Cadmium and selected cadmium compounds

Evaluation of the effects on reproduction, recommendation for classification

To: the State Secretary of Social Affairs and Employment
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Health Council of the Netherlands

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samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad voor cadmium, cadmium-carbonaat, cadmiumchloride, cadmiumfluoride, cadmiumhydroxide, cadmiumnitraat, cadmium-oxide, cadmiumsulfaat en cadmiumsulfide (hierna aangeduid als ‘cadmium’) beoordeeld of beroepsmatige blootstelling invloed kan hebben op de voortplanting. Op basis van deze beoordeling is een classificatievoorstel opgesteld.

Dit advies is opgesteld door de Commissie Classificatie reproductietoxische stoffen, een subcommissie 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 cadmium

Cadmium is een metaal, dat vooral gebruikt wordt voor de productie van batterijen. Ook kan het een bestanddeel zijn van pigment voor verf en coatings. Mensen die werkzaam zijn in bedrijven waar cadmium wordt geproduceerd of verwerkt kunnen tijdens hun werk in aanraking komen met cadmium. Vooral werkzaamheden zoals lassen en slijpen waarbij cadmium verhit wordt kunnen risicovol zijn, omdat dan cadmiumdampen kunnen vrijkomen.

Classificeren naar bewijskracht

Bij de beoordeling van effecten op de voort-planting, 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 zijn 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

Zowel over effecten van blootstelling aan cadmium op de vruchtbaarheid als over effecten op de ontwikkeling zijn verschillende onder-zoeken bij mensen beschikbaar. De meeste onderzoeken laten een verband zien met blootstelling aan cadmium, maar leveren geen duidelijk bewijs. Er zijn ook veel dierstudies gedaan, zowel naar effecten op de vrucht-baarheid als naar effecten op de ontwikkeling. De beschikbare dierstudies, waarin cadmium-chloride en cadmiumoxide zijn geëvalueerd, laten duidelijke nadelige effecten zien.

Voor effecten van blootstelling aan cadmium op of via lactatie baseert de commissie zich vooral op onderzoeken bij mensen. In die onderzoeken zijn concentraties van cadmium in de moedermelk gemeten waarvan de commissie het mogelijk acht dat ze nadelige gevolgen hebben voor de baby na borstvoeding.

Advies aan de staatssecretaris

Op grond van de beschikbare wetenschappelijke gegevens adviseert de commissie om cadmium, cadmiumcarbonaat, cadmiumchloride, cadmiumfluoride, cadmiumhydroxide, cadmiumnitraat, cadmiumoxide, cadmiumsulfaat en cadmiumsulfide, zowel voor effecten op de vruchtbaarheid, als voor effecten op de ontwikkeling en voor effecten op of via lactatie, in te delen in een gevarencategorie.

Classificatievoorstel commissie:

- voor effecten op de fertiliteit: classificeren in categorie 1B (stoffen waarvan verondersteld wordt dat zij toxisch zijn voor de menselijke voortplanting) en te kenmerken met H360F (kan de vruchtbaarheid schaden);
- voor effecten op de ontwikkeling: classificeren in categorie 1B (stoffen waarvan verondersteld wordt dat zij toxisch zijn voor de menselijke voortplanting) en te kenmerken met H360D (kan het ongeboren kind schaden);
- voor effecten op of via lactatie: classificeren en kenmerken met H362 (kan schadelijk zijn via de borstvoeding).

executive summary

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluated the effects of cadmium, cadmium carbonate, cadmium chloride, cadmium fluoride, cadmium hydroxide, cadmium nitrate, cadmium oxide, cadmium sulphate, and cadmium sulphide, (further referred to as 'cadmium') 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.

Cadmium use

Cadmium is a metal that is primarily being used in batteries, though cadmium can also be a component of pigments and coatings. Workers in industries that use or produce cadmium and cadmium compounds are at risk for increased cadmium exposure. In particular, workers whose jobs involve the heating of cadmium such as welding and grinding are at risk of cadmium exposure, as cadmium vapours can be released.

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

Epidemiological studies are available on effects on fertility and effects on development. Most of these studies show associations with exposure to cadmium, but provide insufficient evidence. In addition, many animal studies have been conducted. These studies, which evaluated cadmium chloride and cadmium oxide, indicate that cadmium exposure can cause effects on fertility and development.

Based on measured cadmium levels in breastmilk in humans, the Committee considers it likely that these may cause adverse effects via lactation.

Recommendations to the State Secretary

Based on the scientific data available, the Committee recommends to classify cadmium, cadmium carbonate, cadmium chloride, cadmium fluoride, cadmium hydroxide, cadmium nitrate, cadmium oxide, cadmium sulphate, and

cadmium sulphide, for effects on fertility, for effects on offspring development and for effects on or via lactation.

The Committee's classification proposal:

- for effects on fertility: classify these substances in category 1B (presumed human reproductive toxicant), and label them with H360F (may damage fertility);
- for effects on development: classify these substances in category 1B (presumed human reproductive toxicant) and label them with H360D (may damage the unborn child);
- for effects during lactation: classify these substances for effects on or via lactation and label these substances with H362 (may cause harm to breastfed babies).

01 scope

1.1 Background

As a result of the Dutch regulation on registration of substances 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 substances 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 substances classified as reproductive toxicant (category 1A and 1B and 2) or with effects on or via lactation. The ministry of Social Affairs and Employment asked the Health Council to update the evaluation and classification on reproduction toxicity for a series of substances. In this report, such an update was performed for cadmium and selected cadmium compounds. An evaluation of these substances was published previously in 2000.[1]

1.2 Committee and procedure

This document contains a recommendation for classification of cadmium and several cadmium compounds by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances, hereafter called the Committee. The classification is based on the evaluation of published human and animal studies, including those available in the REACH registration dossiers, concerning adverse effects with respect to fertility and development as well as lactation.

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 classification 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 breastfed babies.

The classification and labelling of substances is performed according to the criteria of the European Union (Regulation (EC) 1272/2008). The classification of substances is ultimately dependent on 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 criteria necessarily leave 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 substance will be classified in category 1A, irrespective of the general toxic effects (see Annex B, 3.7.2.2.1.).
- Adverse effects in a reproductive study, reported without information on the parental 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 standard protocols) for the classification of substances, but non-guideline studies are taken into consideration as well.

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

In 2019, the President of the Health Council released a draft of the report for public review. The Committee has taken these comments 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 Classification for effects on or via 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 which are bioavailable 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 classification for effects during 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 classified for effects during 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 substance as potentially toxic to the breastfed child when this concentration

leads to exceeding the exposure limit for the general population (including sensitive groups), e.g. the acceptable daily intake (ADI).

1.4 Data

Starting point for this evaluation was the literature used in the previous evaluation.[1] An additional literature search using the search terms 'cadmium' AND 'repro*' AND 'toxic*' was conducted in PubMed, through December 2018. Relevance was subsequently determined based on title and abstract. The ECHA database on registered substances was consulted as well. In addition, review documents prepared by SCOEL[2] and ATSDR[3] were consulted. Publications cited in the selected sources were reviewed if considered appropriate.

The Committee describes both human and animal studies in the text. Of each study, the quality and the level of documentation are considered in a qualitative manner. The Committee outlines its considerations in the text, where appropriate.

02 identity of the substances

The Committee previously recommended on a classification for effects on reproduction for ‘cadmium and its compounds’.[1] The Committee notes that data available on cadmium toxicity mainly involve studies with cadmium chloride and cadmium oxide, whereas data on reproduction toxicity of other cadmium compounds are lacking. Also, no data on bioavailability of other cadmium compounds were retrieved with the literature search. According to the Guidance on the Application of the CLP Criteria, ‘the assumption is that all substances and mixtures are considered to be bioavailable to some extent’.[4] The Guidance further states that ‘it should be noted that concluding that there is lack of or reduced bioavailability has a high burden of evidence and needs to be supported by robust data and expert evaluation’. The Committee therefore considers the systemic toxicity data on cadmium chloride and cadmium oxide also applicable to other cadmium compounds with an assumed bioavailability.

For its current classification, the Ministry of Social Affairs and Employment requested a re-evaluation of cadmium and cadmium compounds due to some discrepancies between classifications for reproduction toxicity in the Annex VI of CLP[a], and classifications for reproduction toxicity applied in the Netherlands for workers according to the “Arbeidsomstandighedenbesluit” (artikel 4.2a, tweede lid)[b].

[a] https://echa.europa.eu/nl/information-on-chemicals/annex-vi-to-clp [last accessed June 25th, 2020]
[b] https://wetten.overheid.nl/BWBR0008498/2020-07-01 [[last accessed June 25th, 2020]

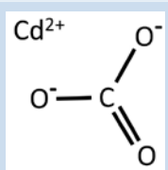
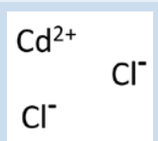
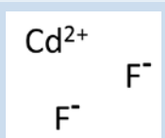
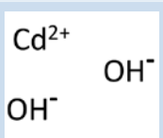
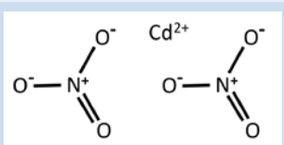
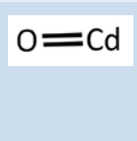
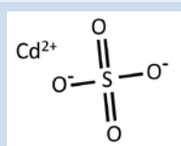
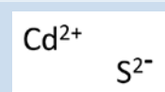
	CAS Number	Harmonised classification (Annex VI of CLP)	Dutch worker classification
cadmium (non-pyrophoric) [1]	7440-43-9 [1]	Repr. 2; H361 fd	Repr. 2; H361fd Lactation
cadmium (pyrophoric)	7440-43-9	Repr. 2; H361fd	Repr. 2; H361fd Lactation
cadmium oxide (non-pyrophoric) [2]	1306-19-0 [2]	Repr. 2; H361fd	Repr. 2; H361fd Lactation*
cadmium fluoride	7790-79-6	Repr. 1B; H360 FD	Repr. 1B; H30 FD Lactation
cadmium chloride	10108-64-2	Repr. 1B; H360 FD	Repr. 1B; H30 FD Lactation
cadmium sulphate	10124-36-4	Repr. 1B; H360 FD	Repr. 1B; H30 FD Lactation
cadmium sulphide	1306-23-6	Repr. 2; H361 fd	Repr. 2; H361fd Lactation*
Cadmium compounds except the sulphate, fluoride and chloride		None**	Repr. 2; H361fd Lactation

* Due to the group classification of cadmium compounds.
** Annex VI of CLP contains a number of additional individual entries for cadmium compounds and an entry for all remaining cadmium compounds with some exception which do not include classification for reproductive toxicity.

The Committee further notes that three other registered cadmium compounds (cadmium nitrate, cadmium hydroxide, and cadmium carbonate) have an harmonised classification for several toxicological endpoints other than reproductive toxicity (See section 2.4). As outlined under ‘Grouping’ (Section 4.2), the Committee assumes bioavailability for all of the above specified cadmium compounds, and applies a group approach for its recommendation. When cadmium without further specification is used in the text of this advice, it pertains to both cadmium metal and the selected cadmium compounds.

The identity and physicochemical properties of cadmium and selected cadmium compounds are given below.

2.1 Name and other identifiers of the substances

EC/EINECS number	231-152-8	208-168-9	233-296-7	232-222-0	244-168-5	233-710-6	215-146-2	233-331-6	215-147-8
EC name	Cadmium	Cadmium carbonate	Cadmium chloride	Cadmium fluoride	Cadmium hydroxide	Cadmium nitrate	Cadmium oxide	Cadmium sulphate	Cadmium sulphide
CAS number	7440-43-9	513-78-0	10108-64-2	7790-79-6	21041-95-2	10022-68-1, 10325-94-7	1306-19-0	10124-36-4	1306-23-6
CAS name	Cadmium		cadmium chloride	Cadmium fluoride			Cadmium oxide (CdO)	Sulfuric acid, cadmium salt (1:1)	215-147-8
IUPAC name	cadmium	Cadmium(2+) carbonate	cadmium dichloride	Cadmium fluoride	cadmium(2+) dihydroxide	Cadmium(II) nitrate	cadmium oxide	Cadmium sulphate	cadmium(2+) sulfanediide
Synonyms		Cadmium monocarbonate; carbonic acid; cadmium salt	Cadmium dichloride; cadmium(II) chloride; dichlorocadmium	Cadmium difluoride; Cadmium(2+) fluoride	Cadmium dihydroxide	Cadmium dinitrate; nitric acid, cadmium salt	Cadmium(II)oxide; Cadmium monoxide; Monteponite; Tienek kadmu	Cadmium sulfate hydrate; Sulfuric acid, cadmium salt (1:1), hydrate (3:8); Cadmium(2+) sulfate hydrate; cadmium(2+) trisulfate octahydrate	Cadmium monosulfide; Cadmium sulfide; yellow; Cadmium yellow
CLP Annex VI index number	048-011-00-X	048-012-00-5	048-008-00-3	048-006-00-2	048-013-00-0	048-014-00-6	048-002-00-0	048-009-00-9	048-010-00-4
Molecular formula	Cd	$CCdO_3$	$CdCl_2$	CdF_2	CdH_2O_2	$Cd(NO_3)_2$	CdO	$Cd.H_2O_4S$	CdS
Molecular weight	112.414	172.4	183.3	150.4	148.4 g/mol	236.4	128.4	208.5	144.5
Structure	Cd								

2.2 Composition of the substances

Not applicable to mono-constituent substances.

2.3 Physico-chemical properties of the selected compounds

In the following table, physico-chemical properties are summarised for cadmium, and selected cadmium compounds (in order of water solubility).

	Cadmium (7440-43-9)	Cadmium chloride (10108-64-2)	Cadmium sulphate (10124-36-4; monohydrate)	Cadmium nitrate (10022-68-1, 10325-94-7)	Cadmium hydroxide (21041-95-2)	Cadmium sulphide (1306-23-6)	Cadmium fluoride (7790-79-6)	Cadmium carbonate (513-78-0)	Cadmium oxide (1306-19-0)
State of the substance at normal temperature and pressure	Brownish powder or massive metal	White powder	White powder	White powder	Greenish white powder	Orange ochre powder	Grey or white-grey crystals	White powder	Red ochre powder
Melting/freezing point	In air, the substance starts oxidizing at ca. 270°C (powder) and circa 470°C (cast metal)	In nitrogen and air, the substance starts melting at 553°C.	105 °C	In air it starts melting at 48 -61°C. The substance starts decomposing at 401 -405°C	186 °C	There is no melting and no decomposition, sublimation starts at 871 -890°C in air.	1,110 °C	356 °C	There is no melting and no decomposition, sublimation starts at ca. 950°C in air
Density	8.64 g/cm^3	3.91 g/cm^3	4.69 g/cm^3	2.52 g/cm^3	4.73 g/cm^3	4.81 g/cm^3	6.33 g/cm^3	4.44 g/cm^3	8.26 g/cm^3
Water solubility (at room temperature)	2.3 and 8.7 mg/L, for the powder and bar samples, respectively	457 g/L	767 g/L	507 g/L	69.5 mg/L	12 mg/L	4.3 mg/L	3.2 mg/L	2.1 mg/L

2.4 International classifications#

EU harmonised classification and hazard statement codes for reproduction toxicity (Repr.), carcinogenicity (Carc.), mutagenicity (Muta.), and specific target organ toxicity (repeated exposure) (STOT RE):

Cadmium (7440-43-9)	Cadmium chloride (10108-64-2)	Cadmium sulphate (10124-36-4)	Cadmium nitrate (10022-68-1, 10325-94-7)	Cadmium hydroxide (21041-95-2)	Cadmium sulphide (1306-23-6)	Cadmium fluoride (7790-79-6)	Cadmium carbonate (513-78-0)	Cadmium oxide (1306-19-0)
Repr. 2; H361fd	Repr. 1B; H360FD	Repr. 1B; H360FD	-	-	Repr. 2; H361fd	Repr. 1B; H360FD	-	Repr. 2; H361fd
Carc. 1B; H350	Carc .1B; H350	Carc. 1B; H350	Carc. 1B; H350	Carc. 1B; H350	Carc. 1B; H350	Carc. 1B; H350	Carc. 1B; H350	Carc. 1B; H350
Muta. 2; H341	Muta. 1B; H340	Muta. 1B; H340	Muta. 1B; H340	Muta. 1B; H340	Muta. 2; H341	Muta. 1B; H340	Muta. 1B; H340	Muta. 2; H341
STOT RE 1; H372	STOT RE 1; H372	STOT RE 1; H372	STOT RE 1; H372	STOT RE 1; H372	STOT RE 1; H372	STOT RE 1; H372	STOT RE 1; H372	STOT RE 1; H372

https://echa.europa.eu/nl/information-on-chemicals/cl-inventory-database [last accessed June 25th, 2020]

03 manufacture and uses

3.1 Manufacture

No data are available.

3.2 Identified uses

Since the early 1900s, cadmium and cadmium compounds have been used in various commercial and industrial applications.[5] Currently, cadmium is primarily used in batteries, although other cadmium-containing products include pigments, electroplates and coatings, and plastic stabilisers. Workers in industries that use or produce cadmium and cadmium compounds, such as the battery, pigment, plastics, construction, and electroplating industries are at risk of increased cadmium exposure. In particular, workers whose jobs involve the heating of cadmium and cadmium compounds are at risk of cadmium exposure, as these substances release harmful vapours when their temperature is increased.

The use of cadmium and cadmium compounds has been restricted under REACH regulation (https://echa.europa.eu/nl/substances-restricted-under-reach/-/dislist/details/0b0236e1807e2518) [last accessed June 25th, 2020].

Information about the current uses (product categories and process categories) can be found on the ECHA website (https://echa.europa.eu/nl/information-on-chemicals/registered-substances) [last accessed June 25th, 2020].

04 toxicokinetics (absorption, metabolism, distribution and elimination) and grouping

4.1 Toxicokinetics

In this section, the Committee provides a short summary based on the evaluations of the SCOEL[2] and ATSDR[3], with additional considerations of the Committee.

Cadmium metal and cadmium salts are not well absorbed; absorption fractions have been reported of approximately 25, 1–10, or <1% of the dose following inhalation, oral, or dermal exposure, respectively. Several factors can influence inhalation and oral absorption efficiency. Cadmium is absorbed by the respiratory route dependent on several factors (e.g. the solubility of the cadmium compound involved, the size of the particles (dusts or fumes), the disposition pattern and ventilation), and the absorbed fraction varies between 2 and 50%. The gastrointestinal absorption of cadmium is dependent on the diet composition and the individual iron and/or calcium status, but is usually less than 5%.

Cadmium is transported from its absorption site in the respiratory and gastrointestinal tracts to the liver where it accumulates. In the liver, cadmium induces the synthesis of metallothionein which sequestrates cadmium. Thereafter the cadmium-metallothionein complex is slowly released and transported to the kidneys, the most critical targets after long-term exposure. Here, cadmium is filtrated through the glomerulus and reabsorbed in the proximal tubule where it may dissociate intracellularly. After long-term low level exposure, approximately half of the cadmium body burden is stored in the liver and kidneys (mainly in the cortex).

The cadmium concentration in the kidneys is generally between 10 and 50 mg/kg wet weight (in non-occupationally exposed individuals), while smokers show 2-5 fold higher values than non-smokers. In the blood, 90% of the cadmium is localized in erythrocytes. Cadmium can cross the placenta; cadmium blood levels of newborns are approximately half of the levels in mothers.

Cadmium is excreted very slowly (<0.02% of the total body burden per day), equal in quantity in the urine and faeces, resulting in an estimated biologic half-life of 10-30 years in the kidney and 5-10 years in the liver. The onset of renal toxicity and tubule loss accelerate the loss of cadmium, particularly in the kidneys. In the absence of occupational exposure, the mean urinary cadmium concentration is generally below 1 µg/g creatinine in adults. In populations with substantial occupational exposure, values can increase up to 50 µg/g creatinine.

4.2 Grouping

The mechanism responsible for cadmium-induced toxicity is suggested to involve several modes of action (reviewed in Rani et al. (2014)[6]). Cadmium induces toxicity in various systems and tissues, including the reproductive system (addressed in the following chapters), respiratory tract, the urinary, cardiovascular, gastrointestinal and nervous systems and the bones. At the cellular level, cadmium induces both the damaging and repair processes in which the cellular redox status plays a crucial role.

Oxidative stress is assumed to be the principal molecular basis underlying cytotoxicity caused by cadmium.

The cadmium-induced effects on the target sites are attributed to the cadmium cation, independently from the anionic species. However, the absorption and the distribution of cadmium to various target sites, and subsequently the severity of cadmium induced effects, vary dependent on the form of cadmium and the route of exposure.[3] The Committee notes that for its evaluation, the toxicological data available primarily involves cadmium chloride (on the oral, subcutaneous and intraperitoneal route) and cadmium oxide (via exposure by inhalation). Cadmium chloride is highly soluble in water, whereas cadmium oxide is not. In general, the solubility in water and biological fluids is thought to be an important determinant for the amount of metal cations that can reach the target site after exposure via the oral or inhalation route. In case of cadmium compounds, the ATSDR states that the absorption of cadmium in lung differs somewhat among chemical forms, but notes that the pattern does not correlate with solubility. The Committee notes that in inhalation studies with cadmium oxide, systemic availability was demonstrated both in rats and mice.[7]

Overall, quantitative differences may exist from different absorption and distribution characteristics but the different forms of cadmium have similar toxicological profiles.[3] The cadmium compounds specified in Chapter 2 have anions with no substantial toxicity and the toxicity of these compounds can therefore be attributed to cadmium. Furthermore, these compounds are water soluble within the range of solubility of cadmium chloride and cadmium oxide, for which toxicological data are available and systemic availability is demonstrated. Overall, the Committee assumes that all specified cadmium compounds are bioavailable to some extent. This includes metallic cadmium, as the Committee assumes the release of cadmium ions following oral or inhalatory absorption. The Committee therefore considers conclusions based on data on cadmium chloride and cadmium oxide also applicable to cadmium nitrate, cadmium sulphate, cadmium sulphide, cadmium hydroxide, cadmium fluoride, cadmium carbonate, and cadmium metal.

05 toxicity for reproduction

Adverse effects reported in animal studies are statistically significant ($p<0.05$), unless specified otherwise. In the summary tables, the substance used in the study is specified whereas in the study summaries, the Committee refers to 'cadmium' only. For the purpose of comparison, doses are expressed in cadmium equivalents. The results are presented in chronological order, separated based on exposure route.

5.1 Adverse effects on sexual function and fertility

Summary table of animal studies on adverse effects on sexual function and fertility.

Reference	Species	Experimental period and design	Substance	Dose	General toxicity	Effects on reproductive organs or reproduction
Oral exposure						
Schroeder and Mitchener (1971)	Mouse, Charles River DC, males and females, N=5/group)	Multi-generation study; administration continuously in drinking water	Cadmium chloride	0 or 10 mg Cd/L (equivalent to 0 or 2.1 mg Cd/kg bw)	2 maternal deaths in F2	Strain could not be bred beyond F2-generation
Krasovskii et al. (1976)	Random bred white rat (males) (N=?)	Administration: continuously via drinking water for 6 m	Cadmium chloride	0, 0.00005, 0.0005 or 0.005 mg Cd/kg bw (reported by authors to correspond to 0.001, 0.01 and 0.1 mg Cd/L)	0.0005 mg: Changes in biochemical parameters and in the conditional reflex activity	0.0005 mg: reduced spermatogenesis
Dixon et al. (1976)	Sprague- Dawley, rats male (N=10)	Acute, serial breeding; single dose; sacrifice: up to 6 w after gavage. Subchronic administration in drinking water; 30, 60, 90 d; sacrifice: 30, 60, 90 d. Fertility was assessed by housing treated males with virgin females, for periods of 7 days each. Nine days after breeding period, females were examined.	Cadmium chloride	0, 6.25, 12.5 or 25 mg Cd/kg bw 0, 0.001, 0.01 or 0.1 mg Cd/L (equivalent to 0, 0.00014, 0.0014 or 0.014 mg Cd/kg bw, according to authors)	No effects on blood chemistry No effects on clinical parameters and bodyweight	No effects on male fertility were observed • No effects on male fertility • No effect on weights of testis, prostate and seminal vesicles • No effect on testis histopathology • No effects on serum hormone levels.

