb,Ht), urinary arsenobetaine (as marker of fish consumption) • Interactions were analysed using a novel method (NLinteraction method)	Birth weight for gestational age and sex, z-scores based on a 2017 US reference (Airs, et al. 2019) Birth weight measures obtained from medical records; if missing (n=22) based on information from mother Gestational age estimates using ultrasound or observation at birth (physician's estimate)	Posterior inclusion probability for tin in the secondary exploratory analysis was 0.45, which ranked in fourth place of importance. By setting all other metals to their median values, an inverse linear relationship was shown for tin with birth weight z-scores	Only subjects with complete covariable information were included Measurement of metals only once in urine (variability) at one point in pregnancy The focus of this study was on mixtures of metals	Study population was an impoverished urban population, probably above average at risk of both exposure to pollution and intra-uterine growth retardation Sample size was quite small (lack of power)

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Howe, et al (2020b)[30]	Design: prospective cohort study Study location: Los Angeles, CA, USA Study period: 2015-2019 Population: participants in the MADRES (Maternal and Developmental Risks from Environmental and Social Stressors) study, i.e., pregnant women recruited at one of four prenatal care providers in LA, mainly lower-income Hispanic populations Exclusion: pregnancy ≥20 wks of gestation at recruitment, <18 years of age, HIV positive, physical, mental or cognitive disability, multiple gestation, incarceration, no urine sample at first visit Analyses restricted to 195 participants enrolled prior to urine metals analysis (fall 2019) and prior to routine anatomy ultrasound scan, not withdrawn from the study and complete covariable information present Other publications in the same cohort: Howe et al. (2020a), other health outcome	Spot urine samples collected by participant during first study visit (median gestational age 12.4 weeks) Tin and 9 other metals measured by ICP-MS in urine samples, expressed as µg/L Urinary concentrations of tin (urine specific gravity corrected): median (IQR): 0.47 (0.28-0.92) µg/L Statistical analysis: • Primary analysis focused on a mixture of 6 metals, including tin. Secondary analysis included four more metals • Association between mixtures of metals and outcome analysed with Bayesian kernel machine regression Directed acyclic graphs (DAG) were used to identify potential confounders: gestational age at ultrasound, recruitment site, maternal age, pre-pregnancy BMI, race by ethnicity and birthplace, education, infant sex, maternal anaemia, prenatal vitamin use, parity, smoke exposure and urinary arsenobetaine (as marker of fish consumption). Metals with high-ranking posterior inclusion probabilities were further analysed with linear regression models Interactions were analysed using a novel method (NLinteraction method)	Mid-pregnancy foetal growth measures, evaluated at 18-22 weeks (median 20.4) of pregnancy and obtained from medical records Abdominal circumference Head circumference Biparietal diameter Femur length Estimated foetal weight (EFW) was main outcome in the statistical analysis	Posterior inclusion probabilities for tin were 0.33 in the primary analysis and 0.22 in the exploratory analysis, the lowest ranking No associations were observed between tin concentration in urine and any of the outcome measures	Only subjects with complete covariable information were included Measurement of metals only once in urine (variability) at one point in pregnancy The focus of this study was on mixtures of metals.	Study population was an impoverished urban population probably above average at risk of both exposure to pollution and intra-uterine growth retardation Sample size was quite small (lack of power)

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Kim, et al (2020)[31]	Design: prospective cohort study Study location: Boston, MA, USA Study period: 2006-2008 Population: participants in LIFECODES study, i.e., pregnant women planning hospital delivery, enrolled before week 15 of pregnancy and participating in up to four study visits. Inclusion criteria: pregnancy resulting in preterm birth (<37 weeks) (n=130, almost all occurrences) or in at term birth (n=352, randomly selected in 3:1 ratio) originally selected for nested case-control study Exclusion criteria: no urine sample from third study visit (=26 weeks of pregnancy) available Final study population: n=390	Tin and 16 other metals in urine samples, collected at 26 weeks of pregnancy, measured with ICP-MS Tin LOD: 0.10 ppb (µg/kg); 6.15% below LOD Tin specific-gravity-corrected concentrations, weighted to account for case-control selection, median (IQR): 0.62 (0.35-1.22) Demographics, lifestyle factors, medical and pregnancy history obtained by questionnaire Statistical analysis: • Linear mixed effect models for associations between metals and repeated outcome measures (at 26 weeks, 35 weeks, birth) • Linear regression for associations with birth weight, birth length, and placental weight • Covariables (in all adjusted models): urine specific gravity, maternal age, race/ethnicity, education, pre-pregnancy BMI, type of insurance, self-reported use of alcohol and tobacco, assisted reproduction, gestational age at time of ultrasound, gestational age at delivery (when appropriate), and metal co-exposure (in multi metal models). • Principal components analysis to identify combinations of covariables • Inverse probability weighting (IPW) to account for case-control selection • Sensitivity analyses (amongst others) on missing data (multiple imputation by chained equation method)	Parameters of foetal growth, measured by ultrasound at weeks 26 (median) and 35 (median), following guidelines of ACOG: • Abdominal circumference (mm) • Head circumference (mm) • Femur length (mm) • Estimated foetal weight (EFW) from these measures, following Hadlock formula • Z-scores based on gestational age at scan, with all singleton pregnancies in the hospital in 2006-2012 as reference • Birth weight (g), birth length (cm), and placental weight (g) (in subset)	In single metal models, tin associated with head circumference z-scores for repeated measures:adjusted β (95% CI), per IQR increase, -0.22 (-0.36, -0.07) and with femur length z-scores among at term deliveries only: adjusted β (95% CI), per IQR increase, -0.21 (-0.40, -0.02) In multi metal models, no associations between tin and z-sores for any of the foetal growth parameters In multi metal models, tin associated with placental weight: Adjusted β (95% CI), per IQR increase, 38.9 (2.79, 75.0), Principle component combining tin, arsenic, and mercury associated with decreased head circumference z-score for repeated measures: adjusted β (95% CI), -0.14 (-0.23, -0.05) and with the combination of estimated foetal weight and birth weight z-scores: adjusted β (95% CI), -0.10 (-0.19, -0.01), Sensitivity analyses showed the same associations with similar precision but with slightly attenuated effect estimates	Ultrasounds at weeks 26 and 35 (visits 3 and 4) were taken at participant's request or when abnormality suspected. Availability of ultrasound measurements was selective (sampling bias) Measurement of metals in urine was done only at one timepoint at varying pregnancy durations, which might impact metal concentrations due to metabolic changes	The authors labelled the principal component combining tin, arsenic, and mercury as "sea food-related". Sensitivity analyses with imputation for missing data was performed, which did not lead to different conclusions.

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Wu, et al (2020)[32]	Design: prospective cohort study Study location: Nanjing, China Study period: 2014-2015 Population: n=183 pregnant women in first trimester recruited at hospital maternity ward, and the children born from their pregnancies. Exclusion criteria: diabetes, other disease requiring medication, alcohol or substance abuse, HIV-positive, <18 years of age, assisted reproduction, infants with disease, genetic abnormalities or malformations.	Concentrations of tin and 11 other heavy metals in maternal urine in first trimester of pregnancy Measurement by ICP-MS expressed as µg/L urine LOD: 0.221 µg/L; detection rate tin 78% Concentration tin, median (IQR): 0.68 (0.29-1.41) µg/L Metabolomics of maternal urine sample by ultrahigh performance LC coupled MS; 172 metabolites were identified Statistical analysis: • Multivariable linear regression to assess associations between single metals and tooth eruption • Covariables (based on questionnaires and hospital medical records): age, education, pre-pregnancy BMI, lifestyle factors, reproduction status, personal health, clinical information (serum phosphorus, alkaline phosphatase, fasting glucose), and perinatal information (delivery method, gestational age, gender, birth weight, duration of breastfeeding, vitamin D supplementation at 6 and 12 months of age).	Primary tooth eruption until age 1 of child Time of teeth eruption by asking mother and number of teeth by oral examination (by two dentists)	No associations between tin and tooth eruption		Study reported according to STROBE guidelines

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Zhao, et al (2020)[33]	Design: prospective cohort study Study location: Hangzhou, China Study period: 2016-beginning of 2017 Population: women (n=512 with urine measurements; n=483 with blood measurements) enrolled in 20-28 weeks of pregnancy in the Hangzhou Birth Cohort and the newborns from these pregnancies, all born in the hospital as specified by protocol Exclusion criteria: subjects with no data on placental weight, multiple pregnancy, assisted conception, or missing data on demographic characteristics.	Concentration of tin was not measured in blood Concentrations of tin and 10 other metals in urine collected at baseline, measured by ICP-MS Concentrations in urine presented as creatinine corrected (CC) levels in µg/g creatinine LOD for tin in urine: 0.051 µg/g creatinine; 100% of samples > LOD Statistical analysis: • Spearman correlations between metal concentrations • Multivariable analysis using elastic net and unpenalized regression models to assess association between outcomes and multiple metals, adjusted for covariables • *Sensitivity analysis*: linear regression with one metal and outcome at a time, with Benjamini-Hochberg method to control for False Discovery Rate Covariables selected using directed acyclic graphs (DAGs): maternal age at conception, maternal education, second hand smoke, household income, pre-pregnancy BMI, infant sex, and gestational age	Placental characteristics, retrieved from medical records by medical personnel: • Placental weight (g) • Chorionic disc plate area (cm2) • Chorionic disc eccentricity (cm) • Placental thickness (cm) • Placental-foetal birth weight ratio (%) • Birth weight (g)	Spearman correlation coefficients for tin with other metals in urine ranged between 0.27 and 0.49 Tin was not retained in any of the multivariable models associating metals in urine with placental characteristics or birth weight. No associations between tin concentrations in urine and any of the outcomes in univariable linear regression analysis.	Approximately 90% of women had higher education Natural labour rate was 99% for participants with placental data and metal levels available, compared to 65.1% for participants included in baseline investigation Metal concentrations only measured once (20-28 weeks of gestation).	

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Goodrich et al. (2019)[34]	Study design: prospective cohort study Study location: Michigan, US Study period: 2012-2015 Population: Subset from ongoing Michigan Mother-Infant Pairs (MMIP) Study including 56 women recruited during their first prenatal visit at 8-14 weeks of gestation. Eligible criteria: at least 18 years old, natural conception, singleton pregnancy, intention to deliver at the University of Michigan hospital, complete survey data. availability of all biospecimen from mother and child, and family not included in previous exposure assessment. Additional criteria: non-Hispanic Caucasian ethnicity, non-smoking, and full-term birth.	Exposure assessment: tin concentrations were measured in spot urine samples collected at first prenatal visit using isotope chromatography plasma tandem mass spectrometry (ICPMS) following a protocol based on CDC method 3018.3 with modifications Statistical analysis: multivariable linear regression models adjusted for gravity, gestational age, and infant gender (when appropriate)	Gestational age, birth weight, birth length, and head circumference measured the day after delivery Foetal anthropometry (biparietal diameter, head circumference, abdominal circumference, and femur length) abstracted from clinical ultrasound in second trimester	No associations were found between urine tin levels and birth weight or any of the foetal anthropometry parameters	No co-exposure to other metals included into the multivariable analysis	The study may have been underpowered to detect all potentially existing associations

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Bloom, et al (2015) (+ correction)[35,36]	Design: prospective cohort study Study location: various counties in central Michigan and along the gulf coast in Texas, USA Study period: 2005-2009 Population: 501 couples planning pregnancy participating in the Longitudinal Investigation of Fertility and the Environment (LIFE) study. Couples recruited from the general population with presumed exposure to persistent organic pollutants Inclusion criteria: heterosexual relationship, women aged 18-40 yrs, no use of injectable contraceptive within 12 months, and menstrual cycle length of 21-42 days. Exclusion criteria: couples with sterilized partner or prior infertility diagnosis: 54 couples without pregnancy; 100 couples withdrew; 2 twin pregnancies; 110 miscarriages Final study population: 235 singleton pregnancies	• Tin and 20 other metals measured in both maternal and paternal urine (some elements other than tin also measured in blood) • Spot urine samples were collected before conception. • Metals measured with ICP-MS expressed as µg/L • Tin in paternal pre-pregnancy urine • Median (33rd %tile-67th %tile): 0.33 (0.20-0.5) • Percentage above LOD: 84 • Tin in maternal pre-pregnancy urine • Median (33rd %tile-67th %tile): 0.31 (0.16-0.62) • Percentage above LOD: 80 • Baseline questionnaire on demographics, health-related behaviours, medical history and reproductive histories • Samples and questionnaires collected and administered at the home by research nurse. Statistical analysis: • Associations between metals and outcomes, Spearman rank and Mann-Whitney U-test • Multivariable linear regression analysis with maternal and paternal exposures entered simultaneously, adjusted for covariables: age mother, age difference mother and father, maternal and paternal smoking, income race, serum lipids, and creatinine • Cox-proportional hazards for outcome time of delivery (gestational age)	Measures of intra-uterine growth • gestational age at delivery (days since ovulation, determined on basis of daily urine hormone measurements (Fertility Monitor)) • birth weight (kg), low birth weight <2500 g • birth length (cm) • head circumference (cm) • ponderal index (100*(kg/m3)) • secondary sex ratio (ratio live male/female births)	No associations between maternal and paternal tin concentrations in urine and any of the outcomes.	Smoking status was defined on the basis of cotinine measurements Serum lipids were included as covariables to adjust for Persistent Organic Pollutants	Strong point of the study is use of pre-conception exposure, including of father Participants presumed to be at risk of environmental exposure, but most values were relatively low compared to US population

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Shirai, et al (2010)[37]	Design: prospective cohort study Study location: Tokyo, Japan Recruitment period: 2007-2008 Study population: 78 pregnant women visiting the obstetrics outpatient clinic of a hospital and the babies born from these pregnancies. Inclusion criteria: no clinical signs of disease.	Various heavy metals measured in single spot urine, collected between 9 and 40 weeks of gestation at regular pregnancy visit to maternity ward: • Tin measured by ICP-MS • Concentrations corrected for urine creatinine concentration, expressed as µg/g creatinine • Detection limit tin: 0.07 µg.(g creatinine)$^{-1}$ • Geometric mean (GSD) urinary concentration of tin in µg.(g creatinine)$^{-1}$: 0.232 (7.28), range <0.06–11.8 (47.4% of samples <LOD). Statistical analyses: • Correlations • Multivariable linear regression analyses with adjustment for confounders and co-exposure to other metals • Covariables: maternal BMI, maternal age, maternal or parental smoking, sex of newborn, birth order, and gestational age. In analysis with birth length, maternal BMI was replaced by maternal height. • Smoking status of mother (n=8, 10.3%) and partner (n=34, 43.6%) obtained through interviews by medical staff.	Primary outcomes: birth weight (in kg), birth length (in cm), and head circumference (cm) of the newborns at time of delivery following standard methods	Univariable analysis of tin versus outcomes: • correlation between tin and head circumference: r=-0.269 (p<0.05) • only samples >LOD (n=41): r=-0.519 (p=0.001) Multivariable regression: final model with only tin as independent variable (other variables excluded on basis of lack of statistical significance). Partial regression coefficient for head circumference: -0.178, p=0.017	Urinary concentrations of tin were low and below limit of detection in almost half of samples Measurement in urine sample only once and at variable stages of pregnancy.	Population: recruitment not clearly described and inclusion and exclusions criteria only globally described Sample size: relatively small study with maybe insufficient power According to the authors, GSD concentrations for tin were much lower than those reported in an American (2.84 µg.(g creatinine)$^{-1}$) and a Japanese study (2.0 µg.(g creatinine)$^{-1}$)

Table 16b Human studies on adverse effects on development: cohort studies: case-control studies