Reference	Species	Experimental period and design	Substance	Dose	General toxicity	Effects on reproductive organs or reproduction
Kotsonis and Klaassen (1978)	Sprague-Dawley rats (males)(N=6)	Administration continuously for 24 w in drinking water; sacrifice: 3, 6, 12, 24 w. Testicular function was assessed by mating with an untreated virgin female in the week prior to sacrifice.	Cadmium chloride	0, 10, 30 or 100 mg Cd/L (equivalent to 0, 1.2, 3.7 or 12.2 mg Cd/kg bw)	At 30 and 100 mg/L tubular necrosis in kidney	• No effect on fertility (fraction of females producing offspring; number of foetuses per animal) • No effects on histopathology and weight of testis •
Laskey et al. (1980)	Sprague-Dawley rat (males and females) (N=9-10)	Administration: continuously via drinking water sacrifice: PN 50, 130	Cadmium chloride	0, 0.1, 1.0 or 5.0 mg Cd/L (equivalent to 0, 0.01, 0.13 or 0.64 mg Cd/kg bw)	• 1.0 mg: PN 130: Decreased liver weight • 5.0 mg: PN 50+130 depressed liver weight	5.0 mg; PN 50+130: • Decreased preimplantation loss • No effect on litter size, • Reduced sperm count
Sutou et al. (1980a,b)	Sprague-Dawley rat (males & females) (N=13-14)	Administration: 6 w by gavage prior to mating, mating, and gestation (NB treated males were mated with treated females).	Cadmium chloride	0, 0,1, 1.0 or 10 mg Cd/kg bw	mid and high dose: reduced body and organ weight	10 mg: • Reduced copulation (statistical significance not indicated) • Reduced average number of total implants per female • Reduced average number live foetuses per female
Zenick et al. (1982)	Sprague- Dawley rat (males) (N=5)	Administration: 70-80 d in drinking water prior to mating with untreated females. Pregnant females were sacrificed at GD 20	Cadmium chloride	0, 17.2, 34.4 or 68.8 mg Cd/L (equivalent to of 0, 0.7, 1.3, and 2.6 mg/kg bw, assuming 15 mL water intake (derived from graph)	• Reduction in water intake • No effects on body weight •	• No effect on reproductive system (testes weight; cauda weight; sperm count; number of normal sperm cells) • No effect on reproductive parameters (mating success; number of pregnancies; number of implantations, corpora lutea) litter size; pup body weight)
Baranski et al. (1983)	Wistar rats female (N=?)	Administration for 5 d/w for 5 w by gavage prior to mating and continued thereafter	Cadmium chloride	0.04, 0.4 or 4 mg Cd/kg bw	No information provided	No effect on fraction inseminated and pregnant females, average number of total implantations and corpora lutea (data not specified)
Baranski and Sitarek (1987)	Wistar rats female (N=11-13/group)	Administration: 5 d/w for 14 w by gavage prior to mating and continued thereafter.	Cadmium chloride	0.04, 0.4, 4 or 40 mg Cd/kg bw	Increased mortality up to 54% after 13-14 w, compared to 0% in controls; decreased body weight	Increase in the mean duration of the oestrous cycle at 40 mg/kg bw/d after 7-8 weeks and after 13-14 weeks
Bomhard et al. (1987)	Wistar rats male N=30/ Cd group N=10/control group Supplementary studies 25 or 35 males/group	Administration by gavage Single dose	Cadmium chloride	0 or 50 mg Cd/kg bw	No increased mortality; no difference in appearance, general behaviour or food and water consumption from the control animals. Slight growth retardation in the first 10 weeks.	No histopathological alterations in the testis
		10 weekly doses of cadmium chloride		0 or 5 mg Cd/kg bw	1 x 50 and 10 x 5: No increased mortality; no difference in appearance, general behaviour or food and water consumption from the control animals.	No histopathological alterations in the testis

Reference	Species	Experimental period and design	Substance	Dose	General toxicity	Effects on reproductive organs or reproduction
		Supplementary studies: Administration of a single dose by gavage		0 or 200 mg Cd/kg bw; 0 or 100 mg Cd/kg bw	Clinical signs, most animals died within 3 days (28/35 at 100 mg; 24/25 at 200 mg)	1 x 100 and 1 x 200: Severe lesions in the testis
Andersen et al. (1988)	CBA/Bom male mice (N=7-15)	Administration of a single dose by gavage; sacrifice at 10 d after dosing	Cadmium chloride	0, 270, 530, 790 µmol Cd/kg bw (0,30,60,90 mg Cd/kg bw), oral (gavage)	Mortality: 0/16 (0), 2/54 (270), 11/60 (530), 36/42 (790). Dose-dependent histological lesions of liver, stomach and duodenum, from270 µmol Cd/kg bw onwards.	Histological lesions of testis at the two highest doses
Borzelleca et al. (1989)	Sprague-Dawley rats (male and female) (N=10/group)	Single dose by gavage	Cadmium chloride	0, 25, 51, 107 or 225 mg $CdCl_2$/kg bw (equivalent to 0, 15, 31, 66 and 138 mg Cd/kg bw)	Reduced spleen weight and increased lung weight in males	No effect on testis or ovary weights
		10 consecutive days by gavage	Cadmium chloride	0, 25, 51, 107 or 225 mg $CdCl_2$/kg bw (equivalent to 0, 15, 31, 66 and 138 mg Cd/kg bw)	Dose-dependent effects on mortality, body weights, organ weights (including testis) of male and females. Histopathological changes in kidney, testis and liver	Histopathological changes in testis; not in ovaries
		10 d via drinking water necropsy: 24 h after last dosing	Cadmium chloride	0 or 13-323 mg $CdCl_2$/L (equivalent to 1.5, 15.3 or 31.3 mg Cd/kg bw)	Dose-dependent effects on body weights and organ weights	No effect on testis or ovary weights
Saygi et al. (1991)	Wistar rats (control N=8; experimental group N=20)	Administration continuously via drinking water for 52 w to males only. Functional fertility was assessed after 52 w. Times of necropsy: 28, 40, 56 w	Cadmium chloride	0 or 10 mg Cd/L (equivalent to 0 or 1.1 mg Cd/kg bw)	Histopathological effects on liver and kidney	• Histopathological effects on testis • Reduced fertility after 52 weeks cadmium exposure (100% in controls versus 60% in cadmium-treated males) •
Massanyi et al. (2007)	Hyla rabbits (females) (N=8)	Administration continuously via diet for 5 m	Cadmium chloride	0 or 1 mg Cd/kg bw	No information provided	• Decreased relative volume of growing follicles • Increased stroma • Increased number of atretic follicles • Ultrastructural alterations
Hu et al. (2014)	Chinese Kun Ming mice (male)(N=?)	Administration continuously via diet for 6 m	Cadmium chloride	0, 0.975 or 1.95 mg Cd/mouse (equivalent to 0, 20 or 40 mg Cd/kg bw)	Slight reduction in body weight	• Reduction in serum testosterone levels in both treatment groups •

Reference	Species	Experimental period and design	Substance	Dose	General toxicity	Effects on reproductive organs or reproduction
Nasiadek et al. (2014; 2018)	Wistar rats (female) (control: N=10; Cd-treated: N=8-10)	Administration for 28 d by gavage. Analysis of uterine tissue on the first day and then after 90 days post exposure	Cadmium chloride	0, 0.09, 0.9,1.8, 4.5 mg Cd/kg bw	No effects on body weight or organ weights	• Changes in catalase (CAT) activity and lipid peroxidation (MDA) levels at a dose of 1.8 and 4.5 mg/kg bw, both after 28 days of exposure and 90 days following the termination of Cd exposure • Disturbance in oestradiol and progesterone in plasma • Increased cycle length (prolonged diestrous) after 30-d exposure at 4.5 mg/kg bw • Increased increase (not dose dependent and reversible) in endometrial thickness at all doses • Ovary damage (degeneration of corpora luteum and granulosa cells; damage to and reduction of oocytes) at the highest dose
Wang et al. (2014)	Sprague-Dawley rats (males and females)	Administration for 28 d by gavage (Enhanced OECD TG 407)	Cadmium chloride	0, 1, 2.5, 5, 10, or 20 mg Cd/kg ·bw	• Reduced body weights at doses exceeding 2.5 mg/kg bw (males) or 1 mg/kg bw (in females). • Reduced thyroid weight was at 2.5 mg/kg bw and higher in males. • Clinical signs (listlessness, anorexia, low hair-gloss, irritation) at 5, 10 and 20 mg/kg bw in both sexes. • Effects on haematology or clinical biochemistry exceeding 2.5 mg/kg bw (females) or 1 mg/kg bw (males)	• Decreased weights of prostate and seminal vesicle glands at 2.5, 10, 20 mg/kg bw in males. • Decreased levels of serum luteinizing hormone and testosterone at doses of 10-20 mg/kg bw groups in males. • Increased uterus weight and histopathological changes at 10-20 mg/kg bw/
Zhao et al. (2015)	Sprague Dawley rats (male) (N=6/group)	Administration every 2 d for 9 w, and allowed to mate with untreated females	Cadmium chloride	0 and 22.15 mg Cd/kg bw	Information on general toxicity not provided	• Reduced sperm motility and viability • Increased sperm malformation rate (including large heads, decollation, and folding and broken tails)
Medina et al. (2017)	Wistar rats (male) (N=6/group)	Administration 5 d/w for 3 m	Cadmium chloride	0 and 10 mg Cd/kg bw	Information on general toxicity not provided	• Morphological changes in testis (after 2 m) and reduced sperm motility (after 3 m)
Wang et al. (2017)	C57BL/6 mice (male) (N=5/group)	Administration for 5 w by gavage	Cadmium chloride	0 and 1.9 mg Cd/kg bw	Information on general toxicity not provided	• Reduced sperm motility and viability
Sapmaz-Metin et al. (2017)	BALB/c mice (female) (N=6/group)	Administration for 30 or 60 d in drinking water	Cadmium chloride	0 and 200 ppm (equivalent to 0 and 43 mg Cd/kg bw)	Information on general toxicity not provided	• No effect on cycle length was observed, and no stage specific microscopic alterations were noted (except the presence of apoptotic cells) • Decreases in endometrial thickness and number of glands in oestrus phase uteri • Decreased endometrial eosinophilia and increased the number of mast cells • Apoptosis in the uterus and the endometrium (at 60 d)

Reference	Species	Experimental period and design	Substance	Dose	General toxicity	Effects on reproductive organs or reproduction
Subcutaneous/intraperitoneal injection						
Kar et al. (1959)	Colony bred albino rat (females)(N=?)	Single dose subcutaneously; sacrifice at 0,6,24,48,96,168,360 h after injection	Cadmium chloride	0 or 10 mg $CdCl_2$/kg bw (equivalent to 6.1 mg Cd/kg bw)	No information on general toxicity provided	• Cellular and vascular changes in the ovary(partly recovered after 96 h, completely recovered after 168 h) • No effect on uterine weight
Parízek (1960)	Rat (males and females) (N=?)	Single dose subcutaneously; sacrifice: up to 4 months after injection	Cadmium chloride	0 or 40 µmol $CdCl_2$/kg bw (equivalent to 4.5 mg Cd/kg bw)	No information on general toxicity provided	• Decreased weights of testis, seminal vesicles and prostate. • Severe histopathological changes of reproductive organs
Nordberg (1975)	Male CBA mice (N=8)	Administration subcutaneously for 5 d/w for 6 m	Cadmium chloride	0 or 2.2 µmol $CdCl_2$/kg bw (equivalent to 0.2 mg Cd/kg bw)	• No abnormal behaviour • Reduced body weight • Reduced urinary excretion of protein	• decreased weight and size of the seminal vesicles • Indications of a lower secretory capacity of seminal vesicles.
Lohiya et al. (1976)	Langurs (male adult) (N=3)	Administration of a single dose subcutaneously; sacrifice at 1) 30 d after injection; 2) 60 d after injection	Cadmium chloride	1) 0 or 4 mg $CdCl_2$/kg bw (equivalent to 0 or 2.5 mg Cd/kg bw) 2) 0 or 12 mg $CdCl_2$/kg bw (equivalent to 0 or 7.4 mg Cd/kg bw)	No information provided	2) Testis small and oedematous; weight reproductive organs reduced. 1) + 2) dose depended histological lesions in testis and epididymis
Bomhard et al. (1987)	Wistar rats male N=10/group	Administration intraperitoneally. Single dose; Necropsy after 12, 18 and 30 months	Cadmium chloride	0 or 2.5 mg Cd/ kg bw	• No difference in appearance, general behaviour or food and water consumption • Transient inflammatory reaction at injection site • Leydig cell tumours in all animals • Slight growth retardation in the first 10 w	Severe lesions testis
	N=10/group	10 weekly doses of cadmium chloride intraperitoneally. Necropsy after 12, 18 and 30 months		0 or 0.25 mg Cd/kg bw		None
	N=?	Supplementary studies: single dose of cadmium chloride subcutaneously		0 or 2 mg Cd/kg bw	Transient inflammatory reaction at injection site and transient decrease body weight	Severe lesions testis
Rehm and Waalkes (1988)	hamster (1 strain) (N=6-48) mouse (3 strains) (N=5-12) rat (2 strains) (N=4-35) (females)	Administration of single dose subcutaneously, at 21-24 d, or 8 w old sacrifice: 1,2,3,4,7,14,28,56 d after administration	Cadmium chloride	0 or 20-47.5 µmol/kg bw (equivalent to 2.2 -5.3 mg Cd/kg bw)	Mortality due to liver necrosis in all species at the highest dose, in particular in immature animals	Haemorrhagic necrosis of the ovaries in all hamsters, most groups mice and high dose groups rats

Reference	Species	Experimental period and design	Substance	Dose	General toxicity	Effects on reproductive organs or reproduction
Wlodarczyket al. 1995	Golden hamsters (males) (N=15)	Administration of a single dose subcutaneously. Necropsy: 1,4,10 w after treatment	Cadmium chloride	0 or 0.5 mg Cd/kg bw	No information provided	• Decreased weights and histopathological changes of testis, epididymis and accessory sex organs • Decreased number of sperm cells in epididymis after 4 weeks of treatment
Laskey et al. (1984)	Sprague-Dawley rats (males) (N=10/ group)	Administration of a single dose subcutaneously. Animals were killed and analysed 14 days after dosing	Cadmium chloride	0, 1.6, 3.1, 7.4, 16 or 33, 74, or 152 µmol/kg bw (0, 0.18, 0.35, 0.83, 1.8, 3.7, 8.3 or 17.1 mg Cd/kg bw	• Mortality at 74 and 152 µmol/kg bw • No effects on body weight at lower doses	• Reduced weight of testis, seminal vesicles and epididymis • Reduced sperm count (at higher doses no sperm was present)
Aoyagi et al. (2002)	Sprague-Dawley rats (males) (N=3-6)	Administration subcutaneously, daily for 6 w Testicular damage was evaluated every week	Cadmium chloride	0 or 0.6 mg Cd/kg bw	There were no differences in the testes /bodyweight ratio between the study and control groups	Reduced number of spermatogonia and spermatocytes in weeks 2-6
Paksy et al. (1989)	CFY rats (females)	Administration: single doses subcutaneously. Exp.1: Sacrifice and collection of blood samples on 13.00, 15.00, 16.30 or 18.00. Exp. 2: measurement of ovarian blood flow, hCG induced hormone secretion, and ovary histology at 48 h	Cadmium chloride	0, 5, 10 or 15 mg $CdCl_2$/kg bw (equivalent to 0, 3.1, 6.1 or 9.2 mg Cd/kg bw)	No information provided	• Exp. 1: 10 and 15 mg/kg: increased PRL serum levels and decreased LH serum levels. 10 mg/kg: decreased FSH serum levels • Exp. 2: 10 and 15 mg/kg: decreased basal secretion of P; 5, 10 and 15 mg/kg: diminished effect of hCG, • Increase of anovulatory at all doses •
Paksy et al. (1996)	CFY rats (females)	Administration: a single dose subcutaneously Groups: A: administration at diestrous 2, mating after 32 h; B: administration at oestrous, mating after 80 h; C: administration at D2, mating after 132 h	Cadmium chloride	0, 2.5, 5 or 10 mg $CdCl_2$/kg bw (equivalent to 0, 1.5, 3.1 or 6.1 mg Cd/kg bw)	A reduced bodyweight later during pregnancy was observed in all groups	A Dose-dependent reduction in the fraction of rats mated in groups B and C. In group A, a statistically non-significant reduction was only observed at the highest dose.
Massanyi et al. (2007)	Hyla rabbits (females) (N=8)	Administration: single dose of 1.5 mg/kg bw orally via diet. Animals were sacrificed 48 h thereafter	Cadmium chloride	0 or 1.5 mg Cd/kg bw	No information provided	• Decreased relative volume of growing follicles • Increased stroma • Increased number of atretic follicles • Ultrastructural alterations
Wu et al. (2017)	Sprague-Dawley rat (males) (N=5)	Administration of a single dose ip of 0, 0.3 or 0.6 mg/kg followed by ethane dimethane sulfonate treatment 20 days later to eliminate adult Leydig cells	Cadmium chloride	0, 0.3 or 0.6 mg Cd/kg bw	A reduced bodyweight at both doses	• Reduced serum testosterone and luteinizing hormone levels • Reduced number of regenerated Leydig cells in the testis

Reference	Species	Experimental period and design	Substance	Dose	General toxicity	Effects on reproductive organs or reproduction
Inhalation						
Baranski 1984	Wistar rats (females) (N=?)	Exposure to aerosols for 5 days a week, 5 h daily for 5 months followed by a maximum period of 3 weeks of mating	Cadmium oxide	0, 0.02, or 0.16 mg Cd/m^3 (equivalent to 0, 0.006 or 0.05 mg Cd/kg bw)	No information provided	0, 0.02, or 0.16 mg Cd/m^3: Gestation indices of 54% (15/28), 44% (11/25) and 41% (7/17)
Baranski 1985	Wistar rats (female) (N=?)	Exposure by inhalation for 1) 5 hours a day and 5 days weekly for a period of 5 months or 2) for 4 months	Cadmium oxide	1) 0, 0.02 0.16 mg Cd/m^3 (equivalent to 0, 0.004, 0.03 mg Cd/kg bw, respectively) 2) 1 mg Cd/m^3 (equivalent 0.18 mg Cd/kg bw)	Increased mortality at 1 mg/m^3	Decrease in fertility at 1 mg Cd/m^3, the magnitude of the fertility effects (gestation index, corpora lutea) are not specified in the publication
Baranski and Sitareka (1987)	Wistar rats (female) (N=?)	Exposure by inhalation for 20 weeks, 5 hours/day, 5 days/week	Cadmium oxide	0.02, 0.16 or 1 mg Cd/m^3 (equivalent to 0.004, 0.03, or 0.18 mg Cd/kg bw)	At the highest concentration, an increase in mortality and an decrease in body weight gain was observed	• Increase in the mean duration of the oestrous cycle mainly due to lengthening of dioestrus at 1 mg Cd/m^3. • Increased percentage of females with oestrous cycles lasting over 6 days was shown 18 weeks after exposure at 0.16 mg Cd/m^3
NTP, (1995)	F344 Rats (male and female)	Exposure by inhalation for 6 h and 20 min/d, 5 d/week for 13 weeks - OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day Study)	Cadmium oxide	0, 0.025, 0.05, 0.1, 0.25 or 1 mg CdO/m^3 (equivalent to (0, 0.005, 0.01, 0.02, 0.05 and 0.20 mg Cd/kg bw)	Enlargement and paleness of the tracheobronchial and mediastinal lymph nodes	In males in the 1 mg/m^3 group: Reduction spermatid heads per gram of testis, spermatid heads per testis and spermatid count. No treatment-related microscopic changes in the testis or epididymis. In females the 1 mg/m^3 group: increased oestrous cycle length but no treatment related histologic changes in the reproductive organs.
NTP (1995)	B6C3F1 mice (male and female)(N=10)	Exposure by inhalation for 6 h and 20 min/d, 5 d/week for 13 weeks - OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day Study)	cadmium oxide	0, 0.025, 0.05, 0.1, 0.25 or 1 mg CdO/m^3 (equivalent to (0, 0.006, 0.01, 0.02, 0.06 and 0.23 mg Cd/kg bw)	Reticulocyte numbers were greater in exposed females (0.025 mg/m^3 and higher); Enlargement of the tracheobronchial lymph nodes and pale grey mottled lungs (0.25 and 1 mg/m^3 groups); significant differences in lung weights occurred from 0.05 mg/m^3	No effects on reproductive organs

5.1.1 Animal studies

Fertility studies, oral exposure

In a multigeneration reproduction study, mice were allowed to breed for 6 months during which cadmium was offered continuously in the drinking water at a level of 10 mg/L (an equivalent dose of 2.1 mg/kg bw/d) (Schroeder and Mitchener (1971)[8]). No statistically significant effects on reproduction were observed. Two maternal deaths occurred in the F2; breeding was discontinued as 3 of 5 pairs failed to breed in the F2.

Chronic exposure of groups of random bred white male rats to 0.00005, 0.0005 or 0.005 mg cadmium/kg body weight in the drinking water (dose levels corresponding to 0.001, 0.01 and 0.1 mg cadmium/L, according to the authors) resulted in the two highest dose group in a reduced spermatogenesis (Krasovskii et al. (1976)[9]). At these doses, also changes in biochemical parameters and in the conditional reflex activity were observed. At the highest dose, several alterations, among them loss of body weight and an increase of number of tubules with cast-off epithelium and with 12th stage meiosis, were noted.

Dixon et al. (1976)[10] studied the effects of (I) a single oral dose of 0, 6.25, 12.5 and 25 mg cadmium/kg body weight or (II) exposure via drinking water containing 0, 0.001, 0.01 and 0.1 mg cadmium/L (equivalent to 0, 0.0001, 0.001, and 0.01 mg/kg bw) for 90 days in male rats. After acute dosing serial matings were performed for 70 days and testes were examined microscopically on day 1 and 7 and for 6 succeeding 7-day intervals. In addition, in the drinking water study, breeding studies were performed. The studies failed to reveal any biologically change in clinical serum chemistry or weight of the body, testis, prostate, or seminal vesicles. No effect on male fertility was observed after acute or chronic (data not shown) cadmium administration.

Kotsonis and Klaassen (1978)[11] studied the toxicity of cadmium in male Sprague Dawley rats after oral administration of cadmium in the drinking water (0, 10, 30 or 100 mg cadmium/L; (equivalent to 0, 1.2, 3.7 or 12.2 mg cadmium/kg bw/d)) for 24 weeks. Fertility was tested after 3, 6, 12 and 24 weeks and appeared not affected. At necropsy after 24 weeks no effect on testis weight and histopathology was observed. At 30 and 100 mg/L, effects on the kidney were detected.

Groups of 9-10 male and female Sprague-Dawley rats were, starting from conception, chronically exposed to 0, 0.1, 1.0 or 5.0 mg cadmium/L in the drinking water (equivalent doses of 0, 0.01, 0.13 or 0.64 mg/kg bw/d) (Laskey et al. (1980)[12]). The F1 offspring was sacrificed either on postnatal day (PND) 50 or around PND 130. Sacrifice on PND 50 revealed a decreased liver weight in the 5.0 mg/L group, and a reduced sperm count. Adult sacrifice showed a decreased liver weight in the 1.0 and 5.0 mg/L groups, and a decreased serum progesterone level and litter size, and a decreased preimplantation loss in the 5.0 mg/L group.

Groups of 14 male or female Sprague-Dawley rats were administered 0, 0.1, 1.0 or 10 mg cadmium/kg body weight/day by gavage for 6 weeks prior to and during a 3 weeks mating period (Sutou et al. (1980a,b)[13,14]). Body and organ weights of males treated with 1.0 and 10 mg/kg body weight/day were depressed. The females of the mid and high dose groups showed mild to overt signs of toxicity as concluded from body weights (only at 10 mg/kg bw) and organ weights. A decrease was observed in the 10 mg group in numbers of copulations, pregnancies, and implantation sites.

Groups of male Sprague-Dawley rats were exposed to 0, 17.2, 34.4 or 68.8 mg cadmium/L (equivalent to 0 of 0, 0.7, 1.3, and 2.6 mg/kg bw/d[a]) in the drinking water for 70 days (Zenick et al. (1982)[15] Following mating with untreated females, no differences were observed in mating success and number of pregnancies. Histological examination of the testis revealed no differences with the controls.

Cadmium was administered by gavage to female rats, at doses of 0, 0.04, 0.4 or 4 mg/kg bw/d for 5 weeks (Baranski et al. (1983)[16]). Thereafter animals were allowed to mate with untreated males, after which exposure continued. It was noted that the fraction of inseminated and pregnant females was similar in each treatment group, and cadmium exposure did not affect the average number of total implantations and corpora lutea (data were not specified).

Baranski and Sitareka (1987)[17] administered female rats an aqueous solution of cadmium for 14 weeks, 5 days/week (0, 0.04, 0.4, 4 and 40 mg cadmium/kg bw/day). A pronounced increase in the mean duration of the oestrous cycle mainly due to lengthening of dioestrus was noted already 6 weeks after treatment of females at 40 mg cadmium/kg bw/d. At this dose, an increase in mortality and a decrease in body weight gain was observed.

Bomhard et al. (1987)[18] studied the chronic effects of single (1x 50 mg cadmium/kg bw) and multiple oral cadmium administrations (10x 5 mg/kg bw, weekly) on the testis of Wistar rats. Rats treated with cadmium at a single dose of 50 mg/kg did not differ in appearance, general behaviour or food and water consumption from the control animals, although growth was noted to be slightly retarded. Body weights of the animals treated 10 times with 5 mg cadmium/kg corresponded to those of the control animals. Necropsy at 12, 18 and 30 months revealed no cadmium-related lesions (including the testis).
Animals having received 1x 100 or 1x 200 mg/kg body weight by gavage showed severe lesions of the whole testicular parenchyma with massive calcification of the necrotic tubules and pronounced fibrosis of the interstitium. Most of the animals died within the first 3 days after administration.

[a] Based on 15 mL water intake (derived from publication) and a mean body weight of 400 g.

Andersen et al. (1988)[19] studied the effects of a single oral dose of cadmium (0, 270, 530 and 790 µmol cadmium/kg body weight (0, 30, 60 and 90 mg Cd/kg) on mortality and tissue damage in CBA/Bom male mice. In the 30 mg/kg bw group effects were observed on liver, stomach and duodenum. Effects on the testis were firstly observed in the 60 mg/kg group. At the highest doses, increased mortality was observed.

Male and female Sprague Dawley derived rats received cadmium by gavage at doses of 15, 31, 67 and 138 mg/kg body weight/day for 1 or 10 consecutive days, or in drinking water solutions at concentrations of 8-198 mg cadmium/L for 10 consecutive days (theoretical doses specified by the authors were 1.5, 15, and 31 mg/kg bw/d) (Borzelleca et al.[20]). After a single dose of cadmium, an apparent treatment-related but not statistically significant decrease in body weight was observed in the males. Furthermore, absolute and relative spleen weights were significantly lower and lung weights were significantly higher. No effects were observed in the females after a single dose. Dose-dependent mortality was observed in the 10 day gavage study. Body weight gain was reduced in a dose-dependent manner in both males and females. Absolute and/or relative brain, liver, spleen, lung, thymus, kidney and testis weights of treated males were reduced in a dose dependent manner. In females, absolute and/or relative liver, spleen, thymus and kidney weights were reduced in a dose dependent manner. Ovary weight was unaffected. Focal necrotic changes were observed in renal tubular epithelium and tubular degeneration was reported in males and females. Testicular and hepatic changes were observed in males. In the drinking water study dose-dependent changes in body weight gain and absolute and/or organ weights were observed. However, the testis weights of the cadmium dosed males were comparable to those in the controls.

Male Wistar rats, age 5 weeks, were given 0 or 10 mg cadmium/L in drinking water (equivalent to 0 or 1.1 mg cadmium/kg bw/d) for 52 weeks (Saygi et al. (1991)).[21] Animals were sacrificed at the end of week 28, 40 and 56 and examined for histopathological examination of testis, kidney and liver. All cadmium-treated male rats showed pathological testicular alterations, and liver and kidney damage after chronic exposure. Cadmium levels were found to be highest in the kidney. At the end of the 52-week period, reproductive capacity of the cadmium-treated rats was investigated by mating the treated males with 2 untreated females. All control males and only 60% (11/18) of the cadmium-treated males were fertile.

Massanyi et al. (2007)[22] studied the effects of cadmium on the structure of ovary, oviduct and uterus in rabbits. Animals received a dose of 1.0 mg/kg bw/d for 5 month in pelletized food. A lower relative volume of growing follicles and a higher volume of stroma was observed in the experimental group receiving cadmium, compared to the control group. The number of atretic follicles was higher after administration of cadmium. Histological analysis revealed structural alterations in the ovaries.