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Frye et al. (2020)[38]	Design: case-control study Study location: Eight states in the US and Canada Study period: Not specified Population: • Cases: 27 patients recruited from a nationally recognized multispecialty ASD (autism spectrum disorder) clinic, with (n=13) or without (n=14) neurodevelopmental regression. • Controls: 7 generally healthy children who were typically developing (2 siblings of cases and 5 unspecified others) Exclusion criteria: chronic treatment with medications that would detrimentally affect mitochondrial function such as antipsychotic medications; vitamin or mineral supplementation exceeding the recommended daily allowance, and prematurity	Exposure assessment: Elemental bio-imaging using laser ablation-inductively coupled plasma mass-spectrometry (LA-ICP-MS) measured concentrations of tin in deciduous teeth with a trimester-by-trimester resolution pre- and postnatally. Statistical analysis: Linear mixed models, considering all interactions. Because of multiple models analysed, the p-value was set at ≤0.01 Age and sex were excluded as co-variables as they did not contribute statistically significantly to the models	Common validated measures were used to assess neurodevelopment and behaviour in children with ASD. The Vineland Adaptive Behaviour Scale (VABS) 2nd edition and a social communication questionnaire were used to document normal development among controls.	Mean prenatal tin concentration was lower among cases compared to controls (0.00012 vs. 0.00022; p<0.05), but did not meet the stringent p-value of 0.01.	Despite not being statistically significant in the analyses, age and sex as well as comorbidity and other confounders may have confounded the results due to large differences between cases and controls. Control selection not well explained and could influence results strongly.	The study was underpowered to detect all potentially existing associations Limitations in reporting selection of controls

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Hou, et al (2019)[39]	Design: nested case-control study Study location: Guangxi Province, China Study period: 2015-2016 Population: 246 women with low birth weight children (cases) and 409 women with normal birth weight children (controls) from the Guangxi Birth Cohort Study Controls were randomly selected in a 1:2 ratio according to maternal age, infant gender, gestational age at sample collection, and enrolment hospital Exclusion criteria: multiple pregnancy, gender information missing, serum sample missing	Tin and 21 other metals measured with ICP-MSin serum samples collected during prenatal examination. LOD=0.010 µg/L; 64.3% samples above LOD Median (IOR) serum concentration tin cases versus controls: 0.38 (0.18-0.79) vs 0.40 (0.18-0.84) µg/L Statistical analysis: • Spearman correlations between 22 maternal serum metal levels. • Single metal analysis using conditional logistic regression with quartiles of metal concentrations • Multi-metal analysis: selection of metals using elastic net regression • Covariables: pre-pregnancy BMI, alcohol intake pre-pregnancy, passive smoking during pregnancy, gravidity, and parity (collected by interview and from medical database)	Health outcome: birth weight • Low birth weight (cases) <2500gr; normal birth weight: 2500-4000 gr Measures obtained from medical records database	No increased or decreased ORs were found for any of the tin concentration quartiles compared to the highest quartile in the single metal analyses.	Pre-pregnancy BMI distribution different (p=0.001) between cases and controls, with more cases being underweight (BMI <18.5), but adjusted for in the analyses Gestational age at delivery lower in cases than controls (35.5 versus 39.1, p<0.001), as expected when selecting low birth weight children	

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Ovayolu, et al (2019)[40]	Design: case-control study Study location: Hospital, Gaziantep, Turkey Study period: 2017-2018 Population: • Cases: n=36 pregnant women with foetuses with a neural tube defect (NTD); • controls: n=39 pregnant women with unaffected foetuses; matched for maternal BMI and gestational age (wks) Exclusion criteria: age <18 yrs, assisted conception, previous NTD, chronic diseases, drug use, non-use of folic acid in early weeks of pregnancy, and obstetric complications	Tin and 13 other metals measured by ICP-MS in amniotic fluid obtained by amniocentesis LOD not reported Statistical analysis: • Differences in metal concentrations using t-tests. • Further case-control comparisons on: maternal age, BMI, parity, gravidity, abortion, gestational age at amniocentesis, frequency of seafood consumption, passive smoking, and presence of dental amalgam (obtained by obstetric anamnesis at amniocentesis) • No multivariable analysis	Neural tube defect (NTD), diagnosed by ultrasound in pregnancy weeks 16-37: • Anencephaly • Spina bifida • Acrania • Encephalocele • Iniencephaly	Tin levels in cases were higher than in controls, mean (SD): -1.35 (2.28) versus 0.40 (0.55), p-value 0.018	Amniocentesis in controls was performed because of age-related risk or increased risk in triple test Measurement of tin in one sample only, obtained at different gravitational ages, but matched between cases and controls with a mean difference of 2 weeks. Measurements in samples collected after embryogenesis; might not be representative of exposure during embryogenesis Cases were younger than controls (27.1 versus 31.3 years, p=0.014) and less frequently had a history of abortion (0.2 versus 0.5, p=0.036)	Relatively small study No multivariable analysis with control for confounding by maternal age and history of abortion or co-exposure to other metals

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Yan, et al (2017)[41]	Design: case-control study Study location: Shanxi and Hebei Provinces, China Study period: 2003-2007 Population: • Cases: 191 women with a pregnancy complicated by a neural tube defect (live births, stillbirths, and pregnancy terminations); Controls: 261 women who delivered healthy infants in the same birthing hospital, loosely matched on county/city of residence and last menstrual period	Tin and 8 other essential trace metals in unpainted maternal hair, grown from 1 month before conception to 2 months after conception, assuming a hair growth rate of 1 cm per month Hair samples were cut into segments of 3-5 mm and metals were measured with ICP-MS Tin was expressed as ng/mg hair Detection rate for tin was 84%. LOD for tin was not reported Statistical analysis: • Comparison of tin hair concentrations between groups: Mann-Whitney U test • Unconditional logistic regression with dichotomized metal concentrations based on median value in controls as cut-off and correction for co-variables. • Dose-response relations were evaluated using quartiles of metal concentrations based on quartiles in controls. • Covariables: maternal age, occupation, education, gravidity, history of previous birth defects, periconceptual folate supplementation, fever or flu during early pregnancy, alcohol consumption (yes/no), active or passive smoking during periconceptual period, and dietary habits (collected by face-tot-face interview within first week after the end of pregnancy).	Neural tube defect in foetus: • Anencephaly (n=85) • Spina bifida (n=79) • Encephalocele (n=24) • Unspecified (n=3)	Tin concentrations in maternal hair, median, interquartile range (IQR) and adjusted odds ratios (95% CI) Total NTD's (n=191): • cases: 0.040 (0.010-0.101) • controls: 0.051 (0.011-0.134) • P-value 0.102 Adjusted OR: 0.76 (0.50-1.16) Anencephaly (n=85): • Cases: 0.034 (0.006-0.076) • Controls: 0.051 (0.011-0.134); • P-value 0.049 Adjusted OR: 0.54 (0.30-0.97) Spina bifida (n=79): • Cases: 0.048 (0.014-0.096) • Controls: 0.051 (0.011-0.134) • P-value 0.536 Adjusted OR: 0.94 (0.54-1.64) Dose-response analyses showed a linear relationship of monotonically decreasing ORs for anencephaly with increasing concentrations.	Differences between cases and controls for several co-variables, that were adjusted for in the logistic regression analyses No multivariable analyses with co-exposure to other metals To maximize the sample size, matched pairs were separated for the analysis with unconditional logistic regression	An unexpected inverse association was observed between tin concentrations in maternal hair and anencephaly in offspring

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Manduca, et al (2014)[42]	Design: case-control study Study location: Gaza, Palestine Study period: 2011 Population: babies born in maternity hospital • Cases: 48/55 newborns with birth defects and enough hair for testing and 9/77 randomly chosen preterm babies without birth defect • Controls: 12/3,892 randomly chosen full term healthy babies Exclusion criteria: Not enough hair at birth. Known history of birth defects within the family (for preterm and full term babies)	Tin and 22 other metals measured in hair samples from newborn, collected immediately after birth, analyzed by ICP-MS Questionnaires administered to the mothers, including occupation, place of residence, reproductive history within the family, if possible verified with objective sources (data on military activity and sequelae collected by NGOs), only for parents of birth defect cases Statistical analysis: • Differences in metal concentrations between cases and controls using Mann-Whitney U test • No multivariable analyses	Birth defects in newborns: neural tube defect (n=11), renal defects (n=5), cleft lip/palate, gastro-intestinal, heart, abdominal, and multiple defects, all not further specified. Preterm birth	Tin concentrations in ppm in birth defect cases versus normal newborns, median (IQR): 0.23 (0.08-0.54) versus 0.04 (0.02-0.09), P=0.002 Tin concentrations in ppm in cases with NTD: 0.32 (0.14-1.04) and in cases with renal defects: 0.15 (0.06-0.30) Tin concentrations in ppm in preterm babies without birth defect versus normal newborns: 0.25 (0.23-0.89) versus 0.04 (0.02-0.09), P=0.002	Exposure assessment of parents by questionnaires for birth defect cases more detailed than for other cases and controls No multivariable analysis with control for confounding by co-variables or co-exposure to other metals	Similar to tin, Hg and Se levels were elevated in birth defect cases versus normal newborns, with all three metals observed in high load in 26 of 48 cases. Individual contributions of these metals were not analyzed/ reported

Table 12c Human studies on adverse effects on development: cohort studies: cross-sectional studies

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Wang, et al (2020)[43]	Design: cross-sectional study Study location: hospital Beijing, China Study period: Nov 2018-Dec 2019 Population: • 56 women with spontaneous abortion (SA) in 1st trimester (median gestational age 8.3 weeks), aged 18-35 yrs • 55 healthy women of similar age with normal early pregnancy (median gestational age 7.4 weeks) who later delivered successfully • 41 non-pregnant healthy women of similar age Exclusion criteria: basal diseases (unspecified), hypertension, polycystic ovary syndrome, uterine polyps, uterine fibroids	ICP-MS measured concentrations of tin and 18 other metals in serum samples collected at enrolment in the study Statistical analysis: • Pearson's correlations between a range of variables including metal concentrations and spontaneous abortion • Random forest regressie for multivariable analysis.	Occurrence of spontaneous abortion in 1st trimester, diagnosed by ultrasound and β-hCG levels G estational age estimates based on ultrasound Measurement of various hormones in blood (thyroid hormones, estradiol, progesterone)	Tin in serum, mean (SD): • Women with SA: 0.28 (0.26) mg/L • Healthy pregnant women: 0.06 (0.04) mg/L • p<0.001 Tin concentration was correlated with spontaneous abortion (r=0.50, no p-value given) The contribution of tin to the occurrence of spontaneous abortion was ranked 6th in the random forest analysis, with several other metals ranked higher	Healthy pregnant women who did not deliver successfully were excuded retrospectively Prevalence of alcohol consumption was twice as high among women with SA (12/56 vs 6/55) History of abnormal pregnancies more frequent among wmen with SA (18% versus 5%)	Pearson correlation coefficients were used inappropriately: correlating concentrations with a dichotomous variable (yes/no spontaneous abortion) Strong risk of bias and confounding Large influence of co-exposure to other metals

Reference	Population and study design	Exposure assessment and statistical analyses	Health assessment	Results on developmental toxicity	Bias and confounding	Remarks
Kot et al. (2019)[44]	Study design: cross-sectional study Study location: Not specified Study period: Not specified Population: 83 women with a properly developing pregnancy and a course of delivery without complications (i.e., preterm delivery, preeclampsia)	Exposure assessment: Tin concentrations measured in the placenta, fetal membrane, and umbilical cord by spectrophotometric atomic absorption in inductively coupled argon plasma Statistical analysis: Correlations were analysed on the basis of Pearson's correlation coefficient (r)	Gestational age, placental parameters (length, width, weight) and newborn parameters (weight, length, and Apgar score).	A negative correlation was found between placenta length and tin levels in the fetal membrane (Pearson's correlation coefficient -0.35, $p<0.05$)	No multivariable analysis with control for confounding by co-variables or co-exposure to other metals Potential bias by inclusion of only properly developing pregnancies	Multiple comparisons (>1200) were not taken into account in the statistical significance level applied The description of the methods was too limited for proper quality assessment
Cabrera-Rodríguez et al. (2018)[45]	Study design: cross-sectional study Study location: La Palma, Spain Study period: March 2015-April 2016 Population: 471 umbilical cord blood samples (91.4% of total number of births)	Cord blood samples were analysed for 44 elements, including tin, using inductively coupled plasma-mass-spectrometry Statistical analysis: correlations between the elements and birth weight were assessed using Pearson's or Spearman's correlation coefficients, as appropriate. Multivariable analyses were performed for selected elements only, but not for tin. Adjustment for baseline characteristics that were associated with the outcome	Birth weight	No correlation was observed between tin levels in cord blood and birth weight		

Prospective cohort studies

Howe et al. (2020a) investigated whether prenatal exposure to mixtures of heavy metals was associated with lower birth weight for gestational age in a predominantly lower-income Hispanic pregnancy cohort in Los Angeles (USA).[29] Ten metals, including tin, were measured in spot urine samples of 262 pregnant women participating in the MADRES cohort. Urine samples were collected in the first half of pregnancy (median gestational age 13.1 weeks). Tin was not included in the primary analysis, but the secondary analysis showed an inverse linear relationship with birth weight adjusted for all relevant covariables while setting all other metals to their median values.

In the same MADRES cohort, Howe et al. (2020b) evaluated the associations between the same exposures and foetal growth parameters assessed at mid-pregnancy.[30] The methods of measurement and analysis were the same as described above, but the study population was restricted to 193 pregnant women who enrolled prior to a routine anatomy ultrasound scan. No associations were observed between tin concentrations in urine and any of the outcome measures.

In a study on a sub-cohort from the LIFECODES birth cohort study, Kim et al. (2020) investigated whether exposure to metals negatively impacted intra-uterine growth.[31] The study included 130 women who experienced a preterm delivery and 352 women with a term delivery, originally selected for a nested case-control study. Inverse probability weighting was applied to account for this selection. Tin and 16 other metals were measured in urine samples, which were collected at 26 weeks of pregnancy (median (IQR) tin concentration 0.62 (0.35-1.22) µg/kg). The outcomes included repeated echocardiographic measures of foetal growth at 26 weeks (median) and 35 weeks (median) of pregnancy, as well as birthweight, birth length, and placental weight. Without adjustment for co-exposures, associations were observed between tin in urine and repeated measures of head circumference and femur length, but no associations between tin and any of the foetal growth parameters were found in multi-metal models. However, tin was associated with increased placental weight (adjusted β coefficient 38.9, 95% CI 2.8-75.0) and seafood-related exposures (arsenic, mercury, and tin) with decreased growth of head circumference and foetal weight.

A possible association between exposure to heavy metals during the first trimester of pregnancy and primary tooth eruption, was studied by Wu et al. (2020).[32] Exposure to 12 metals, including tin, was measured in urine samples collected in the first trimester of pregnancy from 244 women. No associations were found between tin concentration and time of tooth eruption and number of teeth erupted at age one.

Associations between prenatal exposure to heavy metals and birth weight and placental characteristics were studied by Zhao et al. (2020) in the

Hangzhou Birth Cohort Study (China).[33] Women were enrolled in weeks 20-28 of gestation and concentrations of tin and 10 other metals were measured in urine samples collected at baseline from 512 women. Median (IQR) urinary concentration of tin was 9.13 (6.13-13.6) µg (g-creatinine)$^{-1}$. In analyses relating urinary tin concentrations to placental weight, chorionic plate area, chorionic disc eccentricity, placental thickness, placental-foetal birth weight ratio, and birth weight, no associations were observed.

Goodrich et al. conducted a prospective cohort study designed to characterize exposures to various substances, including tin, among pregnant women in the first trimester and to determine associations with birth weight and foetal biometrics (biparietal diameter, head circumference, abdominal circumference, and femur length).[34] Urinary tin concentration were measured in samples collected at 8-14 weeks of gestation among 56 mothers with full-term newborns from the Michigan Mother-Infant Pairs (MMIP) Study. Associations between tin concentrations and birth weight and second trimester foetal biometrics were examined via multivariable linear regression analyses adjusting for a number of baseline characteristics. No associations were found between urinary tin levels and birth weight or foetal anthropometry parameters.

Bloom et al. (2015) investigated the associations between parental exposure to heavy metals and intra-uterine growth and preterm delivery in 235 couples with singleton pregnancies in a prospective cohort study on fertility and environmental factors (LIFE study).[35,36] Concentrations of tin and 20 other metals were measured in maternal and paternal spot urine samples, collected from all participants before conception, and frozen and stored for later analysis. For tin, no associations were found between maternal and paternal urine concentrations and any of the outcome measures, i.e., gestational age, birth weight, birth length, head circumference, ponderal index, and secondary sex ratio.