Hu et al. (2014)[23] studied the effect of cadmium on serum testosterone and testicular transcriptome of mice. Mice received 0, 1.95 mg or 0.975 mg per mouse daily via the diet (doses specified by the authors (presumably erroneously as gram instead of milligram); equivalent to 0, 40 or 20 mg/kg bw/d) for 6 months. A reduction in serum testosterone level was reported in both treatment groups.

Nasiadek et al. (2014)[24] administered cadmium (0.09, 0.9, 1.8 or 4.5 mg cadmium/kg bw/d) to female rats by gavage for 28 days. Animals were dissected on the first day or after 90 days post exposure. In the uterus, cadmium accumulation was reported and at the two highest doses an increase in catalase (CAT) activity, and an increase (at 1.8 mg cadmium/kg bw/d) or decrease (at 4.5 mg cadmium/kg bw/d) of lipid peroxidation (MDA) levels were observed at both time points.
In another publication, Nasiadek et al. (2018)[25] reported on the effects on sex hormones (oestradiol and progesterone) in the plasma and uterus, and on oestrous cyclicity and histopathological changes in uterine and ovary in female rats exposed to cadmium using the same study design, and with a post-exposure period of 3 months. No clinical signs of toxicity and no effect on body weight and brain and uterus weight were observed. Cadmium caused hormonal disturbance in plasma (at all doses) but not in the uterus. Cadmium did not induce oestradiol-like hyperplasia of endometrium, but resulted in (reversible) endometrial oedema irrespective of the dose, and caused damage of the ovaries after the highest dose.

Wang et al. (2014)[26] performed an Enhanced OECD TG 407 test in male and female rats. Animals were administered with 0, 1, 2.5, 5, 10, or 20 mg cadmium/kg bw/day by gavage for 28 days. Rats in 5, 10, 20 mg/kg·bw dose groups showed treatment-related clinical signs, which consisted of listlessness, anorexia, low hair-gloss, irritation, and their severity showed a dose-dependent trend. Body weights were reduced at doses exceeding 1 mg/kg bw/d (in males) or 2.5 mg/kg bw/d (females). Levels of serum luteinizing hormone and testosterone were decreased in males at doses of 10-20 mg/kg bw groups. The weights of prostate, thyroids, and seminal vesicle glands were decreased at doses exceeding 1 mg/kg bw/d.
No significant histological changes were observed in testis; relative testis weight was increased only at the highest dose. With respect to female reproduction, an increase of uterus weight and histopathological change were reported at 10-20 mg/kg bw/d. Female animals in all cadmium-treated groups showed normal oestrous cycle.

Zhao et al. (2015)[27] exposed male rats to cadmium (13.6 mg/kg bw), every two days for 9 weeks in total. The cadmium-treated animals group showed lower sperm motility and viability, and higher sperm malformation rate compared to the control group. The reported abnormalities included large heads, decollation, and folding and broken tails.

Medina et al. (2017)[28] exposed male rats to 10 mg cadmium/kg bw by gavage, 5 days per week for week for 3 months. The animals were

examined after 1, 2, and 3 months of treatment. Treatment resulted in ultrastructural changes of the testis appearing during the second month. The study of sperm with light microscopy showed defects in gamete morphology after 2 months of treatment. In the last month, sperm motility was reduced in the cadmium-treated group.

Wang et al. (2017)[29] exposed male mice to 0 or 1.8 mg/kg cadmium daily by gavage for 5 weeks. Thereafter, several sperm functions including the sperm motility, viability and were examined. Cadmium administration resulted in a reduced sperm total motility, progressive motility and viability.

Sapmaz-Metin et al. (2017)[30] studied the adverse effects of exposure to cadmium in drinking water (0 or 200 ppm, equivalent to 0 or 43 mg/kg bw/d[a]) for either 30 or 60 days on the uteri of mice. The oestrous cycle and uterine morphology was assessed, and immunohistochemistry was performed. No effect on cycle length was observed, and no stage specific microscopic alterations were noted (except the presence of apoptotic cells). Decreases in endometrial thickness and number of glands in oestrus phase uteri were observed. Cadmium decreased endometrial eosinophilia and increased the number of mast cells. The apoptotic index increased with time, while the proliferation index decreased. In the 60-d treated group, increased apoptosis was observed in the endometrium.

[a] Assuming a bodyweight of 30 g and a water intake of 6.5 mL/d (based on TGD calculation)

Fertility studies, subcutaneous and intraperitoneal exposure

A single subcutaneous injection of cadmium 6.1 mg/kg body weight induced profound cellular and vascular changes in the ovaries of prepuberal rats (Kar et al. (1959)[31]). At 96 hours after treatment some recovery of the ovary changes was observed; by 168 hours the process of recovery was complete.

A single subcutaneous injection of cadmium in adult rats (40 µmol cadmium/kg body weight, ~ 4.5 mg/kg bw) resulted in decreased weights of testis, seminal vesicles and prostate and severe histopathological changes of reproductive organs resulting in complete testicular necrosis (Parizek (1960)[32]).

Male CBA-mice were exposed to cadmium by subcutaneous injection of 2.2 µmol cadmium/kg body weight (~ 0.2 mg/kg bw) for 5 days/week for 6 months (Nordberg (1975)[33]). A decrease in normal (testosterone-dependent) proteinuria was shown and morphological examination of the seminal vesicles revealed a smaller weight and size as well as histological indications of lower secretory activity of the epithelium compared to controls. Treated animals did not show clinical signs. After 6 months exposure, body weight and urinary excretion of protein were reduced.

Lohiya et al. (1976)[34] injected male adult Langurs subcutaneously with a single dose of 0, 2.5 or 7.4 mg cadmium/kg bw. Animals dosed with

2.5 mg/kg were sacrificed after 30 days and animals dosed with 7.4 mg/kg were sacrificed after 60 days. No effects of cadmium treatment on body weights were observed. Testes of the 7.4 mg/kg group were small and oedematous; the weight of the reproductive organs was reduced. In the 2.5 mg/kg group, no macroscopical effects on organ weights were observed. Histological examinations of the testis and epididymis of $CdCl_2$-treated animals showed severe lesions in the testis and epididymis which were more severe in the high dose group.

Bomhard et al. (1987)[18] studied the chronic effects of single (0, 2 or 2.5 mg cadmium/kg bw) and multiple subcutaneous cadmium administrations (0, 0.25 mg cadmium/kg bw weekly for 10 weeks) on the testis of Wistar rats. Animals having received 1 x 2 or 1 x 2.5 mg/kg bw showed severe lesions of the whole testicular parenchyma with massive calcification of the necrotic tubules and pronounced fibrosis of the interstitium. All animals receiving 2.5 mg/kg BW subcutaneously had a Leydig cell tumour in at least one testis. Rats treated with 2.5 mg/kg BW did not differ in appearance, general behaviour or food and water consumption of the control animals; some transient inflammatory reactions were observed at the injection site.

Groups of sexually immature and mature female Syrian hamsters (Cr:RGH), mice (BALB/cAnNCr, DBA/2NCr, C57BL/6NCr, NFS/NCr) and rats (F344/NCr, WF/NCr) received a single subcutaneous injection with 2.2 to 5.3 cadmium cadmium/kg bw in the dorsal thoracic midline (Rehm and Waalkens (1988)[35]). They were killed 1 to 56 days after administration. Upon sacrifice ovarian necrosis was observed. The lowest adverse effect levels depended on species (hamster was the most susceptible), strain (BALB mice were most, DBA mice were least susceptible; no difference between the rat strains), and age (immature animals were more susceptible).

Wlodarczyk et al. (1995)[36] studied the effect of cadmium on the male reproductive system of Golden hamsters. Hamsters were subcutaneously injected with a single dose of 0 or 0.5 mg cadmium/kg bw. Five males of each dose group were sacrificed 1, 4 and 10 weeks after treatment. The testis, epididymis and accessory sex glands were weighed and histologically examined. Epididymal sperm was enumerated and sperm morphology was evaluated. In the cadmium-treated animals decrease in organ weight and pathological changes of the reproductive organs were detected at all time intervals but intensified to the end of the experiment (10 weeks). Furthermore, sperm number in the epididymis was decreased.
Lasky et al. (1984)[37] studied the reproductive effects of single doses of 1.6, 3.1, 7.4, 16, 33, 74, 152 µmol cadmium/kg (0.3, 0.6, 1.4, 2.9, 6.0, 13.6, 27.9, mg/kg bw/d) in male rats. Fourteen days after dosing, reproductive organs (including testes, seminal vesicles, and epididymides weights), vas deferens sperm concentration, and hCG-stimulated serum testosterone concentration were analysed. Mortality occurred at the two

highest doses and these doses were further excluded from the study. Rats receiving 33 µmol/kg were noted to have a limited weight gain, however no statistical significant difference between groups was noted. Weights of the tested, seminal vesicles, and epididymides were reduced at doses of 16 and 33 µmol cadmium/kg. At these doses, intact sperm was not found, only separated heads, tails, and other cellular debris were observed. In the 7.4 µmol cadmium/kg group, sperm concentration was reduced. Stimulated serum testosterone concentrations were depressed in all cadmium dose groups.

Piasek et al. (1994)[38] injected female rats subcutaneously on the day of dioestrus, or on day 7 or 16 of gestation with a single dose of 0, 3, or 5 mg cadmium/kg bw. Animals were sacrificed 24 h later, and serum progesterone and oestradiol concentrations were determined. Whole ovary culture was used to evaluate effects of cadmium on the production of progesterone, testosterone, and oestradiol. No effects on body weight or reproductive organ weights and no disruption of oestrous cyclicity were observed.

Paksy et al. (1989, 1990)[39,40] studied the effects of cadmium on serum hormone levels and sex organs in female rats. Animals were subcutaneously injected with 0, 5, 10 or 15 mg cadmium chloride/kg bw/d (equivalent to 0, 3.1, 6.1 or 9.2 mg cadmium/kg bw/d) and blood was collected the next day at different time points. An additional group was sacrificed or on the day of the expected oestrous and ovarian blood flow was measured. From the blood fractions taken, progesterone and oestradiol were determined, and their secretion rates were calculated. In a third group of treated animals, the ovaries were excised for histological examination, and oviducts were flushed for counting oocytes. At the two highest doses, decreased serum hormones were measured depending on time point. A reduced blood pressure was found 48 h after administration of cadmium, however ovarian blood flow was not affected. In animals receiving 10 or 15 mg/kg cadmium chloride a decrease in basal secretion of progesterone occurred. hCG-induced secretion was reduced in the 5 mg/kg group and absent in the 2 highest doses. Secretion of oestradiol was not affected. An increase in the number of anovulatory was reported (independent of dose), but when ovulation occurred normal oocyte numbers were found. No altered histology of the ovary was observed.

In another study, Paksy et al. (1996)[41] administered 0, 1.5, 3.1 or 6.1 mg cadmium/kg bw subcutaneously to rats, during oestrous or diestrous. After 32, 80 or 128 h, the animals were allowed to mate. A dose-dependent reduction in the fraction of rats mated was observed in the two highest dose groups, however this was only for 80-h (5.0 and 10 mg/kg bw) and 128-h interval (10 mg/kg bw) groups statistically significant.

Xu et al. (2001)[42] studied the effect of intraperitoneal injection of cadmium (0, 0.2, 0.4, 0.8 mg cadmium/kg bw/d) for 7 days on rat sperm motility using computer assisted sperm analysis. The sperm head counts and

daily sperm production was decreased in the high dose group. The motility of spermatozoa was reduced in the middle group and absent in the highest dose group.

Aoyagi et al. (2002)[43] injected male rats were subcutaneously with 0.6 mg cadmium/kg per day for 6 weeks. Testicular damage was evaluated by counting the spermatogonia and spermatocytes on one cut-surface of five seminiferous tubules in stages VII or VIII of spermatogenesis every week. There were no differences in the testes /bodyweight ratio between the study and control groups. The number of spermatogonia and spermatocytes was diminished in the exposed group.

Massannyi et al. (2007)[22] studied the effects of cadmium on the structure of ovary, oviduct and uterus in rabbits. In one experiment, cadmium was administered intraperitoneally (1.5 mg/kg bw) and sacrificed 48 h later for the assessment of acute effects. Similar results were found as for a group receiving Cd via the diet for 5 months, namely a lower relative volume of growing follicles and a higher volume of stroma when compared to the control group.

Wu et al. (2017)[44] investigated the effect of cadmium exposure on Leydig cell regeneration in the rat. Rats received a single dose of 0, 0.3 or 0.6 mg/kg of cadmium intraperitoneally, followed by ethane dimethane sulfonate treatment to eliminate adult Leydig cells 20 days later. Compared to controls, cadmium treatment reduced serum testosterone and luteinizing hormone levels. There were fewer regenerated Leydig cells in the testis of cadmium-treated rats. A reduction in bodyweight was observed in the cadmium treated group.

Inhalation

Exposure of female rats to cadmium at concentrations of 0, 0.02, or 0.16 mg cadmium/m^3 (equivalent to 0, 0.005 or 0.04 mg cadmium/kg bw/d) for 5 days a week, 5 h daily for 5 months followed by a maximum period of 3 weeks of mating, resulted in gestation indices of 54% (15/28), 44% (11/25) and 41% (7/17)(Baranski, 1984).[45] The low indices were attributed to the relative old age of the animals.

Female rats were exposed to cadmium at a concentration of 0, 0.02 or 0.16 mg cadmium/m^3 (equivalent to 0.005 or 0.04 mg/kg bw/d) for 5 hours a day, 5 days weekly for a period of 5 months, or 1 mg cadmium/m^3 (equivalent to 0.23 mg cadmium/kg bw/d) for 4 months (Baranski, 1985).[46] Exposure to cadmium resulted in an increased mortality (55.1% at 1 mg/m^3 versus 6.5% in controls). A decrease in fertility was only reported to be observed at the maternally toxic concentration of 1 mg cadmium/m^3, but the magnitude of the fertility effects (gestation index, corpora lutea) was not specified in the publication.

Baranski and Sitareka (1987)[17] exposed females rats to cadmium for 20 weeks, 5 hours/day, 5 days/week to 0, 0.02, 0.16 or 1 mg cadmium/m^3 (equivalent to 0.005, 0.04, or 0.23 mg cadmium/kg bw/d)[a]. An increase in the mean duration of the oestrous cycle mainly due to lengthening of dioestrus was noted already 6 weeks after treatment of females at 1 mg cadmium/m^3. Only at this concentration, an increase in mortality and a decrease in body weight gain was observed. In the 0.16 mg cadmium/m^3 group, an increased percentage of females with oestrous cycles lasting over 6 days was shown 18 weeks after exposure compared to controls.

In an inhalation 13-w repeated dose study of the National Toxicology Program (NTP), male and female rats were exposed 6h/d; 5 d/week to 0, 0.02, 0.04, 0.09, 0.22 and 0.88 mg cadmium/m^3 (0.005, 0.010, 0.020, 0.050 and 0.20 mg cadmium/kg bw/d[b]) (NTP, 1995)[7]. Females were evaluated for necropsy body weight, oestrous cycle length and the percent of cycle spent in the various stages; male rats were evaluated for necropsy body and reproductive tissue weights, spermatozoal data and spermatogenesis. In males in the 1 mg/m^3 group, spermatid heads per gram of testis, spermatid heads per testis and spermatid count were lower than those of control males. There were no treatment-related microscopic changes in the testis or epididymis. In females, there was a greater oestrous cycle length than the controls at the 1 mg/m^3 exposure level, but no treatment related histologic changes in the reproductive organs. There were no histopathologic lesions indicative of toxicity to the reproductive system.

In the NTP, also a repeated dose inhalation toxicity study in mice was performed (NTP, 1995)[7]. Male and female mice were exposed to 0, 0.02, 0.04, 0.09, 0.22 and 0.88 mg cadmium/m^3 (0.007, 0.014, 0.027, 0.068 and 0.27 mg cadmium/kg bw/d) using the study design as described above. No effects on reproductive organs were reported.

Other studies on effects on fertility

Various studies have been conducted with the purpose to study the protective effect of a substance or agent on cadmium-induced reproduction toxicity in mainly male rats and mice.[47-68] In addition to an untreated control group, these studies included a control group treated with cadmium only, using various routes (oral, intraperitoneal, subcutaneous). In males, adverse effects of cadmium on testicular tissue, sperm parameters and testosterone levels were reported. In female mice, effects on uterus and ovaries, and on the viability of follicles and progesterone levels were reported.[57,69-71] These studies are of limited value for classification purposes, as usually only a (single) high dose is applied and general toxicity was not assessed. Therefore, these studies are not further considered by the Committee.

[a] Assuming an inhalatory volume of 150 mL/min (for 90-d study) and a body weight of 200 g

[b] Assuming an inhalatory volume of 175 mL/min, and a body weight of 275 g for males and females combined.

5.1.2 Human data

Humans may be exposed to cadmium either occupationally, via smoking of tobacco, or via the diet and drinking water. Exposure via food is the main route for the non-smoking population.

Studies on reproductive function

In a cross-sectional study with retrospective data collection, Gennart et al. (1992)[72] compared male reproductive function in Belgian cadmium smelters (N=83) to reproductive function in workers from nearby factories not occupationally exposed to cadmium (N=138). The mean urinary cadmium level in exposed workers was 6.9 µg per g creatinine and mean duration of exposure was 24 years (range 1.1-53.2), whereas the mean urinary cadmium level in unexposed workers was 0.7 µg per g creatinine. Fertility in these workers was assessed by examination of birth rates among their wives using logistic regression analysis. Several characteristics that influenced birth rate, including smoking habits, were included as confounders. No differences in fertility were observed between the exposed and unexposed populations. Within the exposed population, variables reflecting different intensities or duration of exposure were not related to the probability of a live birth.

In a prospective cohort study, Buck Louis et al. (2012)[73] studied associations between levels of metals (including cadmium) in blood and various parameters of couple fecundity. In 2005–2009, couples (N=501) desiring pregnancy and discontinuing contraception were recruited and asked to complete interviews and to provide blood specimens for the quantification of cadmium. The couples were followed for 12 months or until pregnant. The longest time-to-pregnancy was observed for the highest tertile of cadmium levels for both men (0.23-3.64 µg/L) and women (0.28, 2.87 µg/L), with women in the highest tertile being more likely to not achieve pregnancy within 12 months. A reduced fecundability odds ratio (FOR; ratio of the odds of conception per menstrual cycle) of 0.78 (95% CI 0.63–0.97), adjusted for age, parity, body mass index, serum cotinine, serum lipids, and lead and mercury concentrations, was observed per standard deviation increase in cadmium concentration among women, while the adjusted FOR for male cadmium exposure was 0.85 (95% CI: 0.71–1.02). The FORs for couple fecundability, with all female and male co-variables included in the model, were 0.80 (0.64–1.00) and 0.94 (0.77–1.13) for female and male cadmium exposure, respectively.

Kim et al. (2014)[74] measured mercury, cadmium and lead in seminal plasma collected from 30 men using in vitro fertilization, to evaluate associations with semen quality parameters and IVF outcomes, such as fertilization, implantation, and ultrasound confirmed pregnancy. Multivariable linear and Poisson regression analyses were used to adjust for smoking, age, and co-exposure to mercury. Due to multicollinearity, lead exposure could not be adjusted for. No statistically significant results were observed for semen cadmium concentration and sperm cadmium concentration.

Tulic et al. (2018)[75] investigated the associations of cadmium and other metal concentrations in blood and the outcome of IVF (achieving pregnancy) in 104 consecutive female patients. Serum samples were obtained before the IVF procedure. Based on the outcome of IVF, all subjects were divided into groups of pregnant (N=41) and non-pregnant women (N=63). Higher concentrations of cadmium were found in the non-pregnant women compared to the pregnant women (1.83±5.44 vs 0.51±0.13, P=0.012). In univariable logistic regression analyses, a 89.4% (95% CI: 14.8-98.7) decreased chance of achieving pregnancy was observed for women with cadmium concentrations ≥ 0.5 µg/L. Cadmium was not retained in the multivariable analyses including lead and magnesium concentrations, age, and IVF parameters, such as gonadotropin dose, number of fertilized oocytes, and embryo class. Adjustment for these IVF parameters, which are potential intermediate factors, may have led to overadjustment, however.

García-Fortea et al. (2018)[76] analysed the associations between the concentration of four toxic elements, including cadmium, in hair and diverse reproductive outcomes (e.g. number of oocytes collected, proportion of fertilized oocytes, clinical pregnancy) in a cohort of 194 women with fertility disorders undergoing IVF. Multivariable analyses for in vitro fertilization outcomes and cadmium concentrations in hair - adjusting for age, body mass index and cigarette smoking – did not show any associations. However, the cadmium concentrations measured were extremely low.

Studies on semen parameters

Xu et al. (1993)[77] determined the concentrations of cadmium and other trace elements (lead, selenium and zinc) in blood and seminal plasma of men (N=221) undergoing initial screening for infertility. In this cross-sectional study, the authors detected an inverse correlation between cadmium concentrations in blood and sperm density (r=-0.15, P<0.05), but not with other parameters of semen quality. The inverse correlation (r=-0.23, P<0.05) was only observed among oligozoospermic (N=99) men (sperm density below 20 million/mL), but not among normospermic (N=91) men. Higher cadmium concentrations in seminal plasma were correlated with lower semen volume (r=-0.29, P<0.05) in a subgroup of 73 men for whom seminal plasma concentrations were measured.

In a cross-sectional study, Keck et al. (1995)[78] did not find correlations (not further specified) between cadmium levels in seminal plasma and semen parameters (semen volume, count, motility and morphology) and fertility among 12 men with proven fertility, 44 normozoospermic infertility patients, and 118 unselected patients of an infertility clinic in Germany.

Taha et al. (2013)[79] evaluated cadmium levels in seminal plasma of 30 men with idiopathic oligo- and/or asthenozoospermia and 30 fertile healthy controls, and correlated these levels with conventional semen parameters, sperm hypo-osmotic swelling (HOS), sperm DNA fragmentation percentage, and semen reactive oxygen species (ROS) levels.

Subjects smoking or occupationally exposed to heavy metals and patients with diseases impairing reproductive capacity were excluded. Among the infertile men, higher seminal lead (44.4 ± 8.6 µg/L versus 21.7 ± 2.6 µg/L) and cadmium levels (3.8 ± 0.3 µg/L versus 2.8 ± 0.5 µg/L) were observed in comparison to the controls ($p<0.001$). Negative correlations were reported between seminal lead and cadmium levels and progressive sperm motility and sperm vitality (HOS), whereas positive correlations were seen for the percentages of sperm DNA fragmentation and semen ROS levels in both infertile and fertile men ($p<0.01$).

Pant et al. (2014)[80] assessed the associations between seminal levels of several environmental toxicants and serum hormone levels (FSH, LH, and testosterone), semen quality, and DNA damage in semen among 60 male partners of couples attending a medical institute to assess their inability to conceive in India. Subjects occupationally exposed or with a medical history ('mainly testicular dysfunction/history of urogenital abnormality/mumps, tuberculosis, or surgical operation; using drugs known to affect gonadal function') were excluded. Although several associations with cadmium appeared to be present, the results of the multivariable linear regression analyses, adjusting for other toxicants (lead and phthalates), age, BMI, tobacco chewing, smoking, alcohol, and diet, showed that cadmium was not associated with any of the outcome parameters independently.

Mendiola et al. (2011)[81] assessed the associations between seminal and hormonal parameters and the concentrations of cadmium, lead, and mercury in seminal plasma, whole blood, and blood plasma. Sixty one men of couples attending infertility clinics in Spain were divided into 30 cases with oligo-astheno-teratozoospermia and 31 normospermic controls according to the WHO criteria. No differences were found between cases and controls in the concentrations of heavy metals in any of the three body fluids. In multivariable linear regression analyses, adjusted for age, body mass index and number of cigarettes per day, no associations were found between serum hormone levels and metal concentrations, but the percentage of immotile sperm was associated with seminal plasma levels of lead and cadmium ($p\leq0.05$).

De Franciscis et al. (2015)[82] measured cadmium levels in both blood and seminal plasma and analysed the associations between cadmium concentrations and lifestyle and semen parameters. In this cross-sectional study, 50 healthy male patients of a fertility clinic were recruited to provide semen and blood samples. Each patient completed an extensive questionnaire. Cadmium blood levels were higher ($p<0.05$) in men from industrialised areas and in current smokers, but were not correlated with cadmium semen levels. Increasing cadmium blood levels were correlated with an increase in the number of immotile spermatozoa and with the teratozoospermia index (TZI; the total number of abnormalities (head, mid-piece, and tail abnormalities) divided by the number of abnormal

spermatozoa) ($p<0.05$). Inverse correlations ($p<0.05$) were also found between cadmium concentrations in blood and fast- and straight-moving spermatozoa, and the fractions of fast- and straight-moving and slow straight-moving spermatozoa.

Jeng et al. (2015)[83] studied associations between concentrations of cadmium, copper, lead, zinc, arsenic, and selenium in seminal plasma and urine and semen quality parameters in 196 male human subjects screened for an annual health examination in a municipal hospital in Taiwan. Subjects were included when they did not have treatment affecting spermatogenesis, self-reported diabetes mellitus, liver disease, malignant disease, use of mood stabilisers, endocrine disrupting medication, or obesity. Fertility status was not included as a criterion. Binary linear regression analyses were performed for semen parameters and all metals, including the covariables age, smoking, drinking, and BMI. Higher urinary cadmium concentrations were found to be associated with lower sperm concentration ($p=0.051$) and viability ($p=0.006$), next to associations between sperm concentration and urinary lead and arsenic concentrations. In multivariable analyses including all metals and covariables, none of the other metals were associated with the sperm quality parameters, but seminal cadmium was retained in the regression model for sperm concentration and urinary cadmium in the model for sperm viability, although the contribution to the models was small.

Riaz et al. (2016)[84] studied the antioxidant status of serum and seminal plasma and the associations with several heavy metals, including cadmium, in 20 fertile and 20 infertile men. Confounders were not taken into account. In fertile men, total oxidant status was increased in both seminal plasma and in serum, compared to infertile men. Compared to fertile men, infertile men had elevated levels of cadmium in both seminal plasma (9.11 ± 2.34 µg/L versus 1.43 ± 0.85 µg/L) and serum (6.44 ± 2.72 µg/L versus 1.89 ± 0.79 µg/L).