Shirai et al. (2010) evaluated the associations between maternal exposure to heavy metals and birth weight, birth length, and head circumference.[37] They measured the concentrations of 10 metals, including tin, in spot urine samples of 78 pregnant women visiting the obstetrics outpatient clinic of a hospital in Tokyo, Japan. Tin concentration (µg per g-creatinine) was negatively associated with head circumference in univariable (correlation coefficient r=-0.269, $p<0.05$) and multivariable analysis (partial regression coefficient -0.178, $p=0.017$).

Case-control studies

Frye et al. (2020) studied the associations between either prenatal or early postnatal exposure to 10 metals (including tin) and autism spectrum disorders (ASD) with or without neurodevelopmental regression (NDR) in children.[38] In 27 cases with autism spectrum disorder and 7 healthy controls, prenatal and early postnatal metal exposures were measured in

deciduous teeth using validated tooth-matrix biomarkers with a trimester-by-trimester resolution. The mean prenatal tin concentration was lower among cases compared to controls (0.00012 vs. 0.00022 (unit unclear); $p<0.05$), but this difference did not meet the p-value of 0.01 taking into account multiple testing. Method of control selection is crucial but was not explained and may have influenced results.

Hou et al. (2019) investigated the associations between prenatal serum concentrations of tin and 21 other metals and low birth weight.[39] A nested case-control study within a prospective birth cohort study was performed, including 246 women with low birth weight infants and 406 women with normal birth weight infants. Serum tin concentrations did not differ between cases and controls: median (inter quartile range (IQR)) 0.38 (0.18-0.79) µg/L in cases versus 0.40 (0.18-0.84) µg/L in controls, and all odds ratios for tin concentration quartiles were close to unity. In a multi-metal model, also adjusted for additional covariables, tin was among 15 metals selected, but the implications of this result for tin were not further discussed.

The possible association between trace metal elements and neural tube defects was studied by Ovaloyu et al (2019) in a case-control study, conducted in Turkey in the period 2017-2018.[40] Cases were 36 pregnant women with foetuses with a neural tube defect. These were matched for maternal BMI and gestational age to 39 pregnant women with unaffected foetuses as controls. Tin and 13 other metals were measured by ICP-MS in amniotic fluid, obtained by amniocentesis around 20 weeks of pregnancy. The mean (SD) tin level in cases was higher than in controls: 1.35 (2.28) µg/L versus 0.40 µg/L (0.55), $p=0.018$. Multivariable analyses including co-exposure to other metals and correction for differences in baseline variables were not performed.

Yan et al. (2017) also conducted a case-control study to investigate the associations between 'essential trace metals', including tin, and neural tube defect in offspring.[41] The researchers identified 191 women (period 2003-2007) with a pregnancy complicated by a neural tube defect in Shanxi Province and Hebei Province, China. These were matched on residence (same county/city) and time since last menstrual period to 261 women who delivered healthy infants in the same birthing hospital. Tin and eight other metals were measured in hair grown in the periconceptional period, using ICP-MS on processed hair segments. An association was found for anencephaly, with lower levels of tin corresponding to higher risk, but not for spina bifida or all neural tube defects together. Median (IQR) tin concentration in the anencephaly group was 0.034 (0.006-0.076) ng/mg hair versus 0.051 (0.011-0.134) ng/mg hair in controls, $p=0.049$. The odds ratio for anencephaly comparing above- versus below-median tin concentrations, adjusted for multiple co-variables, was 0.54 (95% CI: 0.30-0.97). However, co-exposure to other metals was not taken into account.

Manduca et al. (2014) conducted a case-control study in the Gaza strip, investigating whether exposure to heavy metals from military attacks was associated with birth defects and preterm birth.[42] Cases were 48 babies born with a birth defect, including 11 neural tube defects, in the major maternity hospital in 2011 and 9 preterm born infants without birth defects. Controls were 12 full term healthy babies, randomly chosen among 3,892 births in the same hospital. Tin and 22 other metals were analysed by ICP-MS in newborn hair samples, collected immediately after birth. Median (IQR) tin concentrations in hair were higher in birth defect cases and preterm born babies than in healthy newborns without birth defects: 0.23 (0.08-0.54) ppm and 0.25 (0.23-0.89) ppm, respectively versus 0.04 (0.02-0.09) ppm, p=0.002 for both comparisons. The analyses were not controlled for potential confounders or co-exposure to other metals, although increased levels of tin coincided with increased levels of mercury and selenium in more than half of the children with a birth defect.

Cross-sectional studies

Wang et al. (2020) carried out a cross-sectional study to determine whether exposure to metals was associated with spontaneous abortion.[43] The study included 56 women with spontaneous abortion in the first trimester treated at a gynaecology hospital in Beijing, China in the period 2018-2019, as well as 55 women with an undisturbed pregnancy in the 1st trimester who later delivered successfully and 41 non-pregnant healthy women. Tin and 18 other metals were measured by ICP-MS in serum samples collected at enrolment in the study. Tin serum levels were found to be different between women with and without spontaneous abortion: mean (SD) 0.28 (0.26) mg/L versus 0.06 (0.04) mg/L, p<0.001, but large differences were also seen for alcohol consumption and a history of abnormal pregnancy. In multivariable analyses, tin seemed to be less strongly associated with spontaneous abortion than some other metals.

Kot et al. determined the levels of 14 different metals, including tin, in the placenta, foetal membranes, and umbilical cord and examined the correlations with placenta parameters (length, width, weight), gestational age, and newborn parameters (weight, height, Apgar score).[44] A total of 170 samples were obtained, comprising 81 placentas, 67 foetal membranes, and 22 umbilical cords from 83 mothers aged from 17 to 44. The only statistically significant (p<0.05) correlation coefficient (-0.35) found for tin among many comparisons was one between placenta length and tin levels in the foetal membrane. There is high risk that this is a chance finding amidst the >1200 comparisons done. No correlations were observed between tin levels in any of the tissues and gestational age or the neonatal parameters.

Cabrera-Rodríguez et al. analysed a total of 471 umbilical cord blood samples in La Palma, Spain, which amounted to approximately 92% of the total number of births recorded in 1 year.[45] The cord blood levels of 44 elements were assessed and studied in relation to birth weight by use of

multivariable analysis adjusting for risk factors for birth weight deviations. No correlation was observed between tin concentration and birth weight.

6.3 Short summary and overall relevance of the provided information on adverse effects on development

Animal data

Group 1: In reproduction/developmental toxicity screening test in rats, exposure to tin metal powder (0, 100, 300 and 1,000 mg/kg bw/day) did not affect litter development. In a prenatal developmental toxicity study in rats, treatment with 0, 30, 300 or 1,000 mg tin/kg bw did not reduce reproductive performance or affect developmental parameters.[13]

Group 2: A slightly lower average number of pups per mother, accompanied by lower weight of the litter was observed in rats exposed to tin sulphide (0, 100, 300 or 1,000 mg/kg bw/day).[26] No consistent differences were observed in offspring weights and external malformations between exposed groups and controls. In the highest dose group, an increase in number of livers with a marked structure was noted.

Group 3: No reduction in the number of live foetuses, foetal weight, or placental weight was observed in pregnant rats administered tin fluoride in the diet (0, 7.8, 15.6, or 31.3 mg/kg bw/day).[27]

Tin dichloride was tested for developmental toxicity in rats, mice, hamsters, and rabbits. For none of the species, effects on development were reported.[17]

In a multigeneration study in rats, no effects were observed on the numbers of offspring per litter or on birth weight. A teratogenicity study with animals of the F2 generation did not show any visceral or skeletal malformations. Microscopic changes were observed in the liver and spleen in the F3 pups, whereas mortality was increased in the F2 in the first 10 days of lactation.[1,16,17]

In a developmental study with mice, oral exposure to tin dichloride (0, 2, 10, 20 mg/kg bw/day) resulted in increased post-implantation loss and a decreased number of live foetuses at 10 and 20 mg/kg bw/day.[28] A decreased foetal body weight was observed at 2 mg/kg bw/day and higher. A treatment-related reduction in the ossification of the foetal skeleton was reported at 2 and 10 mg/kg bw/day but no details were provided.

No data on developmental toxicity are available for tin compounds of group 4.