Another cross-sectional, environmental study by Li et al. (2016)[85] involved 587 men without a history of reproductive disorders and not occupationally exposed to cadmium, from three provinces in China. The median serum cadmium level was 1.9 µg/L (P25-P75: 1.1-2.9). When outliers were excluded (values > 6.3 µg/L (P95)) and the semen parameters were logarithmically transformed, increasing serum cadmium levels were associated with a reduction in semen volume, progressive motility, and fraction of sperm with normal morphology ($p\leq0.0002$). This was observed for the entire group, after adjusting for age group, occupation, season of semen sample collection, abstinence intervals, smoking, alcohol drinking, and body mass index, but not in all three provinces separately.
Wang et al. (2016)[86] recruited 1,052 men from a fertility clinic in Wuhan, China. Each man provided one semen sample and two urine samples. Men with azoospermia, occupational exposure to metals, or self-reported diseases that may adversely affect the reproductive system or urinary

excretion of chemicals were excluded. Semen quality parameters and urinary levels of 18 metals, including cadmium, were determined. Associations between urinary cadmium levels and semen quality parameters were assessed using multivariable linear and logistic regression analyses, adjusted for various potential confounders, such as age, BMI, smoking status, daily cigarette consumption, alcohol use, and abstinence time, as well as for multiple comparisons. The urinary cadmium levels were associated inversely with progressive sperm motility and total motility (both *P* = 0.03), with a ten-fold increase in urinary cadmium being associated with a decline of 6.15 (95% CI: 1.89-10.41) % in progressive sperm motility and 7.00 (2.19-11.84) % in total motility. In addition, increased odds ratios (with 95% CIs not including unity) were found for below-reference progressive sperm motility and total motility (p=0.07 adjusted for multiple comparisons). A ten-fold increase in urinary cadmium levels resulted in ORs of 2.07 (95% CI: 1.19-3.63) and 1.90 (1.12-3.21), respectively. After additional adjustment for all other metals, very similar effect estimates were found with a slightly higher OR for below-reference total motility (OR 2.17, 1.27-3.68).

In the same population, reduced to 746 men by exclusion of 306 men with inadequate semen volumes, Wang et al. (2017)[87] also studied associations between concentrations of metals in seminal plasma and semen quality (N=746), sperm apoptosis (N=331), and DNA integrity (N=404). Both in the single-element linear regression analyses adjusted for confounders and multiple comparisons and in the multiple-element analyses, in which other metals/metalloids were also considered, inverse associations were found between cadmium level quartiles and progressive (p=0.002) and total sperm motility (p=0.02).

In a study by Famurewa and Ugwuja (2017)[88], 75 male partners of Nigerian couples with infertility were categorised using the WHO guidelines into normospermia, oligospermia, and azoospermia. Lead and cadmium levels were determined in blood and seminal plasma. Men with genital infections or testicular varicocele, with chronic illnesses including endocrine diseases, or using contraceptives or fertility drug were excluded from the study. Smoking, chronic alcohol intake, micronutrient supplementation for the last three months, surgery, and occupational exposure to heavy metals were exclusion criteria as well. Seminal and blood plasma cadmium levels were higher in azoospermic and oligospermic men compared to normospermic men (p<0.01). Inverse associations were found between blood and seminal cadmium levels and sperm count, total motility, and morphology (p<0.01).

Sukhn et al. (2018)[89] studied the associations of levels of heavy metals in blood and urine with various semen quality parameters in male partners of couples attending a fertility clinic in Lebanon. Non-occupationally exposed men were categorised in low- or normal-quality semen groups, based on the WHO criteria for sperm quality. Associations between metal concentration in quartiles and continuous semen quality outcome

measures were assessed using multivariable linear regression for each metal separately with age, cigarette smoking, alcohol consumption, and period of sexual abstinence as confounders. Men with low-quality semen had higher cadmium concentrations in the seminal fluid than men with normal-quality semen ($p<0.05$). In addition, associations were observed between low sperm viability and higher blood cadmium ($p<0.05$) and higher seminal cadmium ($p<0.003$) levels.

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

Various publications concerning the effects of cadmium on human fertility were found. In some studies, functional fertility was assessed. Gennart et al. (1992)[72] did not find an association between urinary cadmium levels and birth experiences of their wives in male workers exposed to cadmium. From a prospective cohort study with adjustment for confounders and other metals, Buck Louis (2012)[73] reported associations between long time-to-pregnancy and reduced fecundability and increased cadmium blood levels, especially for women. Kim et al. (2014)[74] did not find an association between seminal cadmium levels and negative outcome of IVF treatment in a small cross-sectional study. In female IVF patients, Tulic et al. (2017)[75] found an association between blood cadmium levels and a negative IVF outcome. Garcia-Fortea (2017)[76] did not find associations between low cadmium levels in hair and various outcome parameters in female IVF patients.

Most other reports involve clinical or environmental cross-sectional studies on associations between cadmium-levels in blood (serum), seminal fluids and/or urine and sperm quality (e.g. motility, concentration, viability). The majority of these studies reported associations between increased cadmium levels and reduced sperm quality (Xu et al. (1993)[77]; Taha et al. (2013)[79]; Mendiola et al. (2011)[81]; De Franciscis et al. (2015)[82]; Jeng et al. (2015)[83]; Riaz et al. (2016)[84]; Li et al. (2016)[85]; Wang et al. (2016)[86]; Wang et al. (2017)[87]; Famurewa et al. (2017)[88]; Sukhn et al. (2018)[89]) whereas no associations were reported in only two studies (Keck et al. (1995)[78]; Pant et al. (2014)[80]). Taking co-exposure to multiple metals into account, independent associations for cadmium were observed in the studies by Jeng (2015)[83] and Wang (2016, 2017)[86,87].

In animals, effects of oral administration of cadmium on functional fertility parameters in males were mainly assessed in rats. Dixon et al. (1976)[10] reported no effects on male fertility in a breeding experiment with rats (no details were provided), either 6 weeks after a single oral dose up to 25 mg/kg or after exposure up to 0.014 mg/kg via drinking water for up to 90 days. Kotsonis and Klaassen (1978)[11] observed no reduced fertility (as fraction of pregnant females after mating and number of foetuses per pregnant animal) in male rats exposed to cadmium up to 12.2 mg/kg bw/d

for 24 weeks. Zenick et al. (1982)[15] reported no effects on fertility of male rats (as mating success/number of pregnancies) exposed up to 3.2 mg/kg bw/d for 70-80 days. Laskey et al. (1980)[12] reported decreased preimplantation loss after exposing male and female rats from mating at a dose of 0.6 mg/kg via drinking water. Sutou et al (1980a,b)[13,14] exposed male rats for 6 weeks by gavage to 0.1, 1 or 10 mg/kg bw and reported no reduced copulation and no reduced number of implants. A reduction in these parameters was only observed when females also were exposed at the highest dose. Saygi et al. (1991)[21] administered male rats cadmium in drinking water at an equivalent dose of 1.1 mg/kg bw/d for 52 weeks and observed reduced fertility.

Male and female mice, continuously exposed during multiple generations to 2.1 mg/kg bw/d for multiple generations failed to bred beyond the F2b-generation (Schroeder and Mitchener, 1971)[8] All reported effects on functional fertility were observed at doses at which reduced body weight and/or toxicity to other organs were noted as well.

Inconsistent data are available on the effects of cadmium treatment on male reproductive organs or sperm parameters after oral (gavage, drinking water or diet) or subcutaneous administration of cadmium. In studies with male rats (Parizek (1960)[32]; Krasovskii et al. (1976)[9]; Laskey et al. (1984)[37]; Borzelleca et al. (1989)[20], Aoyagi et al. (2002)[43]; Wang et al. (2014)[26]; Zhao et al. (2015)[27]; Medina et al. (2017)[28]; Wu et al. (2017)[44] and male mice (Nordberg (1975)[33]; Andersen et al. (1988)[19], Wang et al. (2017)[29]), effects on testis and/or spermatogenesis have been reported at various dosing schedules. However, Kotsonis and Klaassen (1978)[11], Bomhard et al. (1987)[18], and Zenick et al (1982)[15] did not observe effects on sperm parameters/reproductive organs in rats. In general, effects on sperm parameters or reproductive organs are either observed in combination with effects on body or organ weights, or data on general toxicity is lacking.

In rats, inhalation exposure to cadmium for 90 days at an equivalent dose of 0.20 mg Cd/kg bw/d resulted in effects on spermatids, but also in enlargement and paleness of the tracheobronchial and mediastinal lymph nodes. No effects on reproductive organs were observed in mice with a similar exposure.(NTP, 1995)[7]

Two studies are available on functional fertility in female animals. Baranski et al. (1983)[16] treated female rats for 5 d/w for 5 weeks with cadmium (0.04, 0.4 or 4 mg cadmium/kg bw/d) prior to mating (and continued thereafter) and reported no effect on the fraction inseminated and pregnant females. Inhalation exposure of female rats to a dose of 0.18 mg cadmium/kg bw/d for 4 months was reported to result in reduced fertility (otherwise not specified), but also increased mortality.(Baranski, 1985)[46] Oral exposure of female rats to cadmium resulted in a prolonged oestrous cycle at a daily dose of 40 mg/kg bw for 14 weeks (Baranski and Sitarek 1987)[17]; effects on follicles and stroma at 1 mg/kg bw/d for 5 months (Massanyi et al 2007)[22], biochemical changes in the uterus and increased

uterus weight at a dose exceeding 0.9 mg/kg bw/d for 28 days (Nasiadek et al. 2014)[24]; and increased uterus weight and histopathological changes at a dose exceeding 5 mg/kg bw for 28 days (Wang et al 2014)[26].
Adverse effects on the endometrium and uterus were observed in female mice exposed up to 60 days to a high dose of cadmium (43 mg/kg bw/d). (Sapmaz-Metin 2017)[30] Kar et al. (1959)[31] reported cellular and vascular changes in the ovaries of prepuberal rats. Only in the study of Nasiadek et al. (2014)[24], effects on reproductive organs were reported at doses at which no general toxicity (effects on body or organ weights) were apparent.

In inhalation studies with cadmium, a prolongation of the oestrous cycle has been observed in rats (Baranski and Sitareka (1987); NTP (1995)[7,17]).

The adverse effects on sexual function and fertility observed in animal studies are summarised in the following tables:

Males

Ref.	Species	Exposure duration	Exposure route	Effects on fertility	General toxicity
Krasovskii et al. (1976)	Rat	6-m	Oral (drinking water)	Reduction spermatogenesis NOAEL=0.00005 mg/kg	Changes biochemical parameters and in the conditional reflex activity NOAEL=0.00005 mg/kg
Dixon et al. (1976)	Rat	90-d	Oral (drinking water)	No effects on functional fertility (serial breeding) reported NOAEL=0.01 mg/kg	No information provided NOAEL=0.01 mg/kg
		6 w (single dose)	Oral (gavage)	No effects on functional fertility (serial breeding) reported NOAEL=25 mg/kg (single dose)	No general toxicity reported NOAEL=25 mg/kg (single dose)
Kotsonis and Klaassen (1978)	Rat	24-w	Oral (drinking water)	No effect on functional fertility and testis weight and histopathology NOAEL = 12.2 mg Cd/kg	Tubular necrosis in the kidney NOAEL=1.2 mg/kg
Laskey et al. (1980)	Rat	130-d	Oral (drinking water)	Reduced sperm count, (decreased preimplantation loss only when females were also exposed) NOAEL = 0.6 mg Cd/kg bw/d	Decreased liver weight NOAEL=0.01 mg/kg
Sutou et al. (1980a,b)	Rat	6-w	Oral (gavage)	Reduced copulation, pregnancy and implantation sites (females were also exposed) NOAEL = 1 mg/kg	Reduced body and organ weight NOAEL=0.1 mg/kg
Zenick et al. (1982)	Rat	70-d	Oral (drinking water)	No effects on mating success or number of pregnancies; no effect on testis NOAEL=3.2 mg/kg	No effect on body weight NOAEL=3.2 mg/kg

Ref.	Species	Exposure duration	Exposure route	Effects on fertility	General toxicity
Bomhard et al. (1987)	Rat	10-w (weekly administration); duration experiment up to 30 m	Oral (gavage)	No effect on testis NOAEL=5 mg/kg	No effect on body weight NOAEL=5 mg/kg
Bomhard et al. (1987)	Rat	Single dose; duration experiment up to 30 m	Oral (gavage)	No effect on testis NOAEL=50 mg/kg	Slight growth retardation LOAEL=50 mg/kg
Borzelleca et al. (1989)	Rat	10-d	Oral (gavage)	Testicular atrophy; relative testis weight NOAEL=31 mg/kg	Mortality, kidney toxicity LOAEL=15 mg/kg
	Rat	10-d	Oral (drinking water)	No effect on testis NOAEL=31 mg/kg	reduced body/organ weight NOAEL=1.5 mg/kg
Saygi et al. (1991)	Rat	52-w	Oral (drinking water)	Reduced fertility after 52 w; histopathological changes testis LOAEL=1.1 mg/kg	Histopathological changes liver/kidney LOAEL=1.1 mg/kg
Wang et al. (2014)	Rat	28-d	Oral (gavage)	Decrease weight of prostate and seminal vesicles NOAEL=1 mg/kg	Reduced body weight NOAEL=1 mg/kg
Zhao et al. (2015)	Rat	9-w (administration every 2 d)	Oral (gavage)	Various abnormalities in sperm LOAEL=13.6 mg/kg (every 2 days)	No information provided
Medina et al. (2017)	Rat	3 m (5 d/w)	Oral (gavage)	Morphological changes in testis; sperm motility LOAEL=10 mg/kg	No information provided
Schroeder and Mitchener (1971)	Mouse	Multi-generation	Oral (drinking water)	Strain could not be bred further after 3 generations (exposure to both males and females) LOAEL=2.1 mg/kg	2 maternal deaths; no further information provided LOAEL=2.1 mg/kg
Anderson et al. (1988)	Mouse	10 d (single dose)	Oral (gavage)	Histological lesions of the testis NOAEL=30 mg/kg	Histological lesions of intestinal tract LOAEL=30 mg/kg
Haffor and Abou-Tarboush (2004)	Mouse	4-w	Oral (gavage)	Damage to testicular tissue LOAEL=1 mg/kg	No information provided
Hu et al. (2014)	Mouse	6 m	Oral (diet)	Reduced testosterone levels NOAEL=20 mg/kg	No reduced body weight NOAEL=20 mg/kg
Wang et al. (2017)	Mouse	5 w	Oral (gavage)	Reduced sperm motility and viability LOAEL=1.9 mg/kg	No information provided
Laskey et al. (1984)	Rat	14 d (single dose)	subcutaneous	Reduced sperm count NOAEL=0.3 mg/kg	No effect on body weight NOAEL=3.7 mg/kg
Bomhard et al. (1987)	Rat	10-w (weekly administration)	intraperitoneal	No histological alterations in the testis NOAEL=0.25 mg/kg	No lesions observed at necropsy NOAEL=0.25 mg/kg
		10 w (single dose)		Lesions in the testis LOAEL=2.5 mg/kg	No effect on bw and behaviour NOAEL= 2.5 mg/kg
Aoyagi et al. (2002)	Rat	6-w	subcutaneous	Reduction in spermatogonia and spermatocytes LOAEL=0.6 mg/kg	Decrease in body weight gain LOAEL=0.6 mg/kg
Parizek (1960)	Rat	4 m (single dose)	subcutaneous	Decreased weight reproductive organs LOAEL=4.5 mg/kg	No information provided

Ref.	Species	Exposure duration	Exposure route	Effects on fertility	General toxicity
Xu et al. (2001)	Rat	7 d	intraperitoneal	Decrease motility NOAEL=0.2 mg/kg	No information provided
Wu et al. (2017)	Rat	76 d after a single dose	intraperitoneal	Impaired regeneration Leydig cells after EDS treatment LOAEL=0.3 mg/kg	Reduction in bodyweight LOAEL=0.3 mg/kg
Nordberg (1975)	mouse	6 m	subcutaneous	Decreased weight/size seminal vesicles LOAEL=0.2 mg/kg	Decreased body weight LOAEL=0.2 mg/kg
Wlodarczy et al. (1995)	Hamster	Up to 10 w (single dose)	subcutaneous	Decrease number of sperm cells/weight reproductive organs LOAEL=0.5 mg/kg	No information provided
Lohiya et al. (1976)	Langurs	Up to 60 d (single dose)	subcutaneous	Histological lesions reproductive organs LOAEL=2.5 mg/kg	No information provided
NTP (1995)	Rat	13-w	Inhalation	Reduced number spermatid heads per testis and spermatid count (no histopathologic lesions) NOAEL=0.01 mg/kg	Lesions in larynx LOAEL=0.005 mg/kg
NTP (1995)	mouse	13-w	Inhalation	No effect on reproductive organs NOAEL=0.9 mg/kg	Lesions in the lung NOAEL=0.007 mg/kg

Females

Ref.	Species	Exposure duration	Exposure route	Effects on fertility	General toxicity
Baranski et al. (1983)	Rat	5-w	Oral (gavage)	No effect on functional fertility observed NOAEL=4 mg/kg	No information provided NOAEL=4 mg/kg
Baranski and Sitarek (1987)	Rat	5-w	Oral (gavage)	Increase oestrous cycle NOAEL=4 mg/kg	Increased mortality; decreased body weight gain NOAEL=4 mg/kg
Nasiadek et al. (2014; 2018)	Rat	28-d	Oral (gavage)	Biochemical changes uterus NOAEL=1.8 mg/kg	No effects on body weight or organ weights NOAEL=4.5 mg/kg
Wang et al. (2014)	Rat	28-d	Oral (gavage)	Increased uterus weight; histopathological changes NOAEL=5 mg/kg	Reduced body weight; clinical signs NOAEL=2.5 mg/kg
Sutou et al. (1980a,b)	Rat	6-w	Oral (gavage)	Reduced copulation, pregnancy and implantation sites (males were also exposed) NOAEL = 1 mg/kg	Reduced body and organ weight NOAEL=0.1 mg/kg
Borzelleca et al. (1989)	Rat	10-d	Oral (gavage)	No effect on ovary weight NOAEL=66 mg/kg	Mortality, kidney toxicity NOAEL=15 mg/kg
		10-d	Oral (drinking water)	No effect on ovary weight NOAEL=31 mg/kg	No effect on body/organ weight NOAEL=31 mg/kg
Schroeder and Mitchener (1971)	Mouse	Multi-generation	Oral (drinking water)	Strain could not be bred further after 3 generations (males were also exposed) LOAEL=2.1 mg/kg	2 maternal deaths; no further information provided LOAEL=2.1 mg/kg

Ref.	Species	Exposure duration	Exposure route	Effects on fertility	General toxicity
Sapmaz-Metin et al. (2017)	Mouse	30-60 d	Oral (drinking water)	Apoptosis in uterus and endometrium LOAEL=43 mg/kg	No information provided
Massanyi et al. (2007)	Rabbit	5-m	Oral (diet)	Effects on follicles and stroma LOAEL=1 mg/kg	No information provided
Kar et al. (1959)	Rat	Up to 360 h (single dose)	Subcutaneous	Cellular and vascular changes in ovary (reversible) NOAEL=6.1 mg/kg	No information provided
Paksy et al. (1989)	Rat	48 h (single dose)	Subcutaneous	Reduced effect of hCG; increased anovulatory LOAEL=3.1 mg/kg	No information provided
Paksy et al. (1996)	Rat	32-132 h (single dose)	Subcutaneous	Reduced fraction mated NOAEL=1.5 mg/kg	No information provided
Rehm and Waalkes (1988)	Rat (several strains; mature and immature)	Up to 56 d (single dose)	Subcutaneous	Necrosis in ovaries LOAEL=2.2 kg/bw	Mortality NOAEL=2.2 kg/bw
	Mouse (several strains; mature and immature)			NOAEL=2.2 kg/bw	NOAEL=2.2 kg/bw
	Hamster (several strains; mature and immature)			LOAEL=2.2 kg/bw	NOAEL=2.2 kg/bw
Massanyi et al. (2007)	Rabbit	48h (single dose)	Subcutaneous	Adverse effect follicles LOAEL=1.5 mg/bw	No information provided
Baranski (1984)	Rat	5-m; followed by 3 w mating period	Inhalation	No effects on fertility observed NOAEL=0.04 mg/kg	No information provided
Baranski (1985)	Rat	4-6-m; continued during mating 4-m; continued during mating	Inhalation	Reduced fertility (not further specified) NOAEL=0.04 mg/kg	Increased mortality NOAEL=0.04 mg/kg
Baranski and Sitareka (1987)	Rat	20-w	Inhalation	Increased incidence of females with prolonged oestrous cycle NOAEL=0.005 mg/kg	Mortality and decreased body weight NOAEL=0.04 mg/kg
NTP (1995)	Rat	13-w	Inhalation	Increased oestrous cycle length NOAEL=0.05 mg/kg	Respiratory tract lesions in the lungs LOAEL=0.005 mg/kg
NTP (1995)	mouse	13-w	Inhalation	No effect on fertility observed NOAEL=0.2 mg/kg	Respiratory tract lesions in the lungs LOAEL=0.007 mg/kg

5.3 Comparison with the CLP criteria

As many animal and epidemiological studies evaluated the effects on male or female sexual function and fertility, the results were assessed separately for effects on males and females.

Male fertility

Three studies on cadmium exposure in men and impaired reproductive function are available, of which one large study suggests an association (Buck Louis et al. (2012)[73]), whereas two small studies do not (Gennart et al. (1992)[72]; Kim et al. (2014)[74]. Most other human data involve studies on associations between cadmium levels in biological fluids and parameters of the sperm quality. The majority of these studies reported associations between increased cadmium levels and reduced sperm quality. Most of these studies have several limitations, in particular the presence of possible co-exposures. The Committee notes that in three studies on cadmium exposure and reduced sperm quality (Jeng et al. (2015)[83]; Wang et al. (2016)[86], (2017)[87]; related to the same population)), independent associations were found after adjustment for co-exposure to multiple metals. Overall, the Committee concludes that the epidemiological studies suggest an association between cadmium exposure and adverse effects on male fertility.

In three animal studies a decrease in fertility was reported, in the presence of general toxicity, after prolonged exposure to cadmium compounds. Saygi et al. (1991)[21] reported a reduced fertility in rats at 1 mg/kg bw. This dose also resulted in adverse effects on kidney and liver. In the study of Sutou (1980a,b)[13,14] in rats, copulation and pregnancy was reduced at a dose of 10 mg/kg bw, which also reduced body and organ weights. Schroeder and Mitchener (1971)[8] reported impaired breeding and noted some maternal mortality in mice exposed to 2 mg/kg bw. In the studies of Sutou and Schroeder and Mitchener, females were also exposed to cadmium. The studies by Kotsonis and Klaassen (1978)[11] and Zenick et al. (1982)[15] used higher or comparable dose levels and exposure durations, but no effect on fertility was observed. Several other studies using lower dose levels or shorter exposure periods after which exposed males were mated, did not result in effects on fertility.

Several studies assessed the male reproductive organs and/or sperm parameters after oral exposure to soluble cadmium compounds. Studies in rats showed inconsistent results, with adverse effects mainly seen in studies with higher exposure levels. Generally, general toxicity was observed or information on general toxicity was lacking in these studies. Results in mice are more consistent as all reported studies showed effects on the testis or sperm parameters. However, the information on general toxicity in these studies is limited. The NTP studied the effect of 13-weeks of inhalation exposure to cadmium in rats and mice.[7] No effects on the reproductive organs were observed in mice. However, at the top concentration in rats, effects on sperm counts were

observed, but no microscopic changes of the testis. The general toxicity was limited and was related to the respiratory tract.

Studies using subcutaneous/intraperitoneal exposure also revealed effects of cadmium on the testis or sperm cells, at relatively low dose levels. These results deviate from the results after oral exposure that showed only effects at higher dose levels and prolonged exposure in some studies. This difference may be explained by the sequestration of cadmium in the liver after oral exposure (first pass effect). Since the intraperitoneal and subcutaneous exposure routes are not considered relevant, studies in which cadmium was administered via these routes are attributing less weight and can only be supportive, at most, for classification purposes.

Female fertility

Associations were reported between increased cadmium blood levels in women and long time-to-pregnancy and reduced fecundability (Buck Louis 2012)[73], and between female blood cadmium levels and a negative IVF outcome (Tulic 2018)[75]. Only the results in the study by Buck Louis et al. (2012)[73] were properly adjusted for co-exposures and other confounders, as well as for paternal variables.

Several animal studies assessed the effects on female functional fertility after oral exposure to cadmium. The combined results suggest that the effects are dose-dependent. Reductions in fertility were only observed at higher dose levels, also inducing maternal toxicity up to mortality. Several studies assessed the effects on the female reproductive organs or the oestrous cycle after oral exposure. Effects on the oestrous cycle were only observed at lethal dose levels. Effects on the ovary were reported in several studies at dose levels in the range of 1 to 43 mg/kg bw/day in the presence of general toxicity.

Other studies assessed the effects on the female reproductive organs, the oestrous cycle, or mating behaviour after a single subcutaneous exposure. Most studies showed effects on these parameters. However, as noted above, these exposure routes are not relevant and have limited value for the recommendation of a classification.

Three inhalation studies with cadmium by the group of Baranski showed a reduction in gestation index at 0.006 and 0.05 mg/kg bw/day and a decrease in fertility at 0.18 mg/kg bw/day.[45,46,90] However, the highest dose level also induced mortality. Furthermore, the effect on gestation was not reported in a repeat study. The percentage of females showing prolonged oestrous cycles was increased after exposure to 0.03 mg/kg bw/day. However, these studies have several limitations in reporting. Studies by the NTP (1995)[7] during 13 weeks according to OECD TG 413 showed increased oestrous cycle length without treatment-related histologic changes in the reproductive organs in rats but not in mice. The severity of the general toxicity was limited.

Conclusion

The Committee concludes that in several studies associations were found between cadmium exposure and adverse effects on fertility and cadmium exposure in men, and in one study, in women. The Committee considers these associations insufficient for classification in Category 1A.

The associations found in humans are consistent with both functional effects (in males and females) and effects on testis and sperm observed in animal studies. In these studies, general toxicity was observed or not specifically addressed. The Committee considers it likely that effects on fertility or sexual function in animals may occur in the presence of adverse effects on the kidneys (the critical organ in cadmium-induced toxicity).

It is unclear whether or not effects on fertility are a non-specific secondary effect of the general toxicity. No information is available regarding the mechanism for the effects on fertility and its relevance to humans.

Therefore, it is assumed that the observed fertility effects are relevant for humans. In line with CLP paragraph 3.7.2.2.3, the Committee recommends to classify for effects on sexual function and fertility in category 1B (presumed human reproductive toxicant) and to label with H360F (may damage fertility) based on the associations found between cadmium exposure and reduced sperm quality and reduced fertility in epidemiological studies, and effects on sexual function and fertility observed in animal studies for males and females. This proposal for classification relates to cadmium, cadmium carbonate, cadmium chloride, cadmium fluoride, cadmium hydroxide, cadmium nitrate, cadmium oxide, cadmium sulphate, and cadmium sulphide (See section 4.2 for an explanation of the selection of substances).