Epidemiological data

Cohort studies

Howe et al. (2020a) investigated whether prenatal exposure to mixtures of heavy metals was associated with lower birth weight for gestational age in a pregnancy cohort in Los Angeles (USA).[29] An inverse linear relationship was shown between urinary tin levels and birth weight after adjustment for relevant covariables. No associations were observed between tin concentrations in urine and foetal growth parameters assessed at mid-pregnancy in the same cohort (Howe et al, 2020b).[30]

Kim et al. (2020) investigated whether exposure to metals negatively impacted intra-uterine growth in a cohort study among 130 women who experienced a preterm delivery and 352 women with a term delivery.[31] Without adjustment for co-exposures, associations were observed between tin in urine and head circumference and femur length, but no associations with foetal growth parameters were found in multi-metal models. However, tin was associated with increased placental weight.

Wu et al. (2020) found no associations between urinary tin levels measured in 244 women during the first trimester of pregnancy and time of tooth eruption or number of teeth erupted at age one.[32]

Zhao et al. (2020) did not observe any associations between urinary tin concentrations and placental weight, chorionic plate area, chorionic disc eccentricity, placental thickness, placental-foetal birth weight ratio, and birth weight.[33]

Goodrich et al. (2019) did not observe any associations between urinary tin concentrations and birth weight or the foetal anthropometry parameters biparietal diameter, head circumference, abdominal circumference, and femur length.[34]

Bloom et al. (2015) investigated the associations between parental exposure to heavy metals and intra-uterine growth and preterm delivery in 235 singleton pregnancies.[35] No associations were found between maternal and paternal tin urine concentrations and any of the outcome measures.

Shirai et al. (2010) evaluated the associations between maternal exposure to heavy metals and birth weight, birth length, and head circumference in 78 pregnant women in Tokyo, Japan.[37] A negative association was found between urinary tin concentration and head circumference.

Case-control and cross-sectional studies

Frye et al. (2020) performed a case-control study among 27 children with autism spectrum disorder and 7 healthy controls, assessing prenatal tin exposure in deciduous teeth. The mean tin concentration was lower

among cases compared to controls, but did not reach statistical significance taking into account multiple testing.[38]

Hou et al. (2019) conducted a nested case-control study within a prospective birth cohort study including 246 women with low birth weight infants and 406 women with normal birth weight infants.[39] Serum tin concentrations did not differ between cases and controls.

Ovaloyu et al (2019) investigated the association between trace metal elements and neural tube defects by comparing 36 pregnant women with affected foetuses to 39 pregnant women with unaffected foetuses as controls.[40] The mean tin level in amniotic fluid was higher in cases than in controls, but no multivariable analyses were performed.

Yan et al. (2017) conducted a case-control study including 191 pregnancies complicated by a neural tube defect and 261 women who delivered healthy infants.[41] An association was found between lower tin levels measured in hair grown in the periconceptional period and anencephaly, but not spina bifida or all neural tube defects together. Co-exposure to other metals was not taken into account.

Manduca et al. (2014) conducted a study in the Gaza strip including 48 cases with a birth defect, 9 preterm born infants without birth defects, and 12 full term healthy babies.[42] Median tin concentrations in hair were higher in birth defect cases and in preterm born babies than in healthy newborns without birth defects, but the analyses were not controlled for potential confounders or co-exposures.

Wang et al. (2020) carried out a cross-sectional study including 56 women with spontaneous abortion in the first trimester, 55 women with an undisturbed pregnancy, and 41 non-pregnant healthy women.[43] Tin serum levels were found to be different between women with and without spontaneous abortion and appeared to be highly correlated with other metals. Large differences were also seen for alcohol consumption and a history of abnormal pregnancy

Kot et al. (2019) determined tin levels in 81 placentas, 67 foetal membranes, and 22 umbilical cords from 83 women. No correlations were observed between tin levels in any of these tissues and gestational age, birth weight, birth length, Apgar score, and placenta dimensions, except for tin levels in foetal membranes and placenta length.[44]

Cabrera-Rodríguez et al (2018) analysed a total of 471 umbilical cord blood samples. No correlation was observed between tin concentration in cord blood and birth weight.[45]

6.4 Comparison with the CLP criteria

Developmental toxicity studies have been conducted with metallic tin, tin sulphide, tin fluoride, and tin dichloride.

Group 1: For metallic tin, no treatment-related effects were observed in a reproduction/developmental screening test in rats, with the exception of a decreased offspring weight at the highest dose (1000 mg/kg bw/day).[13] No developmental toxicity was noted in a prenatal developmental toxicity study in rats up to 1000 mg/kg bw/day.

Group 2: No statistically significant developmental effects were observed in a reproduction/developmental toxicity screening test with tin sulphide, administered to rats up to a dose of 1000 mg/kg bw/day.[25]

Group 3: Administration of tin fluoride to rats in the diet (up to 31.3 mg/kg bw/day) during pregnancy did not affect developmental parameters.[27] In a series of prenatal developmental toxicity studies with multiple species (mouse, rat, rabbit, and hamster), no developmental toxicity was reported after exposure to daily doses of tin dichloride up to 50 mg/kg bw/day.[17] In a multigeneration study with rats (only abstracts of this study are available), no developmental effects were observed.[1,16,17] Several effects were reported in pups after birth, however it is unclear in which generation. In a developmental study with mice, increased post-implantation loss and a decreased number of live foetuses at doses of 10 and 20 mg/kg bw/day were observed.[28] Further, a decreased foetal body weight was observed at 2 mg/kg bw/day and higher and a reduction in the ossification of the foetal skeleton was reported at 2 and 10 mg/kg bw/day. The Committee notes that the reporting of the latter study was very limited, and no information was provided on maternal toxicity.

Overall, no consistent and dose-related effects on development were observed in animal studies. Only for tin dichloride, some developmental findings were reported including mortality occurring in offspring from rats during lactation. However, the Committee cannot evaluate the respective study as only abstracts are available.[1,16,17] In a developmental toxicity study with mice, clear developmental toxicity was observed (increased post-implantation loss, decreased number of live foetuses).[28] In absence of data on maternal toxicity no conclusion can be drawn on the origin of these effects.

More than half of the epidemiological studies do not show any associations between exposure to tin and adverse effects on developmental parameters. In three prospective cohort studies with adjustment for multiple co-variables and co-exposure to other metals, however, potential associations are observed between exposure to tin and birth weight, placental weight, and head circumference, each in only one study.[29,31,37] Three case-control studies point towards associations between tin exposure and neural tube defects, but these studies lack

adjustment for co-exposure and confounders.[40-42] A potential association with spontaneous abortion is reported in a cross-sectional study that precludes conclusions due to intrinsic limitations.[43]

As a result, no conclusions can be drawn regarding associations between exposure to tin and adverse effects on development in humans.

Conclusion

The Committee concludes that a lack of appropriate data precludes the assessment of tin and inorganic tin compounds for effects on development.

07 adverse effects on or via lactation

7.1 Adverse effects on lactation

No information was found for adverse effects on lactation.

7.2 Adverse effects via lactation

Animal data

In a multigeneration study with rats, the mortality of F_2 generation litters during the first 10 days of lactation was higher compared to controls, but decreased following an increase in iron in the diet of the dams.[1] Haematological studies showed a marked decrease in haemoglobin in the pups at weaning age, that was related to the tin content of the diet. After weaning and increase of the dietary iron concentration, haemoglobin content returned to normal, and mortality decreased.

The Committee notes that it is not clear whether the observed mortality was related to effects of tin on or via lactation.

Human data

The presence of tin in human milk was measured in five studies and showed that levels are low. There is no information on effects on the infants fed with human milk.

Milk specimens from mothers of the general population of the Venice (n=29) and Rome (n=10) areas were collected over the 1998-2001 period, pooled, and analysed for selected pollutants and heavy metals including tin. The tin concentration in both areas was below the limit of quantification of 2 ng/mL.[46]

Tin concentrations in breast milk in women (n=58) from Brazil showed a median level below the limit of quantification (0.1 µg/L), with a maximum level of 0.230 µg/L. In the same study, the median level in drinking water was 0.240 µg/L and in soil 3.10 µg/L.[47]

The presence of a wide spectrum of major and trace elements, including tin, was analysed in human milk (n=53).[48] Also, exposure of the infant to these chemicals was assessed. The content of tin was higher ($p<0.01$) in infant formula samples (measured as concentration in milk and fat) than in human milk. The concentration of tin in human milk was not influenced by BMI or age of the mothers. Total tin intake via human milk could not be assessed as all samples tested showed tin levels below the limit of detection (30 µg/L).