5.4 Adverse effects on development

Summary table of animal studies on adverse effects on development

Oral route

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Schroeder and Mitchener (1971)	Mouse, Charles River DC (N=5 pairs/group)	Continuous exposure in multi-generation study, continuous breeding	Cadmium chloride	0 or 10 mg Cd/L (equivalent to 0 or 2.1 mg Cd/kg bw) via drinking water	• 2 maternal deaths in treated F2 •	• Increased deaths before weaning (87/285 versus 2/687 in controls) in F1 and F2 • Increased number of animals with runts (34/285 versus 2/687 in controls) • Strain could not be bred beyond F2b-generation
Sutou et al. (1980)	Rat, Sprague-Dawley (N=14/group)	Administration to males and females for 6 w, during mating up to GD 20	Cadmium chloride	0, 0.1, 1.0, and 10 mg Cd/kg bw by gavage	Several signs of general toxicity at the highest dose: • Reduced food intake • Reduced body weight gain • Depilation, whitening of the incisors, salivation • Abnormal haematology	At 10 mg/kg bw: • Reduced foetal body weight and length • Anaemia and malnutrition foetuses • Increased placenta weight • Decreased numbers of implantation sites and live foetuses • Increased number of resorptions No malformations were observed
Zenick et al. (1982)	Rat, Sprague-Dawley, males (N=5/group)	Administration for 70-80 d in drinking water (corresponding to the time for transition of a spermatogonium to a mature sperm cell)	Cadmium chloride	0, 17.2, 34.4 or 68.8 mg Cd/L in drinking water (equivalent doses of 0, 0.7, 1.3, and 2.6 mg Cd/kg bw)	Reduced water intake in all exposed groups	No developmental effects were observed
Baranski et al. (1982)	Rat, Wistar (N=17-25/ group)	Administration from GD 7-16 of gestation. At GD 21, animals were sacrificed	Cadmium chloride	0, 2, 4, 8, 12 and 40 mg Cd/kg bw, by gavage	• Decreased body weight gain during pregnancy at all doses • Increased adrenal weight at ≥ 4 mg/kg • Reduced bw ≥ 8 mg/kg • Mortality (13/25) at 40 mg/kg	• At all doses: increased number of foetuses with delayed ossification • At 8 mg/kg and higher: Decreased foetal weight • At 20 and 40 mg/kg: effects on soft tissue morphology (subcutaneous haemorrhages, hydropericardium) • At 40 mg/kg: Reduced number of live foetuses per litter; increased number of resorptions per litter; increased number of foetuses with a lack of forelimbs and sirenomelia

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Baranski et al. (1983)	Rat, Wistar (number not specified)	Administration for 5 days/week, for 5 weeks, then during mating and gestation. One subgroup was sacrificed on GD 21 for the assessment of the foetuses, whereas another subgroup was allowed to deliver. At the age of 2 months, locomotor activity was assessed.	Cadmium chloride	0, 0.04, 0.4 and 4.0 mg Cd/kg bw by gavage	Paradoxically, no effects on survival were reported but some deaths in the highest dose group were noted	• No differences reported in average numbers of total implantations, corpora lutea, live foetuses, resorptions, foetal body weight • At 0.4 mg/kg: increased fraction of litters with foetuses with subcutaneous oedema • All treatment groups: Decreased locomotor activity of female offspring • At 0.4 and 4 mg/kg: Decreased locomotor activity of male offspring Data were not specified
Baranski (1985)	Rat, Wistar (N=18-6/ group)	Pregnant rats received cadmium from GD 7-16. Females were sacrificed and analysed on GD 21.	Cadmium chloride	0, 2, 12 and 40 mg Cd/kg bw by gavage	Reduced maternal bw gain at all doses	At 12 mg/kg and 40 mg/kg: • Reduced foetus weight At 40 mg/kg: • Reduced number of live foetuses per litter • Increased number of resorptions per litter
Baranski (1986)	Rat, Wistar (N=13/group)	Administration from day 1 to day 20 of gestation. Females were allowed to deliver and nurse their progeny until weaning at 28 days.	Cadmium chloride	0 and 60 ppm cadmium in drinking water (equivalent to 0 and 8.5 mg Cd/kg bw)	No information provided	• Reduced brain weight in 2-w old offspring • No effect on litter size, body weight at birth, body weight gain, viability, and food and water consumption in offspring • No change in performance of surface and air righting reflexes, negative geotaxis and forepaw suspension. • Reduced exploratory locomotor activity dependent on age and sex, reduced grooming activity in males, depressed avoidance acquisition.
Baranski (1987)	Rat, Wistar (N=13/group)	Administration from day 1 to day 20 of gestation	Cadmium chloride	0, 60 and 180 ppm cadmium in drinking water (equivalent to 0, 9.2 and 27.7 mg Cd/kg bw)	Reduced body weight gain and food/water intake	• No effect on implantations, corpora lutea, live foetuses, resorptions, and post-implantation loss • No gross malformations • At 60 and 180 ppm: Reduced foetal length and body weight
Whelton et al. (1988)	CF1 mice (N=10 and 100 respectively)	Administration via diet during 6 consecutive 42-d rounds of gestation-lactation. Diets sufficient and insufficient in vitamins were tested.	Cadmium chloride	0.25, 5.0 or 50 ppm cadmium (equivalent doses of 0.05, 1.0, and 10.4 mg Cd/kg bw for females, and 0.06, 1.1, and 11.4 mg Cd/kg bw for males). No control group was included.	No information provided	Results for sufficient diet, at 50 ppm (compared to 0.25 ppm): • 15% decrease in litter size • 25% decrease in pup growth at 50 ppm

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Sorell and Graziano (1990)	Rat, Sprague-Dawley (N=42-66/ group)	Administration: from GD1-20. At GD20, animals were sacrificed	Cadmium chloride	0. 5, 50 or 100 ppm in drinking water (equivalent to 0, 0.4, 4 or 8 mg Cd/kg bw)	Reduced body weight at 50 and 100 ppm	• No effect on litter size • Reduced body weight at 50 and 100 ppm
Andersson et al. (1997)	Rat, Sprague-Dawley (N=16/group)	From the day of partus (day 0), dams were exposed via drinking water and/or to PND 17, and/or during lactation until postnatal day 42	Cadmium chloride	5 mg/L cadmium in drinking water (equivalent to 0.70, 0.97, and 1.06 mg Cd/kg bw during the first, second, and third weeks of the lactation period for dams, and 0.8-1.2 mg Cd/kg bw in pups).	No effect on food/water intake and mean body weights,	• Increased levels of plasma nitrogen only in pups exposed post-weaning. • No obvious neuropathological effects. • Cortical serotonin levels were reduced in pups of all exposed groups • No effect on body weight offspring
Nagymajtenyi et al. (1997)	Rat, Wistar (N=5-10)	Administration: 5 d/w during pregnancy, lactation and 8 weeks after weaning for 3 generations (females 7 d/w from start mating until weaning). Investigations were performed at 12 w of age	Cadmium chloride	0, 3.5, 7.0 or 14.0 mg Cd/kg bw by gavage	No information provided	• No effects on pup body weights, no visible malformations and no clinical signs • 3.5 mg/kg and higher: open field exploration affected • 7 and 14.0 mg/kg: most behavioural and electrophysiological parameters; reduced bw in generation 2 and 3 • 14.0 mg/kg: reduced kidney and spleen weights in generation 3
Corpas and Antonio (1998)	Rat, Wistar (N=10)	Administration during gestation and early lactation until delivery and (5 days after parturition)	Not specified	10 mg/L in drinking water (equivalent to 1.13 mg Cd/kg bw according to the authors)	No information provided	At day 0 and PND 5: • Reduced pup, testicular and ovary weights • Decreased seminiferous tubule diameter and reduced number of prospermatogonia Reduced DNA/RNA ratio ovary and testis
Desi et al. (1998)	Rat, Wistar males (N=10)	Dams were treated according to three different treatment schedules: GD 5–15; GD 5–15 + 4 w of lactation; GD 5–15 + 4 weeks of lactation followed by the same oral treatment of male rats of the F1 generation for 8 weeks.	Cadmium chloride	0, 3.5, 7.0 or 14.0 mg Cd/kg cadmium by gavage	No visible clinical signs of chronic cadmium intoxication were found in any of the treated groups	• No (statistical significant) effect on litter size, new born body weight, malformations All treatment groups: • Reduced kidney weight; further not specified • Dose-dependent changes in electrocorticogram (not statistically significant) • Treatment GD 5-15, lactation and 8 weeks (at 14 mg/kg): • Statistically significant changes in electrocorticogram Treatment GD 5-15 and lactation (7 and 14 mg/kg): • Decreased horizontal ambulation; decreased rearing

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Salvatori et al (2004)	Rat, Wistar (N=10-12 group)	Administration from GD6 to GD14. One subgroup was sacrificed and analysed for effects on the foetuses. Another treatment subgroup and control group were allowed to give birth and pups were assessed for physical and reflex development at PND21.	Likely cadmium sulphate (cadmium chloride specified in M&M, results specified as cadmium sulphate)	0 and 20 mg Cd/kg bw by gavage	Decreased food consumption; however no effect on body weight	• No effect on number of implantation sites, number of resorptions, number of live foetuses/litter, number of corpora lutea, foetal weight and placental weight • reduced metacarpus ossification in 2 litters; reduced weight in these litters • Increased anomalies and malformations (cleft palate (23/126) and renal cavitation (10/62)) in all litters • Abnormal sexual behaviour in males and females
Kuriwaki et al. (2005)	Rat, Wistar (N=5/group)	Administration from GD9-19. Then, animals were sacrificed and organs and foetuses were collected.	Cadmium chloride	0, 1 and 10 mg Cd/kg bw by gavage (doses appear to relate to cadmium equivalents)	No information provided	• No effect on the number of foetuses • Reduced foetal liver weight
Ishitobi et al. (2005)	Mouse, C57BL/6J Jcl (N=6/group)	Administration from conception until PND10. Pups were left until PND21, subsequently, pups were separated and housed according to sex until PND70.	Cadmium chloride	0, 1 and 10 ppm Cd in the drinking water (equivalent to 0.2 and 2.0 mg Cd/kg bw)	No effect on body weight gain	• No effect on length of gestation, litter size, sex ratio, births weight, number of live births, stillbirths. • Non-statistically significant increase in postnatal deaths • Non-statistically delay in day of vaginal opening •
Jacquillet et al. (2007)	Rat, Wistar (N=6-7/group)	Administration during whole gestation period. Renal function was assessed from PND2-60	Cadmium chloride	0 and 0.5 mg Cd/kg bw by gavage	No information provided	• Reduced pup weight up to 6 days • Increased arterial pressure at PND21, PND45, and PND60 • Reduced glomerular filtration rate at PND60 associated with other signs of kidney toxicity
Ronco et al. (2009)	Rat, Wistar (N=6–9/group)	Administration during gestation, until GD20. Then, pups were delivered by caesarean section.	Cadmium chloride	0, 3, 15, 30, 50 ppm in drinking water (equivalent to 0, 0.5, 1.8, 3.9 and 5.3 mg Cd/kg bw, as specified by the authors)	No effect on body weight	• No differences in the offspring number, size and placenta's weight • At 50 ppm: decreased body weight at birth • At 50 ppm: Increased levels of corticosterone in dams (plasma and placenta; GD20) and offspring (plasma)

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Couto-Moraes et al. (2010)	Rat, Wistar (N=8 or 16/ group)	Administration on GD 18 and 21 and daily from the PND 1 to PND 7.	Cadmium chloride	0, 10 and 20 mg Cd/kg bw, by gavage	• 10 and 20 mg/kg: Reduced body weight gain during pregnancy in both treatment groups • 20 mg/kg: Reduced body weight gain during lactational period and reduced food consumption	• 10 and 20 mg/kg: Reduced pup weight and weight gain at PND1 and PND21 • 20 mg/kg: Reduced mean body length at PND1 and PND21 • 20 mg/kg: reduced anogenital index in pups and delayed physical and reflexes development
Samuel et al. (2011)	Rat, Wistar (N=18/group)	Administration on GD9-21. After birth, female pups were left with the mothers. After weaning, on PND10 and 21, pups were killed	Cadmium chloride	0, 50 and 200 ppm in drinking water (equivalent to 5.8 and 17.7 mg Cd/ kg bw)	Reduced water intake and final body weight Decrease gravid uterine weight	At 50 and 200 ppm: • Increased number of resorption sites • Effects on haematological parameters • Delayed pubertal onset • Oestrous cycle extended in metoestrus and dioestrus stage • Disruption of ovarian histoarchitecture At 200 ppm: • Reduced number of foetuses • Reduced number of implantation sites
Zhao et al. (2015)	Rat, Sprague Dawley (N=6/ group)	Male rats were administered cadmium, every 2 days for 9 weeks. Then, the animals were mated with unexposed females. Neuromotor maturation assessment was done on various days after partus	Cadmium chloride	0 and 22.15 mg $CdCl_2$/kg bw (13.6 mg Cd/kg bw, orally by gavage)	No information provided	Differences observed in various behavioural tests: • surface-righting reflex (PND3-9) • air-righting reflex (PND3-9) • Cliff avoidance (PND4,5,7 and 9) • negative geotaxis reflex (PND2-10)
Luo et al. (2015)	Rat, Sprague Dawley (N=10/group)	Pregnant rats were administered cadmium from GD0-21. Litter size and live pups were followed for 12 weeks	Cadmium chloride	0, 1, 5 and 10 ppm in drinking water (0, 0.089, 0.439, 0.955 mg Cd/kg bw)	No effect on maternal body weight	No effect on: • gestation length, number of pups or sex ratio • Physical development • Sperm parameters/oestrus cycle in offspring 5 and 10 ppm: • reduced body weight 10 ppm: • reduced liver and kidney weights
Mikolic et al. (2014)	Rat, Wistar (N=5-15/ group)	Pregnant rats were administered cadmium during 20 days of gestation. On day 20, animals were killed and analysed	Cadmium chloride hydrate	0 and 50 ppm cadmium in drinking water (equivalent to 7.5 mg Cd/kg bw, according to the authors)	No effect on maternal body weight	No effect on: • Foetal weight • Number of corpora lutea • Number of live or dead foetuses

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Tian et al. (2017)	Rat, Sprague-Dawley (N=not specified)	Rats were administered cadmium from GD0-PND21. At PND21, 35 or 56, F1 male rats were sacrificed and testes were removed and blood samples were collected.	Cadmium chloride	0, 1, or 5 mg Cd/kg bw by gavage	No data provided	• No effect on pup weight 1 mg/kg: • Reduced testis to body weight ratio at PND21 • Reduced levels steroid hormones at PND35 and 56 5 mg/kg: • Reduced testis to body weight ratio at PND21, 35 and 56 • Reduced levels steroid hormones at PND21, 35 and 56 •
Li et al. (2018)	Rat, Sprague-Dawley (N=12-14/ group)	Cadmium was administered from GD 0 to PND 21. F1 female rats were allowed to mate with to obtain the F2 generation	Cadmium chloride	0, 1, or 5 mg Cd/kg bw by gavage	Maternal survival not affected	No effect on pup weight 1 and 5 mg/kg: • Increased ratio of uterus to bw 5 mg/kg: • Increased ratio of ovary to body weight • Advanced day of vaginal opening and first oestrus F1 female offspring • Reduced number of primordial follicles; increased number of secondary follicles in F1 • Increased litter size

Other routes

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Parizek (1964)	Rats, Wistar substrain Konarovice (N=70; 12 controls)	Pregnant rats were injected at GD17-21. No further information was provided	Cadmium chloride	0 and 0.04 mmol/kg bw (4.5 mg Cd/kg bw) subcutaneously	No information provided	• Progressive placental changes, mainly in pars foetalis • Slight changes in pars maternal, slight oedema and hyperaemia • Haemorrhage into the uterine cavity, even by external bleeding • Interruption of pregnancy (either by delivery of the dead conceptus or resorption)
Ferm et al. (1968)	Golden hamsters (N=20/14 per group)	Pregnant hamsters were injected on GD8. Most animals were sacrificed at GD12.	Cadmium sulphate	0, 2 and 4 mg Cd/kg bw (no control group) intravenously	At >10 mg/kg: 100% mortality. No noticeable effect was apparent at a dose of 5-10 mg/kg	2 and 4 mg/kg: Various degrees of facial malformations, including cleft lip and complete palate clefts 2 mg/kg: • 248 embryos; 33 resorptions; 73 normal; 142 abnormal 4 mg/kg: • 190 embryos; 88 resorptions; 16 normal; 86 abnormal 5-10 mg/kg: Nearly 100% resorption

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Samarawickrama and Webb (1979)	Rat, Wistar-Porton	Cadmium was administered on different days of gestation (GD8-15). Animals were sacrificed on GD20.	Cadmium chloride	0, 1.1 and 1.25 mg Cd/kg intravenously	No information provided	1.1 mg/kg: No effects observed 1.25 mg/kg: Increased of resorptions, presence of abnormal foetuses, malformations (including hydrocephalus, an- and microphthalmia, gastroschisis and umbilical hernia).
Saltzman et al. (1989)	Rat, Wistar [Crl:(WI)BR] (N=4-8 group)	Groups of mated female rats received an injection of ~ 4.5 or 5.6 mg cadmium/kg bw on GD 12. Blood flow was determined 16-43 h later in placenta and uterus. Other groups were treated at PND 18. Animals were sacrificed were sacrificed on GD19/20.	Cadmium chloride	40 and 50 µmol/kg bw (equivalent to 4.5 or 5.6 mg Cd/kg bw) subcutaneously	No information provided	Administration at GD12 (4.5 mg/kg): • No adverse effects on foetal viability or growth • Reduced blood flow chorioallantoic placenta (-35%) at 16/18 h post-treatment; unaffected at 38-43 h. • No effect on foetal viability or growth Administration at GD12 (5.6 mg/kg): • No adverse effects on foetal growth; 12% foetal lethality (manifested as resorptions only) • 1 case of cleft palate Administration at GD18 (4.5 or 5.6 mg/kg): • Foetus lethality (manifested as resorptions and dead foetuses) at both doses (53 and 82%, respectively)
Pelletier and Satinder (1991)	Rat (Roman HighAvoidance (RHA), Roman Low Avoidance (RLA) and Satinder's Heterogeneous stock (SHS))(N=9/group)	Pregnant rats received injections once per day throughout gestation (GD 0-20). Animals were weaned and thereafter behavioural studies were performed at various endpoints	Cadmium chloride	0.075 mg Cd/kg bw and 0.225 mg Cd/kg bw subcutaneously	No effect on maternal weight gain and food consumption	• No effect on length of gestation, litter size at birth and weaning, foetal mortality and physical development • Abnormal results on behavioural tests
Soukupova and Dostal (1991a)	Mouse, ICR (N=?)	Pregnant mice were treated once during GD8-14. On GD18 animals were sacrificed and foetuses were analysed	Cadmium chloride	2, 4 and 6 mg Cd/kg bw subcutaneously (no control group included)	No information provided	At 6 mg/kg (compared to 4 mg/kg): • Increased mortality • Reduced thymus weight (2 mg group not analysed) Fraction of embryos with (right-sided) limb malformations appeared to be increased, Inconsistent findings of haemorrhagic bullae, exencephaly, cleft palate, open eyelids and tail deformities were reported (no apparent dose-response). No results of control group were provided.

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Soukupova and Dostal (1991b)	Mouse, ICR (N=4/group)	Pregnant mice were treated once on GD16. At the age of 4 w, proliferative responses of spleen cells were tested.	Cadmium chloride	2.5, and 5 mg Cd/kg bw subcutaneously (no control group included)	No information provided	At 3.1 mg/kg: • Increased lymphoproliferation response of spleen lymphocytes was in male offspring 4 weeks after birth At 1.5 mg/kg bw • Increased titre of haemaglglutination antibodies to sheep red blood cells in the offspring (both sexes)
Hartsfield et al. (1992)	Hamster, golden Syrian (N=10/group)	Pregnant animals were injected on GD 8. Foetuses were analysed at GD 15.	Cadmium chloride	0, 2 and 3 mg Cd/kg bw intravenously	Reduced bodyweight at 3 mg/kg bw	2 and 3 mg/kg bw: • Increased number of non-viable foetuses • Increased proportion of malformed foetuses (mainly neural tube defects and oral—facial clefts) • Decreased foetal weights • Decreased foetal crown—rump length
De et al. (1993)	Mouse, CD-1 (N=3-15/group)	Mice were injected on either GD 2 or GD 4, and killed either on GD 5 or GD 8 to examine implantation sites.	Cadmium chloride	0, 2.8 and 4.3 mg Cd/kg bw subcutaneously	No information provided	2.8 and 4.3 mg/kg bw; Injection at GD 2: • Reduction of number mice with implantation sites at GD 5, but not at GD 8 Injection at GD 4 • Reduced number of mice with implantation sites/implantation sites per uterus at GD 5 and GD 8 • Blastocyst degeneration at GD 5 •
Piasek and Laskey (1994)	Rat, Sprague Dawley (N=10-16/group)	Pregnant animals were injected on the day of dioestrus, or on GD 7 or 16. Dams and foetuses were analysed 24 h later.	Cadmium chloride	0, 3 and 5 mg Cd/kg bw subcutaneously	No effect on maternal body weight	No disruption of oestrous cyclicity; no effect on live implants, resorptions, and foetal weight
Paksy et al. (1996)	Rat, CFY (N=9-13/group)	Female rats were treated during oestrus or dioestrus and allowed to mate. Foetal outcome was assessed at GD 10, or post-natally up to day 21.	Cadmium chloride	0, 1.5, 3.1 and 6.1 mg Cd/kg bw subcutaneously	Reduced maternal body weight in all groups, dependent on treatment schedule	6.1 mg/kg: Reduced percentage of rats mated at 80 and 128h post-treatment 3.1 mg/kg: Reduced percentage of rats mated at 80h post-treatment No effect on litter number and weight, and fraction of males/females up to GD 21.

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Piasek et al. (2004)	Rat, Sprague-Dawley (N=6-16/group)	Pregnant rats were fed diet with either high or low iron level (240 or 10 mg/kg diet) and exposed to cadmium from GD 1-15 (subchronic study) or only at GD 15 (acute study). At GD 19 animals were killed and analysed.	Cadmium chloride	0, 3 and 5 mg Cd/kg bw subcutaneously	Reduced maternal body weight at 3 and 5 mg/kg in acute treatment group	High foetal mortality and placental destruction at 3 and 5 mg/kg in acute treatment group (not further quantified)
Nampoothiri and Gupta (2008)	Rat, Charles Foster (N=14/group)	Animals were treated during the gestational period, with pretreatment of 5 days prior to mating. At GD 19, animals were killed and analysed.	Cadmium acetate	0 and 0.024 mg Cd/kg bw subcutaneously	No effect on maternal body weight, no toxicity observed	Changes in implantation enzymes and steroidogenic enzymes of ovary and placenta, but no effect on: • Litter size • Number of dead/resorbed foetuses • Litter weight • Ovarian/placental weight
Lee et al. (2009)	Rat, F344 Fisher (N=10/group)	Pregnant rats were treated from GD 11-19 and were sacrificed on GD 20 and developmental parameters were assessed and placentas analysed.	Cadmium chloride	0, 0.2 and 2.0 mg Cd/kg subcutaneously	No information provided	At 0.2 and 2.0 mg/kg (dose dependent): • Decreased number of trophoblast cells • Increased resorptions and dead foetuses • Increased post-implantation loss • Reduced average foetal and placental weights • Changes in placental lactogens and genes involved in placental function • Chromosomal DNA fragmentation in the placental junctional zone
Wang et al. (2012)	Mouse, ICR (N=10/group))	Pregnant mice were injected on GD 9 and sacrificed on GD 18.	Cadmium chloride	0 and 2.8 mg Cd/kg bw intraperitoneally	No effect on maternal body weight gain	• Reduced placental weight and histological placental alterations • Increased markers of oxidative stress No effect on: • Number of implantation sites, resorptions per litter, live foetuses per litter and dead foetuses per litter
Del Diaz et al. (2014)	Rat, Wistar (N=10/group)	Pregnant rats were treated with a single injection at GD 4, 7, 10 or 15 and sacrificed at GD 20.	Cadmium chloride	0 and 10 mg Cd/kg bw intraperitoneally	Congestion, haemorrhages, inflammation and necrosis in livers, kidneys and lungs	In all treatment groups: • Reduced total implantations (except in the GD 7 group) • Increased total resorption/resorptions per dam • Skeletal malformations (including amelia, brachygnathia, omphalocele, cauda, and anotia) • Necrosis of the placenta

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Wang et al. (2014)	Rat, Sprague-Dawley (N=6-8/group)	Pregnant rats were exposed to cadmium from GD 5-19.On GD 20 animals were sacrificed and maternal-placental-foetal parameters linked to preeclampsia were evaluated.	Cadmium chloride	0, 0.25 and 0.5 mg Cd/kg bw intraperitoneally	At 0.5 mg/kg: • Decreased maternal body weight • Increased systolic blood pressure • Increased urine protein excretion	At 0.5 mg/kg: • Increased prenatal losses (due to resorption and/or stillbirth) • Reduced foetal body weight • Reduced litter size of and viable foetuses • Decreased foetal weight/placental weight ratio and crown rump length • Increased placental corticosterone production and maternal and foetal plasma corticosterone levels • Changes in expression of placental enzymes involved in corticosteroid synthesis
Zhang et al (2016a)	Rat, Wistar (N=5/group)	Pregnant rats were injected on GD 9-14. Urine protein was measured on GD 3-19, systolic blood pressure from GD 0 to PND 6. For evaluation of the foetuses and placenta, dams were sacrificed at GD 21.	Cadmium chloride	0 and 0.125 mg Cd/kg intraperitoneally	• Increased systemic blood pressure • Histopathological lesions of the kidney and proteinuria	• Damage to placenta and decidua • Reduced foetal weight Decreased crown-rump length
Zhang et al. (2016b)	Mouse, ICR (N=12/group)	Pregnant mice were injected on GD8. On GD 18, the dams were sacrificed on GD18 and live, dead and resorbed foetuses were counted and Placentas were collected for histological examination.	Cadmium chloride	0, 1.5 and 3.1 mg Cd/kg intraperitoneally	No effect on maternal body weight gain	No effect on litter size, live foetuses, and resorptions At 3.1 mg/kg bw: • Increased number of dead foetuses per litter At 1.5 and 3.1 mg/kg bw: • Reduction in foetal weight and crown-rump length • Increased number of neural tube defects • Reduced placental weight, diameter, and blood sinusoids
Zhang et al. (2016c)	Rat, Sprague-Dawley (N=8-10/group)	Pregnant rats were injected on GD 4-19. Systolic blood pressure was monitored on GD 3, 11, and 18. On GD 20, rats were sacrificed and tissues were collected.	Cadmium chloride	0, 0.25 and 0.5 mg Cd/kg intraperitoneally	At 0.25 and 0.5 mg/kg: • Increased urine protein levels At 0.5 mg/kg: • Decreased maternal body weight • Increased systolic blood pressure At 0.25 mg/kg (0.5 not assessed): • Morphological changes in kidney	At 0.25 and 0.5 mg/kg: • Reduced number of live foetuses At 0.5 mg/kg: • Increased number of dead foetuses • Decreased foetal weight At 0.25 mg/kg (0.5 not assessed): • Morphological changes in placenta • Increased markers of oxidative stress in placenta

Reference	Investigated species	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Li et al. (2018)	Rat, Sprague-Dawley (N=6/group)	Dams received a single injection on GD 12. On GD 20, animals were sacrificed and the testes of the male foetuses were weighed and analysed.	Cadmium chloride	0, 0.25, 0.5, and 1.0 mg Cd/kg intraperitoneally	No effect on maternal bodyweight	At 0.25 and 0.5 mg/kg (but not at 1.0 mg/kg): • Decreased foetal bodyweight At 0.25 and 0.5 mg/kg: • Reduced testosterone levels • Reduced number of Leydig cells

Inhalation route

ref	Investigated species and sex	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Baranski (1983; 1984; 1985)	Rat, Wistar (N=17-28/group)	Female rats were exposed for 5 h/d, 5 d/w for 5 months (high dose group for 4 months), during mating and from GD 1-20. Toxicity to the foetuses was assessed at GD 21. Remaining animals were allowed to deliver offspring, on which behavioural tests were performed at various at different time points after birth.	Cadmium oxide	0, 0.02, 0.16, 1.0 mg Cd/m^3 (equivalent to 0, 6, 48 and 300 µg Cd/kg bw bw)	At 1.0 mg/m^3: Mortality (55.1% vs 6.5% in control group)	• No foetal mortality or malformations At 0.02 and 0.16 mg/m^3: • Retarded ossification • Decreased exploratory motor activity in males • Reduced avoidance acquisition in both males and females At 0.16 mg/m^3: • Reduced pup viability on PND 4 • Reduced bw gain after birth • Decreased exploratory motor activity in males and females • Impaired open field-behaviour in males
NTP (1995)	Rat, Sprague-Dawley (N=26-30/group)	Pregnant rats were exposed for 6 h/d, 7 d/w days per week, on gestation Day 4 through 19.	Cadmium oxide	0, 0.044, 0.44 or 1.75 mg Cd/m^3 (equivalent to 0, 0.008, 0.08, and 0.34 mg Cd/kg bw)	At 1.75 mg/m^3: Decreased body weight Dyspnoea and hypoactivity	No effect on foetal mortality, resorptions, litter size At 1.75 mg/m^3: • Reduced foetal bw • Reduction of skeletal ossifications •
NTP (1995)	Mouse, Swiss (CD-1) (N=32-4/group)	Pregnant rats were exposed for 6 h/d, 7 d/w days per week, on gestation Day 4 through 17.	Cadmium oxide	0, 0.044, 0.44 or 1.75 mg Cd/m^3 (equivalent to 0, 0. 0.014, 0.14, and 0.59 mg Cd/kg bw)	At 1.75 mg/m^3: Decreased body weight Decreased gravid uterine, liver, and kidney weights Dyspnoea, hypoactivity, Lower pregnancy rate (30% vs. 97% in the control group).	At 0.44 and 1.75 mg/kg: • Reduced foetal body weights At 1.75 mg/m^3: • Reduced fraction live male foetuses • Increased total resorptions/litter

ref	Investigated species and sex	experimental period and design	Substance	Dose and method of administration	Maternal toxicity	developmental toxicity
Jacobo-Estrada et al. (2016)	Rat, Wistar (numbers not specified)	Pregnant rats were exposed during GD 8–20 to cadmium chloride mist. On GD 21, dams were euthanized, markers for kidney toxicity were quantified in amniotic fluid samples and foetal kidneys were examined.	Cadmium chloride	0 and 17.43 mg/m^3 (equivalent to 0 and 1.48 mg Cd/kg bw (specified by the authors)	No effect on weight gain No effect on liver and kidney weights	• No effect on number of foetuses per litter • No malformations • No effect on kidney, liver or placental weight • Reduced foetal bw • Increased kidney injury biomarkers; histological tubular damage and precipitations in the renal pelvis •

5.4.1 Animal studies

Oral exposure

Schroeder and Mitchener (1971)[8] conducted a multigeneration reproduction study with CD mice in which cadmium was offered continuously in the drinking water at a level of 10 mg/L (an equivalent dose of 2.1 mg/kg bw/d[a]). An increase in young deaths and in number of runts were observed in F1 and F2.

Sutou et al. (1980)[13,14] administered 0, 0.1, 1.0 or 10 mg cadmium/kg bw/day for 6 weeks by gavage to groups of 14 female and 14 male Sprague-Dawley rats, after which they were mated. Exposure continued during mating and gestation up to GD 20, when the females were sacrificed. Adverse effects were observed in the 10 mg/kg group on foetal body weight and length; the foetuses were anaemic and malnourished, and the placenta weight was increased. Numbers of implantation sites and live foetuses were decreased, and the number of resorptions was increased in the 10 mg group. No malformations were observed. The females of the mid and high dose groups showed mild to overt signs of toxicity. The treated males also mated with untreated females which showed no effects upon sacrifice. Untreated female Sprague-Dawley rats were mated to males, previously exposed to 0, 17.2, 34.4 or 68.8 mg cadmium/L in drinking water (equivalent to 0, 0.7, 1.3, and 2.6 mg/kg bw/d[b]). (Zenick et al., 1982)[15] Some females were sacrificed on GD 20. No adverse effects were observed. The other females were allowed to litter; the resulting offspring was followed for general and behavioural changes, which were not detected.

Baranski et al. (1982)[91] administrated cadmium (0, 2, 4, 8, 12, 20 and 40 mg/kg bw/d) by gavage to pregnant Wistar rats, from day 7 to day 16 of gestation. Body weights were measured on day 1 and day 21 of gestation. On day 21, pregnant rats were euthanized and organs were collected.

[a] Assuming a body weight of 35 gram, and a calculated 7.3 mL water intake/day

[b] Calculated based on a mean water intake of 15 mL (derived from graph) and mean body weight estimated on the weights reported in the publication

The number of corpora lutea was counted and the number of live foetuses, dead foetuses, and early and late resorption sites were recorded. All doses of cadmium caused a decrease in body weight gain of rats from day 1 to day 21 of pregnancy. From doses of 2 mg/kg bw/d and higher, delayed ossification was observed. Foetal body weight was reduced at doses 8-40 mg/kg bw. At the highest dose, the number of live foetuses was decreased and the number of resorptions per litter was increased. Effects on gross external and soft tissue morphology of foetuses were observed at the two highest doses. Decreased maternal body weight gain was observed at all doses, whereas absolute body weight was decreased at 8 mg/kg bw and higher. The highest dose resulted in maternal deaths.

Baranski et al. (1983)[16] also exposed female rats to cadmium by gavage (0, 0.04, 0.4, and 4 mg cadmium/kg bw) for 5 days/week for 5 weeks before, and throughout gestation. At gestation day 21, animals were divided in two subgroups. One group was sacrificed and foetuses were analysed while another group was allowed to deliver progeny. After two months, locomotor activity was measured in the offspring. No effect on survival of the F0 females was noted, however some mortality in the highest dose group was also mentioned. No effect on the number of resorptions was found, also foetal length and body weight, and placental weight was similar in all treatment groups. No malformations were reported, however, at 0.4 mg cadmium/kg bw an increase in foetal subcutaneous oedema was noted. At all doses, a reduction of locomotor activity at 2 months in females was observed. In males, this was observed at the two highest doses.

In another publication, Baranski (1985)[46] reported results of a study in pregnant rats exposed to 0, 2, 12 or 40 mg/kg bw from GD 7-16. Animals were sacrificed at GD 21. A reduced body weight was noted at all doses. At 12 and 40 mg/kg bw/d, the foetus weights were reduced. At the highest dose, the number of live foetuses per litter was reduced and the number of resorptions per litter was increased.
In another study, Baranski (1986)[92] administered cadmium in drinking water (0 and 60 ppm cadmium; equivalent to 0 and 8.5 mg/kg bw/d[a]) to pregnant rats from day 1 to day 20 of gestation. Females were allowed to deliver and nurse their progeny until weaning at 28 days. Litter size was not affected, and body weight at birth, body weight gain, viability, and food and water consumption in the control group and the exposure group were similar. The absolute weight of the whole brain was reduced, and ratio liver weight/body weight was increased in 2-w old male offspring, absolute weights of liver and kidneys were not affected. Prenatal exposure to cadmium led to changes in several parameters in behaviour tests.
In a follow up study, Baranski (1987)[90] administered cadmium at levels of 0, 60 and 180 ppm drinking water (equivalent to 0, 9.2 and 27.7 mg

[a] Assuming a body weight of 175 g, and a calculated 24.8 mL water intake/day.

cadmium/kg bw/d[a]) from day 1 to day 20 of gestation. The female rats were sacrificed on day 21 of gestation. Increased cadmium intake with drinking water containing 60 and 180 ppm cadmium did not affect the survival of pregnant rats. Body weight gain and daily food and water intake were reduced. The average numbers of live and dead foetuses, resorptions, and postimplantation losses were not different in cadmium-treated and control groups. The haematocrit was reduced in foetal blood in the 60-ppm cadmium group. The foetal body weight and length were decreased in both groups though litter size was not affected.

Female CF1 mice were bred for 6 consecutive generations. (Whelton et al., 1988)[93] During rounds of gestation-lactation, both females and males were exposed via the diet to levels of 0.25, 5.0 and 50 mg cadmium/kg food (equivalent doses of 0.05, 1.0 and 10.4 mg/kg bw/d, and 0.06, 1.1 and 11.4 mg/kg bw/d, respectively[b]). No control group was included. The highest dose had no effect on fertility or pup survival during lactation, but caused a 15% decrease in litter size at birth and a 25% decrease in pup growth.

In a study by Sorell and Graziano (1990)[94], rats were exposed to 0, 5, 50, or 100 ppm cadmium in the drinking water (equivalent to 0, 0.4, 4 or 8 mg/kg bw/d[c]) on days 6 through 20 of pregnancy. In comparison to controls, foetal and maternal weights were slightly reduced in the 50- and 100-ppm groups, but not in the 5-ppm group. Average litter size was not affected.

Andersson et al. (1997)[95] administered cadmium in the drinking water (5 mg/L[d]) to female Sprague Dawley rats during the lactation period, from parturition to postnatal day 17, and/or to the offspring until PND 42. Mean body weights of the dams and offspring, food and water intake were comparable to controls. Relative weights of liver, kidney and brain were comparable as well. Plasma urea nitrogen levels in rats exposed to cadmium postweaning were significantly higher than in the control group, whereas exposure during lactation and postweaning did not induce differences. No obvious neuropathology was observed after cadmium exposure. Exposure to cadmium during lactation as low as 5 mg/L in drinking water resulted in neurochemical disturbances of the serotonergic system in offspring.

Three consecutive generations of Wistar rats were orally (gavage) treated with 0, 3.5, 7.0 and 14.0 mg cadmium/kg bw over the period of gestation, lactation and 8 weeks after weaning. (Nagymajtenyi et al., 1997)[96] Behavioural tests were performed in male rats from each generation at the age of 12 weeks. Main results of the behavioural tests were changed in vertical exploration activity (rearing) and increased exploration of an open field centre. The spontaneous and evoked electrophysiological variables

[a] Based on a starting body weight of 195 g, and a calculated 26.9 mL water intake/day.
[b] Calculated based on starting weights (F0) of 25 g (females) and 29 g (males), and calculated feed intakes of 5.2 g (females) and 5.7 g (males).
[c] Assuming a body weight of 175 g and a water intake of 24.8 mL
[d] Equivalent to 0.70, 0.97, and 1.06 mg cadmium/kg body weight during the first, second, and third weeks of the lactation period for dams, and 0.8-1.2 mg/kg bw in pups, according to the authors.

showed dose-and generation dependent changes. In most tests, the 3.5 mg/kg bw group was not affected. Treatment with the mid- and high-dose resulted in significantly lower body weights. Pup body weights were comparable to those in the control groups and there were no visible malformations. In the F3-generation reduced relative kidney and spleen weights were observed in the high-dose group.

Corpas and Antonio (1998)[97] exposed Wistar rats to cadmium (10 mg/L; equivalent to 1.13 mg/kg bw/d, according to the authors) via drinking water during gestation, or during early lactation (from delivery until postnatal day 5). Pups exposed in utero were sacrificed on day 0. Pups exposed during early lactation were sacrificed on postnatal day 5. Pup weight, testicular and ovary weight were recorded at necropsy. Furthermore, seminiferous tubule diameter and number of prospermatogonia in the testis of the pups were measured. On postnatal day 5, ovary and testis weights were reduced in the cadmium-treated pups. In addition, seminiferous tubule diameter and number of prospermatogonia were reduced and a reduced DNA/RNA ratio was observed in ovary and testis of the cadmium-treated pups on day 0 and postnatal day 5.

Female Wistar rats were given orally (gavage) 0, 3.5, 7.0 or 14 mg cadmium/kg body weight 3 different treatment regimens: (I) GD 5-15, (II) GD 5-15 and 4 weeks postnatally or (III) GD 5-15, 4 weeks postnatally followed by the same treatment of male rats of the F1-generation for 8 weeks. (Desi et al., 1998)[98] Behavioural tests were performed in F1-males at the age of 12 weeks. The number of pups/litter was slightly lower and the pup weights were slightly (not significantly) decreased in the high dose group. Body weight gain of the male offspring was comparable to the control group. At necropsy kidney weights of all treatment regimes were decreased. Behavioural changes were observed in the 7 and 14 mg/kg group in the groups exposed during gestation and lactation. Dose-dependent changes in electrocorticogram were seen in pups from all treatment groups, but were only statistically significant at the highest dose in the treatment group which included the postweaning period.

Salvatori et al. (2004)[99] administered 0 and 20 mg/kg bw to pregnant rats from GD 6 to GD14. One subgroup was sacrificed after treatment and analysed for effects on the foetuses. Another treatment subgroup and control group were allowed to give birth and pups were assessed for physical and reflex development at PND 21. Cadmium-treatment decreased food consumption, however no effect on body weight was measured. Treatment had no effect on number of implantation sites, number of resorptions, number of live foetuses/litter, number of corpora lutea, foetal weight, and placental weight. However, reduced metacarpus ossification was observed in 2 litters together with a reduced weight of these litters. In addition, an increase in malformations (cleft palate and renal cavitation) was observed.

In a study by Kuriwaki et al. (2005)[100], female rats were treated with 0, 1 or 10 mg cadmium/kg bw from GD 9-19. Then, animals were sacrificed and organs and foetuses were collected. Cadmium exposure had no effect on the number of foetuses. A reduced foetal liver weight was reported.
Ishitobi et al. (2005)[101] studied the effects of lower level cadmium exposure on the reproductive organs of female offspring. Mice were exposed to 0, 1 and 10 ppm cadmium in the drinking water (0, 0.2 and 2.0 mg/kg bw/d) from conception to 10 days after birth. Subsequently, littermates were separated and housed according to sex until PND 70. No effects were observed on litter size, sex ratio, birth weight, livebirth, and stillbirth. An increase in deaths after birth and a delay in vaginal opening were also reported (not statistically significant).

Jacquillet et al. (2007)[102] administered cadmium (0.5 mg/kg bw/d) to pregnant rats during the whole gestation period. After birth, pups were assessed for renal dysfunction up to PND 60. A reduced pup weight was observed up to 6 days whereas an increased arterial pressure was measured at PND 21, PND 45, and PND 60. A reduced glomerular filtration rate, associated with other signs of kidney toxicity, was observed at PND60.

Ronco et al. (2009)[103] administered 0, 3, 15, 30, 50 ppm in drinking water (equivalent to 0, 0.5, 1.8, 3.9 and 5.3 mg/kg bw, as specified by the authors) to pregnant rats until gestation day 20. Then, pups were delivered by caesarean section and analyses were performed.
No differences between groups were observed in maternal body weight, offspring number and size, and placenta's weight. In the highest dose group, a decreased offspring body weight at birth was reported. Also increased levels of corticosterone were measured in both dams (plasma and placenta) and offspring (plasma).

Couto-Moraes et al. (2010)[104] administered cadmium (0, 10 and 20 mg/kg bw) by gavage to rats during pregnancy (at GD18 and 21) and during lactation (daily from PND 1-7). In both treated groups, a reduced body weight gain during pregnancy was observed. At the highest dose, body weight gain was also reduced in the lactational period. At 10 and 20 mg/kg bw, pup weight and weight gain were reduced at PND 1 and PND 21. At 20 mg/kg bw only, mean body length was reduced and physical and reflex development was affected.

Samuel et al. (2011)[105] exposed female rats to cadmium through drinking water at concentrations of 0, 50 or 200 mg/L (equivalent to 5.8 and 17.7 mg/kg bw/d[a]), from embryonic day 9 to 21. Gravid uterine/body weights were decreased in both treatment groups. The number of foetuses and the number of implantation sites were decreased at the highest exposure level, and the number of resorption sites was increased at both 50 and 200 mg/L

[a] Calculated based on drinking water intake and mean body weight specified by the authors.

exposure groups. Haematological analyses in rat pups showed increased numbers of red blood cells, and a reduction in haematocrit and mean corpuscular volume at both doses of cadmium studied, while a reduced haemoglobin level and an increased mean corpuscular haemoglobin concentration was observed only in the 200 ppm cadmium treatment group. A disrupted ovarian histoarchitecture, an extended oestrous cycle, and delayed pubertal onset was reported in both treatment groups.
Zhao et al. (2015)[27] exposed male rats to cadmium (13.6 mg/kg) by gavage, every two days for 9 weeks in total. Animals were allowed to mate and subsequently, the nervous system development of the offspring was studied on different days after partus. The cliff-avoidance reflex, surface-righting reflex and negative geotaxis results showed differences between the cadmium-exposed and control groups.

Luo et al. (2015) studied the effects of low doses administered orally in offspring during pregnancy and lactation in rats.[106] Females rats were allowed to mate, pregnant rats were divided in groups receiving either 0, 1, 5 or 10 mg/L (0, 0.09, 0.44 or 0.96 mg/kg bw/d, respectively (doses calculated by the authors)). From PND 21, pups of all groups received distilled water. The body weight gains of the rats were not different between the treatment groups, nor did the reproductive parameters differ (including gestation length, number of pups and sex ratios). There was no maternal mortality, and there were no apparent clinical signs of toxicity in either male or female offspring after birth. The body weights of the offspring exposed to 5 or 10 ppm cadmium during pregnancy and lactation were significantly lower than in the control group until postnatal week 12. Also the absolute weights of some organs were decreased in males and females at the highest dose group. The only relative reduction in organ weight was reported for kidney and liver, in females exposed to 10 ppm cadmium. Tests on various physical developmental parameters did not show differences between the exposed groups and the control group. Also sperm counts, motility, and incidence of abnormal sperm observed in males, nor the oestrous cycle in females differed between cadmium exposed animals and control animals.

Mikolic et al. (2014)[107] administered cadmium via drinking water (50 ppm, equivalent to 7.5 mg/kg bw/d[a]) to pregnant rats during 20 days of gestation. On GD 20, animals were killed and analysed. Cadmium treatment had no effect on maternal body weight. Foetal weight, the number of corpora lutea and the numbers of live or dead foetuses did not differ between the cadmium-exposed group and the control group.

Tian et al. (2018)[108] administered either 0, 1, or 5 mg/kg bw by gavage, from GD 0 to PND 21. At PND 21, 35 or 56, F1 male rats were sacrificed and testes were removed and blood samples were collected. The authors noted that there were no differences in body weights of rats with different

[a] As specified by the authors

treatments at PND 21, 35, and 56. The ratio of testis to body weight was reduced at the middle dose (at PND 21) and the highest dose (at PND 21, 25 and 56). In addition, serum steroid hormone levels were reduced and the development of Leydig cells appeared delayed.

Li et al. (2018)[109] studied the effect of cadmium exposure on the reproductive development in rats for two generations. Cadmium was administered to the F0 from GD 0 to PND 21 at doses of 0, 1 or 5 mg/kg bw/d. According to the authors, survival was unaffected and no mortality or deformity was observed (no data provided). F1 female rats were allowed to mate with to obtain the F2 generation. There was no difference in body weight of offspring with different treatments at PND 21, 35 and 56. The days of vaginal opening and first oestrus were advanced in F1 female offspring with maternal exposure (to 5 mg/kg bw/d), not in F2 female offspring. The ratio of uterus to body weight was increased, both in offspring of the 1 mg/kg group (at PND 35 and PND 56) and the 5 mg/kg group (at PND 21, 35 and 56). The ratio of ovary to body weight was only increased in offspring of the highest dose group, and only at PND 56. In the F1 generation, the number of primordial follicles was reduced and the number of secondary and antral follicles was increased at PND 21, 35 and 56. The increased number of antral follicles eventually caused a big litter size. In the F2 females, the number of primordial follicles was reduced and the number of antral follicles was increased, only at PND 21. No differences in total follicle numbers were observed for F1 and F2 at any time point.

Subcutaneous, intraperitoneal and intravenous exposure

Parízek (1964)[110] studied the effects in rats of cadmium on the placenta after injection of 4.5 mg/kg bw/d between GD 17 and 21. Subcutaneous injection of cadmium resulted in all cases in rapidly progressive placental changes, chiefly in the pars foetalis, which was completely transformed within 24 hours into an extensive blood clot with little remaining necrotic tissue. In most cases the placental changes were accompanied by haemorrhages into the uterine cavity and were found within 6 hour after cadmium injection. Complete destruction of the pars foetalis resulted in interruption of pregnancy, with either delivery of the dead conceptus or resorption.

Ferm et al. (1968)[111] studied the effects of intravenous injection of cadmium (2 and 4 mg/kg bw) to pregnant golden hamsters on GD 8. Animals were killed on GD 12. The number of embryonic resorptions and malformed foetuses was increased in the cadmium-treated groups. The observed malformations concerned various degrees of facial malformations, including cleft lip and complete palate clefts). Data on higher doses were not specified, but the authors noted that maternal animals injected with >10 mg cadmium/kg bw all died shortly after injection. Furthermore, cadmium levels from 5-10 mg induced foetal resorption rates of almost 100% without noticeable effect on the mothers.

Groups of 15 pregnant Wistar-Porton rats received a single intravenous injection of 1.1 or 1.25 mg cadmium/kg body weight between GD 9-15. (Samarawickrama and Webb, 1979)[112] Animals were sacrificed on GD 20. No effects were observed after administration of the low dose; the effects of the higher dose depended on, amongst others, the moment of injection: the later exposed, the stronger the increase of resorptions and the larger the decrease in number of abnormal foetuses (no results of a control group were specified). The observed malformations included hydrocephalus, an- and microphthalmia, gastroschisis and umbilical hernia.

Groups of 4 to 8 mated female Wistar rats [Crl:(WI)BR] received a subcutaneous injection of ~ 4.5 or 5.6 mg cadmium/kg bw on GD 12 or GD 18.(Saltzman et al. 1989)[113] Blood flow was determined 16-43 h later in placenta and uterus. Other groups were treated at PND18. Animals were subsequently sacrificed on GD 19 or 20. A reduced blood flow in the chorionallantoic placenta was measured 16-18h after administration of 4.5 mg/kg at GD 12. No foetal changes were inflicted in the lowest dose group on GD 12. Administration on GD 18, this dose resulted in resorptions; the highest dose group resulted on GD 12 in foetal lethality, and on GD18 both foetal lethality and a decreased foetal body weight. Malformations were not observed, apart from 1 case of cleft palate in the 5.6 mg/kg on GD 12 group.

Pelletier and Satinder (1991)[114] studied the effects of daily subcutaneous injection of 0.075 or 0.225 mg cadmium/kg bw during gestation in 3 genetic lines of rats: Roman High Avoidance (RHA), Roman Low Avoidance (RLA) and Satinder's Heterogeneous stock (SHS). Maternal body weight gain, food consumption, length of gestation, litter size at birth and weaning, foetal mortality and physical development were not affected by cadmium treatment. Cadmium-exposed progeny from the RHA line weighed significantly less than control RHA progeny (PND 41-44); however, SHS progeny of the low-dose group weighed significantly more than progeny from any other group (PND 14-44). Unconditioned response level (UER) was determined on PND 39 and acquisition of conditioned avoidance responses was tested from PND 41-44. Effects on behaviour were observed in the high dose group.

Soukupova and Dostal (1991a)[115] administered a single subcutaneous dose of 0, 2, 4 or 6 mg cadmium/kg bw to random bred ICR mice (number not specified) on GD 8, 9, 10, 11, 12, 13 or 14. The embryolethal effect was highest after treatment with 6 mg/kg on GD 12 and 13 (50.0 and 61.3%, respectively), mortality of a control group was not specified. Among surviving animals, foetuses with haemorrhagic bullae, limb malformations, exencephaly, cleft palate, open eyelids and tail deformities occurred. Mainly right-sided limbs were malformed. Foetal weight was only reduced in the 6 mg group dosed on GD 12. Reduction of the foetal thymus weight was observed in the 6 mg group dosed from GD 9-14.

Soukupova et al. (1991b)[116] exposed mated random bred ICR mice, subcutaneously, to 0, 1.5 or 3.1 mg cadmium/kg body weight on GD 16 and tested the immune response of the offspring at an age of 4 weeks. At 3.1 mg/kg bw, the lymphoproliferation response of spleen lymphocytes was increased in male offspring 4 weeks after birth. The titre of haemogglutination antibodies to sheep red blood cells in the offspring (both sexes) was increased in the 1.5 mg/kg-group, at 4 and 8 weeks after birth.

Hartsfield et al. (1992)[117] injected pregnant Syrian golden hamsters intravenously with 0, 1.2 or 1.9 mg cadmium on GD 7. Animals were sacrificed on GD 14 and foetuses were weighed and examined for viability and external malformations. Maternal body weight of the 1.9 mg/kg bw treatment group was reduced. In both dose groups, an increased number of non-viable foetuses, an increased proportion of malformations (mainly neural tube defects and oral-facial clefts), a decreased foetal weight, and a decreased foetal crown-rump length were observed.