The concentration of twelve elements, including tin, was analysed in human milk from Brazilian donors (n=50) with a lactation period greater than 15 days. The mean tin concentration in human milk was 2.78 µg/L (SD=1.48), with a maximum level of 9.46 µg/L.[49]

In random samples of breast milk from first time Swedish mothers (n=60) in early lactation (days 14-21), a mean tin concentration of 0.40 µg/L (SD=0.099) was determined, with a maximum level of 0.77 µg/L.[50]

Assuming a mean infant body weight during lactation of 4.5 kg, a daily milk intake of 900 mL, and a (worst case) tin level in human milk of 10 µg/L, the Committee calculates an exposure to the breastfed infant of 2 µg/kg bw/day. This exposure levels is three orders of magnitude lower than the tolerable daily intake (TDI) of 2 mg/kg bw/day previously set by the WHO[51], which is based on gastric irritancy with a threshold concentration of about 200 mg/kg in the food.[16] The Committee notes that the TDI is not based on data representative for exposure of small infants.

7.3 Comparison with the CLP criteria

No data on tin in lactating animals are available. In humans, tin levels up to 10 µg/L have been determined. These levels are approximately 1000-fold below the TDI previously set by the WHO. It should be noted that this TDI is based on local toxicity after a high exposure, but infants were not taken into account when establishing the TDI. In absence of indications for effects of tin on the development of offspring, the Committee considers the margin between tin exposure and the TDI sufficiently large to conclude that effects via lactation are not expected. No data on effects on lactation as such are available.

08 conclusions on classification and labelling

The Committee recommends classification according to Regulation (EC) 1272/2008 of the European Union. For tin and inorganic tin compounds, the Committee concludes that:

- Lack of appropriate data precludes the assessment for effects on fertility;
- Lack of appropriate data precludes the assessment for effects on development;
- Classification for effects on or via lactation is not indicated.

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annex A literature search strategy

A scientific evaluation of the data on the toxicity of tin and inorganic tin compounds was already performed by the Dutch Health Council in 2005, therefore, in agreement with the Health Council, the search is limited to data from 2002 or later. To be complete, the developmental toxicity study by Theuer et al. (1971) that was mentioned in the report from 2005 was also included in this report.

Embase

Table 1 presents the search terms and the results for the database Embase. Keywords were searched for in title and abstract.

Table 1 Search strategy and result for Embase

Query	Results	Number of records
#27	#25 AND [2019-2021]/py	64
#26	#25 AND [2002-2020]/py	344
#25	#10 OR #13 OR #17 OR #24	528
#24	#4 AND (#21 OR #23)	173
#23	#20 AND #22	140,180
#22	'murine'/exp OR 'experimental animal'/exp OR 'animal experiment'/exp OR 'leporidae'/exp OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR hamster*:ti,ab OR pig*:ti,ab OR monkey:ti,ab OR rabbit:ti,ab	5,388,125
#21	#20 AND [humans]/lim	170,069
#20	#18 OR #19	436,152
#19	'metabolism':ti OR 'adme':ti,ab OR 'absorption distribution metabolism excretion':ti,ab	236,847
#18	'xenobiotic metabolism'/exp OR 'metal metabolism'/mj OR 'metabolism'/mj	227,567
#17	#4 AND (#14 OR #15 OR #16)	58
#16	((environment* OR human OR biologic*) NEAR/3 'exposure monitor*'):ti,ab	122
#15	'bioaccessibility' OR 'bioelut*':ti,ab	2,961
#14	'toxicokinetics'/exp OR toxicokinetic*:ti,ab	13,954
#13	#4 AND (#11 OR #12)	209
#12	'pregnancy outcome*':ti,ab OR pregnan*:ti OR fertilit*:ti OR 'fecundit*':ti OR (((differential OR effect* OR agent*) NEAR/3 fertilit*):ti,ab) OR ((breast NEAR/3 milk):ti,ab) OR ((milk NEAR/3 secret*):ti,ab) OR 'lactation':ti,ab OR 'infertil*':ti OR 'subfertil*':ti	428,025
#11	'fertility'/exp OR 'lactation'/exp OR 'breast milk'/exp OR 'pregnancy'/exp OR 'parameters concerning the fetus, newborn and pregnancy'/exp OR 'infertility'/exp	1,220,775
#10	#4 AND #9	166
#9	#5 OR #6 OR #7 OR #8	276,736
#8	(((repro* OR development*) NEAR/3 toxic*):ti,ab) OR teratogen*:ti,ab OR reprotox*:ti,ab OR 'embryotox*':ti	38,787
#7	'reproductive toxicity'/exp OR 'teratogenicity'/exp OR 'developmental toxicity'/exp OR 'fetotoxicity'/exp OR 'embryotoxicity'/exp OR 'organogenesis'/exp	218,329
#6	((prenatal OR maternal OR paternal) NEAR/3 expos*):ti,ab	28,619
#5	'prenatal exposure'/exp OR 'maternal exposure'/exp OR 'paternal exposure'/exp	27,798
#4	#1 OR #2 OR #3	26,616
#3	'12013-46-6':rn OR '68187-53-1':rn OR '68187-12-2':rn OR '12185-56-7':rn OR '12027-61-1':rn OR '12027-70-2':rn OR '12058-66-1':rn OR '15578-26-4':rn OR '12067-23-1':rn OR '69011-60-5':rn OR '69029-52-3':rn OR '1374645-21-2':rn OR '85536-73-8':rn OR '69012-35-7':rn OR '68187-05-3':rn OR '7440- 31-5':rn OR '68187-54-2':rn OR '301-10-0':rn OR '13814-97-6':rn OR '7772-99-8':rn OR '7783-47-3':rn OR '18282-10-5':rn OR '1315-01-1':rn OR '21651-19-4':rn OR '84776-04-5':rn OR '7488-55-3':rn OR '1314-95-0':rn OR '7646-78-8':rn OR '49556-16-3':rn OR '53408-94-9':rn OR '814-94-8':rn OR '69011-52-5':rn OR '84696-55-9':rn	10,381
#2	'stannic chloride'/exp OR 'stannous chloride'/exp OR 'stannous fluoride'/exp OR 'stannous pyrophosphate'/exp OR 'tin derivative'/exp	4,239
#1	'tin'/exp OR 'tin':ti,ab OR 'tin(ii)':ti,ab OR 'stannous':ti,ab OR 'stannum':ti,ab OR 'stannate':ti,ab OR 'stannium':ti,ab OR 'dipotassium hexahydroxostannate' OR 'ditin pyrophosphate' OR 'ditin trisulphide' OR 'zinc hydroxystannate'	24,106

Ti, ab: search in title and abstract; mj: major topic, term is major focus of the article.

PubMed

The following search terms were used for the database PubMed:

Table 2 Search strategy and result for PubMed

Search	Query	Items found
#17	#16 AND 2002:2021[dp]	343
#16	#6 OR #9 OR #12 OR #15	683
#15	#1 AND #13 AND #14	163
#14	rat[tw] OR rats[tw] OR mouse[tw] OR mice[tw] OR hamster*[tw] OR pig[tw] OR pigs[tw] OR monkey*[tw] OR rabbit*[tw] OR human*[tw] OR man[tw] OR men[tw] OR woman[tw] OR women[tw] OR child*[tw] OR infant*[tw] OR newborn*[tw] OR fetus*[tw] OR neonate*[tw]	23,056,508
#13	"Tin/metabolism"[Majr] OR "Metabolism"[Majr:NoExp] OR metabolism[ti] OR adme[tw] OR absorption distribution metabolism excretion[tw]	219,558
#12	#1 AND (#10 OR #11)	311
#11	Exposure monitor*[tw] AND (environment*[tw] OR human[tw] OR biologic*[tw])	514
#10	"Toxicokinetics"[Mesh] OR "Toxicological Phenomena"[Mesh] OR toxicokinetic*[tw] OR bioaccessib*[tw] OR bioelut*[tw]	459,192
#9	#1 AND (#7 OR #8)	176
#8	Pregnancy outcome*[tw] OR pregnan*[ti] OR fertilit*[ti] OR differential fertilit*[tw] OR breast milk[tw] OR milk secret*[tw] OR lactation[tw]	363,275
#7	"Fertility"[Mesh] OR fertility[tw] OR "Lactation"[Mesh] OR "Milk, Human"[Mesh] OR "Milk"[Mesh:NoExp] OR "Pregnancy"[Mesh:NoExp] OR "Pregnancy Outcome"[Mesh]	1,048,611
#6	#1 AND (#2 OR #3 OR #4 OR #5)	105
#5	Reproductive toxic*[tw] OR developmental toxicity[tw] OR fetotoxic*[tw] OR teratogen*[tw] OR reprotox*[tw] OR embryotox*[tw]	29,557
#4	"Teratogens"[Mesh] OR "Toxicogenetics"[Mesh]	8,629
#3	Prenatal exposure[tw] OR maternal exposure[tw] OR paternal exposure[tw] OR infertility[tw] OR subfertility[tw] OR fecundity[tw] OR organogenesis[tw]	160,319
#2	"Prenatal Exposure Delayed Effects"[Mesh] OR "Maternal Exposure"[Mesh] OR "Paternal Exposure"[Mesh] "Organogenesis"[Mesh] OR "Infertility"[Mesh]	220,019
#1	"Tin"[Mesh]OR "Tin Compounds"[Mesh] OR tin[tw] OR "tin(II)"[tw] OR stannous[tw] OR stannum[tiab] OR stannate[tw] OR stannium[tw] OR dipotassium hexahydroxostannate[tw] OR ditin pyrophosphate[tw] OR ditin trisulphide[tw] OR zinc hydroxystannate[tw]	22,394

This resulted in 289 records.

Scopus

The following search terms were used for the database Scopus:

((TITLE-ABS-KEY (tin OR "tin(II)" OR stannous OR stannum OR stannate OR stannium OR "dipotassium hexahydroxostannate" OR "ditin pyrophosphate" OR "ditin trisulphide" OR "zinc hydroxystannate")) AND ((TITLE-ABS-KEY ((prenatal OR maternal OR paternal) W/3 expos*)) OR (TITLE-ABS-KEY (((repro* OR development*) W/3 toxic*) OR teratogen* OR reprotox* OR embryotox*)) OR (TITLE-ABS-KEY (pregnancy-outcome* OR differential-fertilit* OR (breast W/3 milk) OR (milk W/3 secret*) OR lactation)) OR (TITLE (pregnan* OR fertilit* OR subfertil* OR infertil* OR fecundit* OR organogenesis*)))) OR ((TITLE-ABS-KEY (tin OR "tin(II)" OR stannous OR stannum OR stannate OR stannium OR "dipotassium hexahydroxostannate" OR "ditin pyrophosphate" OR "ditin trisulphide" OR "zinc hydroxystannate")) AND ((TITLE-ABS-KEY (toxicokinetic* OR bioaccessib* OR bioelut* OR ((environment* OR human OR biologic*) W/3 exposure-monitor*))) OR (TITLE-ABS-KEY (adme OR absorption-distribution-metabolism-excretion) OR TITLE (metabolism))) AND (TITLE-ABS-KEY (rat OR rats OR mouse OR mice OR hamster* OR pig OR pigs OR monkey* OR rabbit* OR human* OR man OR men OR woman OR women OR child* OR infant* OR newborn* OR fetus* OR neonate*))) AND PUBYEAR > 2001

This resulted in 212 records.

Toxcenter

A search was performed in Toxcenter using the searches as shown below:

Table 3 Search strategy and result for Toxcenter

Search number	Search term	# records
L1	SEA 12013-46-6 OR 68187-53-1 OR 68187-12-2 OR 12185-56-7 OR 12027-61-1 OR 12027-70-2 OR 12058-66-1 OR 15578-26-4	242
L2	SEA 12067-23-1 OR 69011-60-5 OR 69029-52-3 OR 1374645-21-2 OR 85536-73-8 OR 69012-35-7 OR 68187-05-3 OR 7440-31-5	20,719
L3	SEA 68187-54-2 OR 301-10-0 OR 13814-97-6 OR 7772-99-8 OR 7783-47-3 OR 18282-10-5 OR 1315-01-1	9,243
L4	SEA 21651-19-4 OR 84776-04-5 OR 7488-55-3 OR 1314-95-0 OR 7646-78-8 OR 49556-16-3 OR 53408-94-9 OR 814-94-8 OR 69011-52-5 OR 84696-55-9	2,112
L5	SEA L1 OR L2 OR L3 OR L4	30,577
L6	SEA (PRENATAL OR MATERNAL OR PATERNAL)(3W)EXPOS?	55,239
L7	SEA (REPRO? OR DEVELOPMENT?) (3W)TOXIC? OR TERATOGEN? OR REPROTOX?	114,855
L8	SEA PREGNANCY-OUTCOME? OR DIFFERENTIAL FERTILIT? OR BREAST(3W)M ILK OR MILK(3W)SECRET? OR LACTATION	43,767
L9	SEA (PREGNAN? OR FERTILIT?)/TI	82,021
L10	SEA TOXICOKINETIC? OR BIOACCESSIB? OR BIOELUT? OR (ENVIRONMENT? OR HUMAN OR BIOLOGIC?)(3W) EXPOSURE MONITOR?	27,220
L11	SEA ADME OR ABSORPTION DISTRIBUTION METABOLISM EXCRETION OR METABOLISM/TI	137,277
L12	SEA L5 AND (L6 OR L7 OR L8 OR L9)	124
L13	SEA L5 AND (L10 OR L11)	153
L14	SEA L13/HUM,ANI	22
L15	SEA L12 OR L14	144
L16	SEA L15 AND 2002-2020/PY	80

ECHA database

A list of 30 tin and inorganic tin compounds was searched for in the REACH database. Registration dossiers of 12 compounds were available and were consulted: tin, tin sulphide, tin oxide, ditin pyrophosphate, tin dichloride, tin difluoride, tin sulphate, tin disulphide, tin dioxide, disodium tin trioxide, disodium tin hexahydroxide and tin bis(tetrafluoroborate).

Secondary sources

The secondary sources that were consulted were as followed:

- A concise international chemical assessment document number 65 on tin and inorganic tin compounds, from the World Health Organization (WHO), within the framework of The International Programme on Chemical Safety (IPCS);
- A toxicological profile for tin and tin compounds, from the Agency for Toxic Substances and Disease Registry (ATSDR);
- A recommendation from the Scientific Committee on Occupational Exposure Limits (SCOEL) for tin and inorganic tin compounds.

In addition, RIVM-reports and evaluations and the RIVM-website ‘Risico’s van stoffen’[a] were consulted.

[a] https://rvs.rivm.nl

Overall evaluation of results literature search

The obtained records were evaluated, duplicates were removed, and records were included if considered relevant based on title and abstract. Additionally, publications cited in the selected publications, but not selected during the primary search, were reviewed if considered appropriate.

Committee and consulted expert[a]

Members of the Subcommittee on the Classification of Reproduction Toxic Substances

for the advisory report Tin and selected inorganic tin compounds

- M.B.M. van Duursen, Professor Environmental Health and Toxicology, Vrije Universiteit Amsterdam, *chair*
- W.M.L.G. Gubbels-Van Hal, Regulatory expert (toxicology and risk assessment) (retired), Oss
- M.W.G.D.M. van de Loo, Study Director Developmental and Reproductive Toxicology, Charles River Laboratories, Den Bosch
- N. Roeleveld, Reproductive epidemiologist; Radboud university medical center, Nijmegen (until March 18th, 2022)
- L.J.M. Smits, Professor of Clinical Epidemiology and Risk-Based Care, Maastricht University
- J.G. Theuns-Van Vliet, Reproductive toxicologist; Erasmus UMC, Rotterdam (until March 18th, 2022)
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- E.C.M. Tonk, Toxicologist; Charles River Laboratories BV, Den Bosch *structurally consulted expert*

Observer[a]

- J.J.A. Muller, Bureau Reach, National Institute of Public Health and the Environment, Bilthoven

Scientific secretaries

- D. Boers, Health Council of the Netherlands, Den Haag
- S.R. Vink, Health Council of the Netherlands, Den Haag

[a] Consulted experts are consulted by the committee because of their expertise. Consulted experts and observers are entitled to speak during the meeting. They do not have any voting rights and do not bear any responsibility for the content of the committee's advisory report.

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
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