De et al. (1993)[118] studied the effects of cadmium exposure during the preimplantation period of pregnancy on the development and implantation of mouse embryos. CD-1 mice were injected with 0, 25 or 38 µmol cadmium/kg body weight (~0, 2.8 or 4.3 mg cadmium/kg bw) on GD 2 resulted in a reduction of mice with implantation sites at GD 5, but had little effect on the number of implantation sites at GD 8. At examination of groups treated on GD 4, a reduction of animals with implantation sites was observed at GD 5 and GD 8 (total absence of mice with implantation sites was noted at the highest dose). Furthermore, blastocyst degeneration assessed at GD 5 amounted to 30 and 80% of blastocysts at doses of 2.8 and 4.3 mg kg/bw, respectively.

Piasek and Lasky (1994)[38] injected female Sprague-Dawley rats subcutaneously on the day of dioestrus, or on day 7 or 16 of gestation with a single dose of 0, 3, or 5 mg cadmium/kg bw and evaluated 24h later. No general toxic effects, no disruption of oestrous cyclicity, and no change in foetal viability were seen. Histologic evaluation revealed moderate cadmium-related thecal congestion in the ovaries at GD 8 (ovaries were not evaluated at GD 17).

Paksy et al. (1996)[41] treated female CFY rats, having regular ovarian cycles, with 0, 1.5, 3.1 or 6.1 mg/kg cadmium on the day of the oestrus or dioestrus. After 32, 80 or 128 h post-treatment animals were mated. Foetal outcome was assessed at GD 10, or postnatally up to day 21. At the highest dose, a reduced maternal body weight was observed in the 80 and 128 h-post treatment groups at GD 10. The percentage of rats mated was reduced at doses of 3.1 mg/kg bw (80 h post-treatment) and 6.1 mg/kg (80 and 128 h post-treatment). No treatment-related effect was observed on the number of litters, litter weight, or the rate of males and females up to GD 21.

Piasek et al. (2004)[119] studied the effect of iron deficiency combined with cadmium exposure on development of offspring in Sprague-Dawley rats. Rats were fed diets with either high iron (240 mg/kg food) or low iron (10 mg/kg). Animals were exposed to cadmium (0, 3 and 5 mg/kg bw from GD 1-15 by a subcutaneously implanted mini pump (subchronic study) or a single subcutaneous injection at GD 15 (acute study). Animals were killed at GD 19 and foetuses, selected organs and blood were analysed. Maternal body weight, maternal and foetal liver weights, and placental weights were reduced in the low iron group. Acute cadmium exposure caused lower maternal body weight and organs weights, decreased foetal weights and high foetal mortality in both high and low iron groups.

Nampoothiri and Gupta (2008)[120] treated female Charles Foster rats subcutaneously with 0 or 0.024 mg cadmium/kg bw during the gestational period (GD 11-19), with a pretreatment of 5 days prior to mating. Animals were sacrificed on GD 20 and developmental parameters were assessed and placentas analysed. No maternal toxicity was noted. Differences in implantation and steroidogenic enzymes were measured, however no differences in reproductive performance (litter size, number of dead/ resorbed foetuses, litter weight, ovarian weight and placental weight) were observed.

In a study by Lee et al. (2009)[121], pregnant F344 rats were injected subcutaneously with 0, 0.2, and 2.0 mg/kg bw/day of cadmium from days GD 11-19, and sacrificed on GD 20. A decrease in placental and foetal weights and a decrease in the number of live foetuses were observed, while the numbers of resorptions, dead foetuses, and post-implantation losses were increased in the cadmium-treated groups compared to the control group. Furthermore, the authors reported transcriptional and cellular abnormalities in the placental junctional zone of cadmium treated animals.

Wang et al. (2012)[122] injected pregnant ICR mice intraperitoneally with cadmium (4.5 mg/kg) on GD 9 and sacrificed the animals on GD 18. No effect on maternal body weight gain was noted, and the number of implantation sites, resorptions per litter, live foetuses per litter and dead foetuses per litter did not differ between treated animals and controls. Experiments involving biochemical analyses of the placenta revealed a reduced placental weight, histological placental alterations and increased markers of oxidative stress.

Del Díaz et al. (2014)[123] studied analyse the effect of a single cadmium dose (10 mg/kg bw, intraperitoneally) administered at GD 4, 7, 10 or 15 on the offspring of pregnant Wistar rats. Animals were sacrificed on GD 20. Maternal uteri, livers, kidneys and lungs, and foetuses were examined at necropsy. In all treatment groups, similar results were found. In the dams, circulatory disturbances were observed in all organs (mainly congestion and haemorrhage). Histopathological examination of liver, kidneys and lungs revealed mild inflammatory infiltration, degenerative changes and

necrosis. Cadmium exposure did not affect the gestational sac weight, and the size and weight of the foetuses. However, an increase in the number of resorptions and a decrease in total implantations (except for the group treated at GD 7) were noted. Also malformations in skull bones, vertebrae and thoracic, and pelvian limbs were reported.

Wang et al. (2014) [124] exposed pregnant Sprague-Dawley rats to cadmium intraperitoneally at doses of 0, 0.25, and 0.5 mg/kg bw/day from GD 5-19. On GD 20, animals were sacrificed and maternal-placental-foetal parameters linked to preeclampsia were evaluated. Statistically significant effects were almost exclusively observed in the 0.5 mg/kg bw-dose group. In the dams, maternal body weight was decreased and systolic blood pressure and urine protein excretion were increased. Pup weight was significantly reduced and prenatal losses (due either to resorption and/or stillbirth) were increased. A reduction in the number of viable foetuses (not statistically significant) was observed. Also the foetal weight/placental weight ratio and crown rump length were decreased. These developmental effects were associated with increases in placental corticosterone production, maternal and foetal plasma corticosterone levels and changes in expression of placental enzymes involved in corticosteroid synthesis.

As a preeclampsia model, Zhang et al. (2016a)[125] administered pregnant rats 0.125 mg/kg bw cadmium intraperitoneally from GD 9-14. Urine protein was measured on GD 3-19, systolic blood pressure from GD 0 to PND 6. For histopathological analysis, a group of dams were sacrificed at GD 21. In the dams, increased systemic blood pressure, kidney damage and proteinuria were observed. Damage to placenta and decidua was noted and the weight of the pups of the cadmium-exposed group was reduced.

To investigate the effect of cadmium on neural tube formation, Zhang et al. (2016b)[126] administered a single intraperitoneal dose of 0, 1.5 and 3.1 mg cadmium/kg bw to Wistar rats at GD 8. On GD 18, the dams were sacrificed and live, dead and resorbed foetuses were counted and placentas were collected for histological examination. No maternal mortality and no effect on maternal body weight gain were observed (no details provided). Cadmium exposure had no effect on litter size, live foetuses, and resorptions. At 3.1 mg/kg bw, the number of dead foetuses per litter was increased. At both doses, the number of neural tube defects was increased and the foetal weight was reduced. Also placental development was impaired, illustrated by reduced placental weight, diameter, and blood sinusoids area. In embryos of cadmium-treated dams, reduced folate levels were measured (dose group was not specified).

In a study by Zhang et al. (2016c)[127], pregnant Sprague-Dawley rats were injected intraperitoneally with a dose of 0, 0.25, or 0.5 mg cadmium/kg bw from GD 4 to 19. Systolic blood pressure was monitored on GD 3, 11, and 18. On GD 20, rats were sacrificed and tissues were collected. At 0.25 mg/kg, morphological change were observed in the kidney and placenta

(the 0.5 mg/kg was not evaluated). Urine protein levels were increased in both treatment groups. At the highest dose, maternal body weight was decreased and systolic blood pressure increased. The number of live foetuses was reduced in both the 0.25 and 0.5 mg/kg group, whereas foetal weight was reduced and the number of dead foetuses was increased only at the highest dose.

Li et al. (2018)[128] injected pregnant Sprague-Dawley rats with a single intraperitoneal dose of 0, 0.25, 0.5, or 1.0 mg cadmium/kg on GD 12. On GD 20, animals were sacrificed and the testes of the male foetuses were weighed and analysed. Cadmium caused a decrease of body weights of foetal male rats in the 0.25 and 0.5 mg/kg groups (but not the 1.0 mg/kg group). A dose-dependent reduction was observed for the testosterone production of foetal testis Leydig cell numbers. Downregulation of gene and protein expression in Leydig cells and Sertoli cells was also reported.

Inhalation

The developmental effects of cadmium in rats after exposure by inhalation were studied by Baranski (1983, 1984, 1985).[45,46,129] Female rats were exposed to 0, 0.02, 0.16, or 1 mg cadmium/m^3 for 5 h/d, 5 days/w (equivalent to 0, 6, 48, and 300 µg Cd/kg bw bw/d[a]) for 6 months before fertilisation by untreated males, and from day 1 to 20 of gestation. Half of the animals were sacrificed for assessment of foetal toxicity. Remaining animals were allowed to deliver and feeding. Functional behaviour tests were performed on 3-months old female offspring. Analysis of postnatal development was only undertaken in the offspring of females exposed to cadmium at concentrations of 0.02 and 0.16 mg/m^3 due to the high death rate (55.1%) of females exposed to 1.0 mg/m^3.
No foetal mortality or malformations were observed at 0.02 and 0.16 mg cadmium/m^3. At 0.16 mg/m^3, a slight decrease in body weight gain was reported for male and female offspring. Viability was also reduced at this concentration. A reduction of exploratory motor activity was observed in 3-month-old pups from the 0.16 mg/m^3 group, and male offspring also from the 0.02 mg/m^3 group. A dose-related reduction of avoidance acquisition was observed in offspring from cadmium exposed mothers at both exposure groups. In the open-field test, the ambulation of 5-month-old males from the 0.16 mg/m^3 was lowered, whereas in females from the 0.02 mg/m^3 group it was enhanced when compared to controls.

In an prenatal developmental inhalation toxicity study by the NTP (1995)[7], pregnant rats were exposed to 0, 0.044, 0,44 and 1.75 mg cadmium/m^3 (0, 0.008, 0,08 and 0.34 mg cadmium/kg bw/d[b]) on gestation day 4-19, for 6 hours a day, 7 days per week. On gestation day 20, animals were sacrificed and maternal and foetal examinations were performed.

[a] Assuming an inhalation volume of 200 mL/min and a body weight of 200 g.

[b] Assuming an inhalation volume of 175 mL/min and a body weight of 175 g.

Maternal toxicity was observed in Sprague-Dawley rats exposed to 1.75 mg cadmium/m^3 and included body weights lower than those of the controls and clinical signs of toxicity (dyspnoea and hypoactivity). There was no evidence of embryo-lethality in rats at any exposure level. However, in rats exposed to 1.75 mg/m^3, developmental toxicity was evidenced by lower foetal weights and a significant increase in the incidence of reduced skeletal ossifications.

By the NTP (1995)[7], also a prenatal developmental study was performed in mice exposed to 00, 0.044, 0,44 and 1.75 mg cadmium/m^3 (0, 0.014, 0,14 and 0.54 mg cadmium/kg bw/d[a]), performed according to the study design noted above. Maternal toxicity was observed in mice exposed to 1.75 mg/m^3. Clinical signs were dyspnoea, hypoactivity, lower body weight, and a lower pregnancy rate (30% vs. 97% in the control group). One female rat in the highest exposure group died on gestation Day 17.The total number of resorptions per litter, and the percentage live male foetuses per litter were increased at the 1.75 mg/m^3 level. Developmental toxicity was evidenced by lower foetal weights in the 0,44 and 1.75 mg/m^3 groups and an increase in the incidence of reduced sternebral ossification in the 1.75 mg/m^3 group.

[a] Assuming an inhalatory volume of 30 mL/min and a body weight of 35 g.

Jacobo-Estrada et al. (2016)[130] exposed pregnant rats to cadmium by inhalation (delivered dose of 1.48 mg Cd/kg bw/d) during GD 8–20. On GD 21, dams were euthanized, markers for kidney toxicity were quantified in amniotic fluid samples and foetal kidneys were examined. No effect on maternal weight gain, or liver and kidney weights were observed. Cadmium exposure had no effect on the number of foetuses per litter, and no increased incidence of malformation was reported. However, foetal body weight was reduced and increased levels of kidney injury biomarkers were measured. Also, histological findings showed tubular damage and precipitations in the renal pelvis.

5.4.2 Human data

Huel et al. (1984)[131] investigated the associations between occupational exposure to heavy metals and levels of cadmium and lead in hair of exposed mothers and in hair of newborns. The exposed group mainly involved solders, who were generally enrolled in the study during the third month of pregnancy. A total of 26 exposed women were matched with 26 controls (mostly housewives) for age, parity, smoking history, and, when possible, similar paternal socioeconomic status. The geometric means of cadmium values in in hair of the exposed group were higher than the values in the control group, both for mothers (1.45 ppm and 0.59 ppm respectively; $P < 0.01$) and newborns (1.27 ppm and 0.53 ppm respectively; $P < 0.05$). For lead, a similar difference was observed for the exposed mothers, but not for the exposed newborns. Both unadjusted and

sex- and gestational age-adjusted birthweights of exposed newborns were approximately 250 g less than those in controls. Due to small numbers of cases and controls, these differences were not statistically significant. No further adverse effects were documented.
Six years later, the cognitive function (with subscales verbal, perceptual, and quantitative), memory, and motor abilities were tested in each of the 26 children of the exposed group by Bonithon-Kopp et al. (1986)[132] using the McCarthy Scales. All scores for children in the highest quartile of cadmium levels measured in mothers and newborns were lower than those for children in the lowest quartile. Inverse correlations ($p<0.05$) were found between the general cognitive, perceptual, quantitative, and motor abilities of the child and the cadmium levels in mothers, as well as between perceptual and motor abilities and cadmium levels in newborns. After adjustment for birthweight, the latter correlations were no longer statistically significant, which may be due to overadjustment. Similar but slightly weaker correlations with cognition were reported for lead.

Kuhnert et al. (1987)[133] studied the effects of smoking during pregnancy on decreased infant weight. In smokers (N=77), maternal whole blood cadmium, placental cadmium, and placental zinc levels were inversely related to birth weight. In multivariable regression analysis on smokers and non-smokers combined (N=202) with adjustment for clinical factors and smoking status, maternal whole blood cadmium and cord blood red cell zinc levels were associated with birth weight independently.

Loiacono et al. (1992)[134] studied the effects of cadmium on birth weight of children of non-smoking mothers who lived in the vicinity of a lead smelter in Titova Mitrovica, Yugoslavia. Emissions from this lead smelter contained approximately 0.02% cadmium. Control subjects were studied in Pristina, a non-exposed town located 25 miles to the south. A higher mean placental cadmium concentration ($p<0.0007$) was found in the exposed women (N=106) compared with those not exposed (N=55). Birth weights and gestational age of the children did not differ between women from Titova Mitrovica and women from Pristina. In multivariable regression analyses with adjustment for multiple confounders and mid-pregnancy blood lead levels, no associations were observed between placental cadmium concentrations and birth weight or gestational age.

Kippler et al (2012)[135] studied the associations of prenatal cadmium and arsenic exposure with five foetal growth parameters measured by ultrasound in gestational weeks 14 and 30 in a population-based mother-child cohort in rural Bangladesh. Cadmium levels were measured in 1616 pregnant women in gestational week 8. Smoking during pregnancy was not reported, but it was noted that less than 1% of rural Bangladeshi women smoked. Bivariable and multivariable spline linear regression analyses showed that all foetal growth parameters in both GW 14 and GW 30 were associated positively with urinary cadmium levels in GW 8 up to 1.5 µg cadmium/L and inversely with cadmium levels of 1.5-7.0 µg cadmium/L (P-values ranging from <0.001 to 0.02 in GW 14 and from

<0.001 to 0.27 in GW 30). The multivariable analyses were adjusted for maternal BMI in early pregnancy, socioeconomic status, birth order, and foetal sex. Similar results were found in longitudinal analyses using linear mixed models which were also adjusted for urinary arsenic levels, but the associations between urinary cadmium levels and foetal growth from GW 14 to GW 30 were much stronger for girls than for boys, for whom the associations were no longer statistically significant. In the same cohort, the association between maternal cadmium exposure in pregnancy and size at birth was studied.[136] Multivariable linear regression analyses adjusted for sex and other potential confounders, including urinary arsenic levels in GW 8 showed that maternal urinary cadmium was negatively associated with birth weight and head circumference (p<0.05). Notably, these associations appeared to be limited to girls, with little evidence of effects in boys.

In addition, Kippler et al. (2012)[137] assessed the associations between cadmium exposure during early pregnancy and the neurodevelopmental outcome of children at 5 years of age. From a larger micronutrient supplementation trial, children were selected with assessment of cadmium levels in maternal urine (generally measured at GW 8) and concurrent children's urine (at 5 years of age), and data on basic demographic factors, maternal IQ, assessment of home environment, and developmental measures (N=1,305). Data on the various developmental outcomes at 5 years and the two (log2-transformed) exposure measures were analysed using multivariable linear regression analysis, adjusted for age, sex, birth order, weight, and height, home stimulation, socioeconomic status, maternal BMI in early pregnancy, and maternal IQ. Maternal and concurrent urinary cadmium levels (separately and combined) were inversely associated with verbal IQ, performance IQ, and full-scale IQ (p<0.05), but not with behavioural parameters. These results were stronger for girls than for boys and for high versus low socioeconomic status. Further adjustment for maternal and childhood exposure to arsenic (through drinking water) and lead did not markedly change the associations between cadmium and child IQ.

Vidal et al. (2015)[138] studied the associations between maternal cadmium, iron, and zinc levels in early pregnancy and DNA methylation and birthweight in offspring in a prospective cohort study with women recruited from five prenatal clinics and obstetric care facilities. Cadmium levels were measured in maternal blood of 319 women ≤12 weeks of gestation. In multivariable regression analysis, adjusted for sex, race/ethnicity, prepregnancy BMI, preconceptional antibiotic use, maternal smoking, and gestational age, but not for iron and zinc levels, elevated maternal blood cadmium levels were associated with lower birth weight (p=0.03). As prenatal growth is partly under control of paternal and maternal imprinted genes, effects of cadmium on several differentially methylated regions (DMRs) were also studied. Association were observed between maternal cadmium levels and lower offspring methylation. However, the association between birth weight and methylation status was not analysed.

In a prospective cohort study, Buck Louis et al. (2017)[139] assessed levels of cadmium, mercury, lead, and arsenic in 501 couples and followed them throughout pregnancy to estimate the risk of pregnancy loss. During the enrolment home visit, whole blood and urine samples were taken and analysed. Of the 501 couples, 344 (68%) got pregnant. The incidence of pregnancy loss was 28%. Time-to-pregnancy loss was defined as the number of days from observed ovulation as measured by the peak LH day to the date of reported loss. Hazard ratios for pregnancy loss were estimated using Cox proportional hazard models, with adjustment for multiple covariates, for each partner individually and combined. The blood and urine cadmium levels were neither associated with pregnancy loss in the individual partner models (highest hazard ratios 1.08 (95% CI 0.81-1.44) and 1.09 (95% CI 0.84-1.41) for women and men, respectively), nor in the couple-based models (hazard ratios 1.01 (95% CI 0.75-1.37) and 0.92 (95% CI 0.68, 1.25), respectively).

Karaer et al. (2017)[140] investigated the association between blood cadmium level and the occurrence of ectopic pregnancy in a case-control study with 41 patients with an ectopic pregnancy and 41 uncomplicated intrauterine pregnant patients as controls. Using a logistic regression model adjusted for age, parity, spontaneous abortions, and smoking, no association was observed between blood cadmium concentrations and ectopic pregnancies (odds ratio 0.88; 95% CI 0.26-2.97).

Pi et al. (2018)[141] examined whether concentrations of heavy metals (cadmium, lead, mercury, and arsenic) in placental tissues were associated with risks of orofacial clefts in offspring. This population-based case-control study included 103 newborns affected by orofacial clefts with available placental tissues and 206 controls randomly selected from 509 non-malformed newborns with available placenta samples.
For cadmium, lead, and mercury, the median concentrations were statistically significantly higher in orofacial cleft cases than in controls.
In logistic regression analysis, adjusted for sex, gestational age, previous history of birth defects, maternal occupation, maternal flu or fever, and passive smoking (only 3 mothers in the control group and 1 mother in the case group smoked actively), placental cadmium concentrations above the median were associated with an increased risk of orofacial clefts (odds ratio 2.33; 95% CI 1.33-4.09). An increased risk was observed in the second and third cadmium concentration tertiles compared to the first tertile (odds ratios of 1.00, 3.06 (95% CI 1.36-6.88), and 8.18 (95% CI 6.64-18.37 in consecutive tertiles), respectively; *P* for trend < 0.001). Similar results were observed for placental lead concentrations, but not for mercury and arsenic.

Zhang et al. (2018)[142] investigated whether urinary cadmium levels during pregnancy were associated with adverse birth outcomes in a sex-dependent manner. Cadmium levels in maternal urine samples were measured in 237 subjects from Guiyu (electronic waste recycling area) and 212 subjects

from Haojiang (reference area). The maternal urinary cadmium levels in Guiyu residents were higher than in Haojiang (p<0.001). Both male and female neonates from Guiyu had a lower mean birth weight, neonatal BMI, head circumference, and 1 min Apgar score compared to the Haojiang neonates (all p<0.001), whereas birth length was higher. Using multivariable linear regression analysis, adjusted for maternal age, weight, height, BMI, and education, inverse associations were found between urinary cadmium concentrations and birth weight, birth length, head circumference, and Apgar scores at 1 min and 5 mins for female neonates (p≤0.036). For male neonates, only the 1 min Apgar score was negatively associated with maternal urinary cadmium levels (p=0.004).

Suhl et al. (2018)[143] used data from a large, population-based case-control study in the USA to compare maternal occupational cadmium exposure from 1 month before through 3 months after conception between orofacial cleft cases (N=1,185) and unaffected controls (N=2,832). Exposure was assessed by expert raters based on self-reported occupational histories taken in telephone interviews until 2 years after birth. Only 45 mothers (cases = 13, controls = 32) were rated as having had occupational cadmium exposure. Multivariable logistic regression analyses, adjusted for multiple confounders, did not result in increased odds ratios for any occupational cadmium exposure, or for high versus low levels of cumulative cadmium exposure and orofacial clefts (either all combined, cleft lip with or without cleft palate and cleft palate only).

5.4.3 Other relevant information

No other relevant information was available to the Committee.

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

Several human studies concern the associations between cadmium exposure and effects on growth and body weight in offspring, and report an inverse association. Huel et al. (1984)[131] reported a non-statistically significant reduction in birth weight (of approximately 250 gram) in newborns of occupationally exposed mothers compared to newborns of a control group. Kuhnert et al. (1987)[133] found an association between increased blood/placental cadmium levels in smokers and a reduction in infant weight. Multivariable regression analysis among smokers and non-smokers showed that blood cadmium levels were associated with birth weight, adjusted for smoking and blood zinc levels. Loiacono et al. (1992)[134] found no association between higher placental cadmium levels in non-smoking mothers living near a lead smelter and birth weight, when compared to mothers from a non-exposed control population. Multivariable linear regression analyses performed by Kippler et al (2012)[135] showed that maternal urinary cadmium levels ≥ 1.5 µg/L were inversely associated with foetal growth parameters. Mixed model analyses adjusted for arsenic exposure showed similar results, but with stronger associations for girls compared to boys. Maternal urinary cadmium levels were also inversely associated with birth weight and head circumference,

but only in girls. Vidal et al. (2015)[138] found an association between increased maternal blood cadmium levels during early pregnancy and lower birth weight in offspring. Zhang et al. (2018)[142] investigated whether urinary cadmium levels during pregnancy were associated with adverse birth outcomes. In multivariable analyses, associations were found between urinary cadmium concentrations and birth weight, birth length, head circumference, and Apgar scores, primarily in female neonates.

Studies on maternal cadmium exposure and other effects in offspring are also available. Two studies addressed neurodevelopmental parameters. In the occupationally exposed cohort of Huel et al. (1984)[131] studied by Bonithon-Kopp et al. (1986)[132], an association was found between increased cadmium levels in either mothers or newborns and decreased cognitive and motor abilities. Kippler et al. (2012)[137] assessed the associations between cadmium exposure during early pregnancy and the neurodevelopmental outcome of children at 5 years of age. Maternal urinary cadmium levels were inversely associated with verbal IQ, performance IQ and full-scale IQ, independent of childhood cadmium exposure and maternal and childhood arsenic and lead exposure. Buck Louis et al. (2017)[139] assessed levels of cadmium in couples and followed them throughout pregnancy to estimate the risk of pregnancy loss. No increased risks for females and males with high blood cadmium levels were observed in individual partner models or in couple-based models. Karaer et al. (2018)[140] investigated the association between the blood level of cadmium and the occurrence of ectopic pregnancy in a case-control study and found no association. In two recent studies, associations between cadmium exposure and the risk of orofacial clefts were assessed. Pi et al. (2018)[141] reported that placental cadmium concentrations were associated with an increased risk of orofacial clefts in a dose-dependent manner. Suhl et al. (2018)[143] compared expert rater assessed maternal occupational cadmium exposure from self-reported occupational histories around conception between orofacial cleft cases and unaffected controls. No differences were found.

In multiple animal studies, mainly with rats, adverse effects on development have been observed after oral administration in a dose range of 0-40 mg cadmium/kg bw. In general, effects on development are either observed in combination with effects on body or organ weights, or data on general toxicity is lacking.
Most notably, exposure to cadmium during gestation consistently resulted in a decrease of growth (in weight or length) in foetuses or pups (Sutou et al. (1980)[13]; Baranski et al. (1982, 1985, 1987)[46,90,91]; Sorell and Graziano (1990)[94]; Corpas and Antonio (1998)[97]; Jacquillet et al. (2007)[102]; Ronco et al. (2009)[103]; Couto-Moraes et al. (2010)[104]; Luo et al. (2015)[106] and a decrease in organ weights (in some cases involving testis and ovary) (Nagymajitenyi et al (1997), Corpas and Antonia (1998) Sutou et al. (1980), Desi et al. (1998), Kuriwaki et al (2005), Luo et al. (2015), Tian et al. (2017)[108], Li et a. (2018)[109]).

Severe developmental effects have also been observed in rats.
These effects include a decrease in number of (live) foetuses (Sutou et al. (1980a,b)[13,14], Baranski et al. (1982)[91], Baranski (1985)[46]; an increase in resorptions (Sutou et al. (1980a,b)[13,14], Baranski et al. (1982)[91], Baranski (1985)[46]; and Samuel et al. (2011)[105]), and malformations (lack of forelimbs or sirenomelia, (Baranski et al. (1982)[91], cleft palate and renal cavitation (Salvatori et al. (2004)[99]).
Further, delayed ossification (Baranski et al. (1982)[91], Salvatori et al. (2004)[99] and disturbances in various behavioural parameters were reported (Baranski (1986)[92]; Nagymajitenyi et al (1997)[96]; Salvatori et al. (2004)[99]; Couto-Moraes et al. (2010)[104]; Zhao et al. (2015)[27].
In mice, increased pup mortality (Schroeder and Mitchener, 1971)[8] and reduced pup growth and litter size (Whelton et al (1988)[93] has been reported.

In animal studies (mainly with rats, but also mice and hamsters) in which cadmium was administered parenterally, similar effect on development were observed. As noted previously, these include a consistent decrease in foetal body weight or growth (Saltzman et al. (1989)[113]; Soukupova and Dostal (1991a)[115]; Hartsfield et al. (1992)[117]; Wang et al. (2014)[124]; Zhang et al. (2016a,b,c)[125-127], Li et al. (2018)[128]). Severe developmental effects consist of a reduction in implantation sites/post implantation loss (De et al. (1993)[118], Lee et al. (2009)[121]), an increase in resorptions (Parizek (1964)[110], Ferm et al. (1968)[111]; Samarawickrama and Webb (1979)[112]; Saltzman et al. (1989)[113]; Lee et al. (2009)[121]; Del Diaz et al. (2014)[123]; Wang et al. (2014)[124]) a reduced foetal viability and increased mortality (Parizek (1964)[110]; Saltzman et al. (1989)[113]; Soukupova and Dostal (1991a)[115]; Hartsfield et al. (1992)[117]; Lee et al. (2009)[121]; Wang et al. (2014)[124]; Zhang et al. (2016b,c) [126,127], an increase in malformations including cleft palate, cleft lip, neural tube defects, malformations of limbs and skeletal malformations (Ferm et al. (1968)[111]; Samarawickrama and Webb (1979)[112], Soukupova and Dostal (1991a)[115]; Hartsfield et al. (1992)[117], Del Diaz et al. (2014)[123], Zhang et al. (2016b)[126]. Also damage to maternal organs relevant for development (placenta, ovaries and uterus) has been noted (Kar et al. (1959)[31]; Parizek (1964)[110], Piasek et al. (2004)[119], Lee et al. (2009)[121], Del Diaz et al. (2014)[123], Wang et al. (2014)[124], Zhang et al. (2016a,b,c)[125-127].

Only in few studies, absence of severe developmental toxicity was reported after parenteral administration of cadmium. In three of these studies, in rats, this could be related to either the use of relatively low doses (≤ 0.2 mg/kg bw) (Pelletier and Satinder (1991)[114]; Nampoothiri and Gupta (2008)[120] or a short exposure duration (Piasek and Laskey (1994)[38]. In one study with mice (Wang et al. (2012)[122], a single injection of 2.8 mg/kg bw did not affect foetal viability.
Inhalation studies performed with rats and mice at equivalent doses up to 1.48 mg/kg bw/d also revealed reductions in foetal body weight in rats and mice (NTP (1995)[7]; Jacobo-Estrada et al.(2016)[130]). In inhalation studies in

rats by Baranski (Baranski (1983, 1984, 1985)[45,46,129], with equivalent doses up to 0.3 mg/kg bw, abnormal findings in behavioural tests and a reduced post-natal survival (only at the highest concentration) was observed. Also in the inhalation studies, maternal toxicity was observed.

The adverse effects on development observed in animal studies are summarised in the following table:

Ref.	Species	Exposure window	Exposure route	Effects on development	General toxicity
Sutou et al. (1980)	Rat	From 6 weeks pre-mating (males and females) to GD 20	Oral (gavage)	Decreased number of implantation sites and live foetuses; decreased foetal weight; increased placental weight NOAEL=1.0 mg/kg	Decreased food intake and body weight; clinical signs of toxicity NOAEL=1.0 mg/kg
Zenick et al. (1982)	Rat	Male rats were exposed for 70-80 pre-mating	Oral (drinking water)	No effect on development observed NOAEL=2.6 mg/kg	Reduced water intake LOAEL=0.7 mg/kg
Baranski et al. (1982)	Rat	From GD 7-16, sacrifice at GD 21	Oral (gavage)	Decreased foetal weight NOAEL=4 mg/kg	Decreased body weight gain LOAEL=2 mg/kg
Baranski et al. (1983)	Rat	For 5 w (5 d/w) and during mating and gestation	Oral (gavage)	Foetuses with oedema NOAEL=0.04 mg/kg Decreased locomotor activity LOAEL=0.04 mg/kg	Mortality NOAEL=0.4 mg/kg
Baranski (1985)	Rat	From GD 7-16; sacrifice at GD 21	Oral (gavage)	Reduced foetal weight NOAEL=2 mg/kg	Reduced maternal body weight gain LOAEL=2 mg/kg
Baranski (1986)	Rat	From GD 1-20, pups analysed at weaning	Oral (drinking water)	Reduced brain weight; effects on behaviour LOAEL=8.5 mg/kg	No information provided
Baranski (1987)	Rat	From GD 1-20	Oral (drinking water)	Reduced foetal length and body weight LOAEL=9.2 mg/kg	Reduced body weight gain and food/water intake LOAEL=9.2 mg/kg
Sorell and Graziano (1990)	Rat	From GD 1-20	Oral (drinking water)	Reduced foetal body weight NOAEL=0.4 mg/kg	Reduced maternal body weight NOAEL=0.4 mg/kg
Andersson et al. (1997)	Rat	From partus to PND 17 and/or PND 42	Oral (drinking water)	Reduction in cortical serotonin levels LOAEL=1.0 mg/kg	No effect on food/water intake and body weight NOAEL=1.0 mg/kg
Nagymajtenyi et al. (1997)	Rat	5 d/w during pregnancy, lactation and 8 w after weaning. Measurements at 12 w	Oral (gavage)	Open field exploration affected LOAEL=3.5 mg/kg	No information provided
Corpas and Antonio (1998)	Rat	Through gestation until PND 5	Oral (drinking water)	Reduced pup, testis and ovary weights LOAEL=1.13 mg/kg	No information provided

Ref.	Species	Exposure window	Exposure route	Effects on development	General toxicity
Desi et al. (1998)	Rat	During GD 5-15, and/or 4 w of lactation	Oral (gavage)	Reduced kidney weight and changes in electrocorticogram Affected behaviour (when exposed during lactation) LOAEL=3.5 mg/kg	No visible signs of toxicity
Salvatori et al. (2004)	Rat	From GD 6-14. Foetal effects assessed at GD20, pup behaviour at PND 21	Oral (gavage)	Malformation (cleft palate and renal cavitation); abnormal sexual behaviour LOAEL=20 mg/kg	Decreased food intake; no effect on body weight NOAEL=20 mg/kg
Kuriwake et al. (2005)	Rat	From GD 9-19	Oral (gavage)	Reduced foetal liver weight LOAEL=1 mg/kg	No information provided
Jacquillet et al. (2007)	Rat	During gestation. Assessment up to PND 60	Oral (gavage)	Reduced pup weight, kidney toxicity LOAEL=0.5 mg/kg	No information provided
Ronco et al. (2009)	Rat	During gestation until GD 20	Oral (drinking water)	Decreased foetal body weight; increased corticosterone levels NOAEL=3.9 mg/kg	No effect on body weight NOAEL=5.3 mg/kg
Couto-Moraes et al. (2010)	Rat	At GD 18 and 21, and from PND 1-7	Oral (gavage)	Reduced pup weight LOAEL=10 mg/kg	Reduced body weight gain LOAEL=10 mg/kg
Samuel et al. (2011)	Rat	From GD 9-21, assessed at PND 10 and 21. Only female offspring was assessed	Oral (drinking water)	Increased number of resorption sites; disruption oestrous cycle and histologically, in ovaries LOAEL=5.8 mg/kg	Reduced water intake and body weight LOAEL=5.8 mg/kg
Zhao et al. (2015)	Rat	Male rats, every 2 days for 9 w, females were not treated. Offspring was assessed at various time point after birth	Oral (gavage)	Abnormal behaviour LOAEL=13.6 mg/kg	No information provided
Luo et al. (2015)	Rat	From GD 0-21. Offspring was followed for 12 w	Oral (drinking water)	Reduced body weight NOAEL=0.089 mg/kg	No effect on body weight NOAEL=0.955 mg/kg
Mikolic et al. (2014)	Rat	From GD 0-20	Oral (drinking water)	No effect on development observed NOAEL=7.5 mg/kg	No effect on body weight NOAEL=7.5 mg/kg
Tian et al. (2017)	Rat	From GD 0-PND 21. Male offspring was assessed up to PND 56.	Oral (gavage)	Reduced testis/bw ratio; reduction steroid hormone levels LOAEL=1 mg/kg	No information provided
Li et al. (2018)	Rat	From GD 0-21. Female offspring were allowed to mate to obtain F2	Oral (gavage)	Increased ration uterus/bw LOAEL=1 mg/kg Effects on ovary, oestrous cycle and litter size at 5 mg/kg	No reduction in survival NOAEL=5 mg/kg
Schroeder and Mitchener (1971)	Mouse	Continuous, multiple generations	Oral (drinking water)	Pup mortality Runts LOAEL=2.1 mg/kg	2 maternal deaths; no information provided. LOAEL=2.1 mg/kg
Whelton et al. (1988)	Mouse	During 6 consecutive rounds of gestation-lactation	Oral (diet)	Decreased litter size and pup growth NOAEL=? (No control group included)	No information provided

Ref.	Species	Exposure window	Exposure route	Effects on development	General toxicity
Ishitobi et al. (2005)	Mouse	From GD 0-PND 10. Pups were assessed at PND 70	Oral (drinking water)	No statistically significant effects NOAEL=2 mg/kg	No effect on bodyweight gain NOAEL=2 mg/kg
Parizek (1964)	Rat	From GD 17-21	Subcutaneous	Abnormalities in placenta and uterus, interruption of pregnancy LOAEL=4.5 mg/kg	No information provided
Ferm et al. (1968)	Rat	Single injection at GD 8, sacrifice on GD 12	Intravenous	Resorptions and malformations LOAEL=2 mg/kg	Not observed NOAEL=4 mg/kg
Samarawick and Webb (1979)	Rat	From GD 8-15, sacrifice at GD 20	Intravenous	Increased resorptions, abnormal foetuses, malformations NOAEL=1.1 mg/kg (LOAEL=1.25 mg/kg)	No information provided
Saltzman et al. (1989)	Rat	Single injection at GD 12 or 18; sacrifice at GD 19/20	Subcutaneous	Foetal mortality and case of cleft palate LOAEL=4.5 mg/kg	No information provided
Pelletier and Satinder (1991)	Rat	From GD 0-20, behaviour studied after weaning	Subcutaneous	No effect on length of gestation, litter size, foetal mortality, physical behaviour NOAEL=0.225 mg/kg	No effect on food consumption and body weight NOAEL=0.225 mg/kg
Piasek and Laskey (1994)	Rat	Single injection on day of diestrous, or on GD 7 or 16. Analyses were done 24 h later.	Subcutaneous	No effect on oestrous cycle, live implants, resorptions, foetal weight NOAEL=5 mg/kg	No effect on maternal body weight NOAEL=5 mg/kg
Paksy et al. (1996)	Rat	Single injection on day of oestrus, GD 7 or GD 8. Foetal outcome was assessed at GD 10, or PND 21.	Subcutaneous	No effect on litter number/weight NOAEL=6.1 mg/kg	Reduced maternal body weight NOAEL=1.5 mg/kg
Piasek et al. (2004)	Rat	Sub-chronic (on GD 1-15) or acute (on GD 15) exposure, analyses on GD 19.	Subcutaneous	Only in acute study: Foetal mortality; placental destruction LOAEL=3 mg/kg	Only in acute study: Reduced maternal body and organ weights LOAEL=3 mg/kg
Nampoothiri and Gupta (2008)	Rat	Treated during gestation, with 5 days pretreatment. Analyses on GD 19.	Subcutaneous	No effect on litter size and weight, number of dead/ resorbed foetuses, and ovarian/placental weight NOAEL=0.024 mg/kg	No effect on maternal body weight NOAEL=0.024 mg/kg
Lee et al. (2009)	Rat	From GD 11-19; analyses on GD 20	Subcutaneous	Increased post-implantation loss, reduced foetal weight, increased resorptions and dead foetuses LOAEL=0.2 mg/kg	No information provided
Del Diaz	Rat	Single injection on GD 4, 7, 10 or 15. Analyses on GD 20.	Intraperitoneal	Reduced number of implantations, increased number of resorptions and malformations LOAEL=10 mg/kg	Severe lesions in liver, kidney and lung LOAEL=10 mg/kg
Wang et al. (2014)	Rat	From GD 5-19; analyses on GD 20	Intraperitoneal	Increased prenatal loss, reduced body weight, reduced litter size/viable foetuses NOAEL=0.25 mg/kg	Decreased maternal body weight, increased systolic blood pressure, increase urine protein excretion NOAEL=0.25 mg/kg

Ref.	Species	Exposure window	Exposure route	Effects on development	General toxicity
Zhang et al. (2016a)	Rat	From GD 5-14; developmental parameters analysed on GD 21.	Intraperitoneal	Reduced foetal weight, decreased crown-rump length, damage to the placenta LOAEL=0.125 mg/kg	Increased systemic blood pressure, kidney damage LOAEL=0.125 mg/kg
Zhang et al. (2016c)	Rat	From GD 4-19; developmental parameters analysed on GD 20.	Intraperitoneal	Reduced number of live foetuses, morphological changes placenta LOAEL=0.25 mg/kg	Kidney damage LOAEL=0.25 mg/kg
Li et al. (2018)	Rat	Single injection at GD 12. Sacrifice and analysis at GD 20.	Intraperitoneal	Decreased foetal body weight LOAEL=0.25 mg/kg	No effect on maternal body weight NOAEL=1 mg/kg
Soukupova and Dostal (1991a)	Mouse	Once, during GD 8-14. Analyses on GD 18.	Subcutaneous	Increased mortality and malformations NOAEL=? (no details control group provided)	No information provided
Soukupova and Dostal (1991a)	Mouse	Once, on GD 16. Analyses at 4 w after birth.	Subcutaneous	Affected immune response LOAEL=1.5 mg/kg	No information provided
De et al. (1993)	Mouse	Once, either on GD 2 or 4. Analyses at GD 5 or 8.	Subcutaneous	Reduced number of implantation sites LOAEL=2.8 mg/kg	No information provided
Wang et al. (2012)	Mouse	Once, on GD 9. Analyses at GD 18.	Intraperitoneal	Reduced placenta weight; histological alterations (no effect on implantation sites, resorptions, live/dead litter) LOAEL=2.8 mg/kg	No effect on body weight gain NOAEL=2.8 mg/kg
Zhang et al. (2016b)	Mouse	Once, on GD 8. Analyses on GD 18.	Intraperitoneal	Reduced foetal weight and crown-rump length, increased number of neural tube defects LOAEL=1.5 mg/kg	No effect on maternal body weight gain NOAEL=3.1 mg/kg
Hartsfield et al. (1992)	Hamster	Once, on GD 8. Analyses were done on GD 15.	Intravenous	Increase non-viable foetuses and, malformations, decrease foetal weights and crown-rump length LOAEL=2 mg/kg	Reduced body weight NOAEL=2 mg/kg
Baranski (1983; 1984; 1985)	Rat	For 5 h/d, 5 months, during mating and from GD 1-20	Inhalation	Abnormal behaviour LOAEL=0.02 mg/m^3 ((~6 µg/kg) (Reduced pup survival at 0.16 mg/m^3)	Mortality NOAEL=1 mg/m^3 (~48 µg/kg)
NTP (1995)	Rat	For 6 h/d, 7 d/w, from GD 4-19	Inhalation	Reduced foetal bw NOAEL=0.44 mg/m^3 ((~80 µg/kg)	Clinical signs; decreased bw, reduced fertility NOAEL=0.44 mg/m^3 (~80 µg/kg)
Jacobo-Estrada et al. (2016)	Rat	From GD 8-20	Inhalation	Reduced foetal weight; kidney toxicity LOAEL=17.4 mg/m^3 (~1.5 mg/kg)	No effect on bw and kidney weight NOAEL=17.4 mg/m^3 (~1.5 mg/kg)
NTP (1995)	Mouse	For 6 h/d, 7 d/w, from GD 4-17	Inhalation	Reduced foetal bw NOAEL=0.044 mg/m^3 (~14 µg/kg)	Clinical signs; decreased bw, reduced fertility NOAEL=0.44 mg/m^3 (~140 µg/kg)

5.6 Comparison with the CLP criteria

In epidemiological studies, associations between maternal cadmium exposure and effects on development were reported. Five studies found associations between increased cadmium levels in maternal blood, urine or placenta, and decreased birth weight in offspring (Huel et al. (1984)[131]; Kuhnert et al. (1987)[133]; Kippler et al. (2012)[136]; Vidal et al. (2015)[138]; Zhang et al. (2018)[142]). In the small-scale study by Huel et al. (1984)[131], the association was not statistically significant. Huel et al. (1984)[131], Vidal et al. (2015)[138], and Zhang et al. (2018)[142] did not adjust the analyses for co-exposure to other metals, whereas Kuhnert et al. (1987)[133] and Kippler et al. (2012)[135] adjusted for zinc and arsenic exposure, respectively, in addition to adjustment for other relevant factors. Kippler et al. also found associations between maternal cadmium levels and foetal growth parameters and head circumference, especially in girls. The latter association was also observed by Zhang et al. (2018)[142].

Several epidemiologic studies addressed other developmental parameters. In two case-control studies, the association between cadmium exposure and orofacial clefts was studied. Pi et al. (2018)[141] reported a dose-dependent increased risk of orofacial clefts for placental cadmium levels adjusted for confounders, whereas Suhl et al. (2018)[143] did not find an increased risk of orofacial clefts (based on only 13 exposed cases) in mothers assumed to be exposed to cadmium. Bonithon-Kopp et al. (1986)[132] and Kippler et al. (2012)[137] reported adverse effects on neurodevelopment measured in offspring at the age of 6 and 5 years, respectively. The results of Kippler et al. (2012)[137] were adjusted for several confounders and co-exposure to lead and arsenic.

Multiple animal studies, mainly with rats, revealed adverse effects on the development of offspring. In general, exposure to cadmium during gestation resulted in a decreased body weight of foetuses and pups (reported after cadmium exposure in a dose range of 0.2 mg/kg bw and higher). Severe developmental toxicity was observed in rats and mice at doses that were generally higher than the doses at which effects on body weight are observed, and include a decrease in live foetuses, an increase in foetal mortality and resorptions, and an increase in malformations (including cleft palate/lip and malformations of limbs). These developmental effects were observed after both oral and parenteral administration. General toxicity is either observed in these studies or information on general toxicity is lacking.

Conclusion

In epidemiological studies, associations were reported between exposure to cadmium and reduced birth weight, increased risk of orofacial clefts, and impaired neurodevelopment. Due to lack of adjustment for relevant co-exposures in most studies, the Committee considers these associations insufficient for classification in Category 1A.
In animal studies, severe developmental toxicity (increased foetal

mortality, reduced foetal viability, increased resorptions and malformations) has been observed in rats and mice, following different routes of administration. In these studies, general toxicity (indicated by a reduction in body weight) was observed, or not specifically addressed. The Committee considers it likely that effects on development in animals occur in the presence of maternal toxicity, which likely involve the kidneys (the critical organ in cadmium-induced toxicity). It is unclear whether or not effects on development are a non-specific secondary effect of the general toxicity. As the mode of action is unknown, the Committee assumes that the observed developmental effects are relevant for humans.

Based on associations observed in epidemiological studies, which are consistent with developmental toxicity observed in animal studies, the Committee recommends to classify for effects on development in category 1B (presumed human reproductive toxicant), and to label with H360D (may damage the unborn child) (CLP paragraph 3.7.2.2.3). This proposal for classification relates to cadmium, cadmium carbonate, cadmium chloride, cadmium fluoride, cadmium hydroxide, cadmium nitrate, cadmium oxide, cadmium sulphate, and cadmium sulphide (See section 4.2 for an explanation of the selection of substances).

5.7 Lactation

5.7.1 Animal data

Toxicity studies

Halder et al. (2016) exposed female lactating mice to cadmium (1.2 mg/kg/day intraperitoneally) for seven days just after delivery.[144] On postnatal day 21, the pups were tested for learning and memory function by passive avoidance task and Morris water maze test. Pups from cadmium-exposed dams showed impairment of memory and an increased escape latency compared to pups from unexposed dams. Malondialdehyde levels (biomarker for oxidative stress) were increased in brain tissue of pups from the treatment group.

Andersson et al. (1997)[95] administered cadmium in the drinking water (5 mg/L[a]) to female Sprague Dawley rats during the lactation period. One week later (45-51 days after birth) offspring was sacrificed and analysed. Mean body weights of the dams and offspring, food and water intake were comparable to controls. Relative weights of liver, kidney and brain were comparable as well. Exposure during lactation did not induce changes in plasma urea nitrogen levels. No obvious neuropathology was observed after cadmium exposure. Exposure to cadmium during lactation resulted in reduced levels of serotonin and its metabolite 5-Hydroxyindoleacetic acid in foetal brain.

[a] Equivalent to 0.70, 0.97, and 1.06 mg cadmium/kg bw during the first, second, and third weeks of the lactation period for dams, and 0.8-1.2 mg/kg bw in pups, according to the authors.

Petersson Grawé and Oskarsson (2000)[145] infused lactating Sprague Dawley rats intravenously with $^{109}CdCl_2$ (doses of 0, 8.8, 62 and 300 µg Cd/kg bw/d) in 0.9% saline via osmotic mini-pumps from day 3 to day 16 after parturition. Plasma and milk were collected at day 10 and 16 after parturition. Cadmium levels were higher in milk (up to 5.4 µg/mL at day 16) than in plasma, with milk/ plasma ratios varying from 2 to 6. Only a fraction of the cadmium dose given to the dams (< 0.05%) was retained in the litters on day 16 of lactation. No effects were observed on body weights of pups and dams. Histological evaluation of mammary tissue did not reveal any abnormalities at any dose level (pups were not further analysed).

Studies on cadmium transfer to milk

Bhattacharyya et al. (1982)[146] examined the maternal transfer of cadmium administered in drinking water, to pups during gestation and lactation in mice. Approximately 11% (as fraction of the amount of ^{109}Cd present in the dams) was measured in the pups following lactation-only exposure.

Lucis and Shaikh (1972)[147] injected ^{109}Cd subcutaneously to rats during pregnancy or during the lactation period. In both cases, ^{109}Cd was present in low concentrations (not further specified) in the milk recovered from the stomach of the pups.

Houpert et al. (1997)[148] studied the amount of cadmium eliminated through milk in ewes. The ewes received two successive doses of cadmium chloride at a 21-day interval in a crossover design. One involved 25 mg/kg of cadmium orally, the other dose 0.1 mg/kg intravenously. Cadmium levels in milk increased rapidly and could be detected 6 hours after administration. Levels reached a maximum value on the 2nd or 3rd day after administration. These values then decreased, first quickly and later slowly. Seventy days after the second administration, 1.1 ± 0.8 mg/day of cadmium was being excreted in milk.

5.7.2 Human data

In multiple studies, cadmium levels were quantified in breast milk of women from different regions of the world, who were not occupationally exposed to cadmium (summarised by the Health Council (2000)[1] (including literature up to 1999) and by Rebelo and Caldas (2016)[149] (including literature published from 2000 to June 2016). In a total of 40 publications, a range of cadmium levels of 0-25 µg/L[a] in colostrum and mature milk was measured. The Committee is not aware of data available on the amount of cadmium that is transferred to breast milk.

Calculation safe level of cadmium in (human) breast milk

The European Food and Safety Authority (EFSA) established a tolerable weekly intake (TWI) of 2.5 µg cadmium/kg bw in 2009, and confirmed this value in 2011.[150,151] The TWI was based on urinary β2 microglobulin as

[a] Excluding a study reporting outlier levels of 94.8–97.8 µg/L measured in Nigeria.

early biomarker of cadmium-induced tubular toxicity, to protect the most sensitive groups of the population. For the calculation of a safe cadmium level in breast milk, the Committee applies a default breast milk intake value of 900 mL/d.

Assuming a mean infant body weight during lactation of 4.5 kg, and a daily milk intake of 900 mL, a TWI of 2.5 µg cadmium/kg bw corresponds with a safe cadmium level in breast milk of: (2.5 x 4.5) / (0.9 x 7) = 1.8 µg/L.

5.8 Short summary and overall relevance of the provided information on effects on or via lactation

In rats, mice and ewes, excretion of cadmium in breast milk has been measured. In mice, lactational transfer resulted in reduced learning and memory function in pups. The transfer appears to be relatively low (≤ 11%). The available human data consist of levels of cadmium detected in breast milk (both colostrum and mature) quantified in breast milk of women from different regions of the world, who were not occupationally exposed to cadmium.

5.9 Comparison with the CLP criteria

A substance can be classified if:

(a) human evidence indicates a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals provide clear evidence of adverse effects in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

Cadmium was detected in breast milk of non-occupationally exposed women in amounts leading to doses that exceed the tolerable weekly intake (TWI) derived by EFSA. Occupational exposure to cadmium will most likely lead to additionally increased cadmium levels in breast milk. The TWI derived by EFSA is noted to protect also sensitive groups in the population. The Committee notes that although no specific data on cadmium-sensitivity of the infant are available, infants are most likely sensitive to the adverse effects of cadmium. Therefore the Committee considers it likely that cadmium is present in potentially toxic levels in human milk and is of the opinion that classification for effects on or via lactation is warranted.

5.10 Conclusions on classification and labelling

The Committee recommends classification according to Regulation (EC) 1272/2008 of the European Union. For cadmium, cadmium carbonate, cadmium chloride, cadmium fluoride, cadmium hydroxide, cadmium

nitrate, cadmium oxide, cadmium sulphate, and cadmium sulphide, the Committee recommends:

- for effects on fertility, to classify these substances in category 1B (presumed human reproductive toxicant), and to label them with H360F (may damage fertility);
- for effects on development, to classify these substances in category 1B (presumed human reproductive toxicant) and to label them with H360D (may damage the unborn child);
- for effects on or via lactation, to classify these substances for effects on or via lactation and label them with H362 (may cause harm to breastfed babies).

Proposed classification for fertility

Category 1B, H360F.

Proposed classification for developmental toxicity

Category 1B, H360D.

Proposed classification for effect on or via lactation

H362.

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