ECHA Scientific report

for evaluation of limit values for cadmium and its inorganic compounds at the workplace

Prepared by the European Chemicals Agency

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Preamble

The Commission, in view of the preparation of the fifth proposal for amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD), and in line with the 2017 Commission Communication '*Safer and Healthier Work for All' - Modernisation of the EU Occupational Safety and Health Legislation and Policy*[1], asked the advice of RAC to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances.

Therefore, the Commission made a request on 08/01/2020 to ECHA in accordance with the Service Level Agreement (SLA) (Ares(2019)18725), to evaluate, in accordance with the Directive 2004/37/EC, the following chemical compound(s): cadmium and its inorganic compounds.

In support of the Commission's request, ECHA has prepared a scientific report concerning occupational limit values for cadmium and its inorganic compounds at the workplace.

In the preparatory phase of making this report, a call for evidence was started on **02/03/2020** to invite interested parties to submit comments and evidence on the subject by **02/06/2020**. The evidence collected was made publicly available at: https://echa.europa.eu/oels-cce-current-consultation. The scientific report was made publically available at: https://echa.europa.eu/oels-pc-on-oel-recommendation on **14/09/2020** and interested parties were invited to submit comments by **12/11/2020**.

The Committee for Risk Assessment (RAC) will develop its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion on occupational limit values for cadmium and its inorganic compounds, the scientific report will be further developed as the Annex to the RAC opinion.

Following adoption of an opinion on cadmium and its inorganic compounds, recommending an Occupational Exposure Limit for cadmium and its inorganic compounds by RAC, the Annex will be amended to align it appropriately with the view of RAC. It supports the opinion of the RAC and gives the detailed grounds for the opinion[2].

[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes

[2] https://echa.europa.eu/documents/10162/13579/interim_wponevaluation_oel_agreed_rac_42_en.pdf/021bc290-e26c-532f-eb3f-52527700e375

Table of Contents

Tables

Scope of the task and literature search

ECHA has been tasked by the European Commission "*to assess the option of an airborne occupational exposure limit (OEL) and/or a combination of an airborne occupational exposure limit and a biological monitoring value for cadmium and its inorganic compounds based on their possible equal effectiveness in protecting the health of workers*".

This report is based on the SCOEL Opinion which was adopted 8 February 2017 (SCOEL 2017)[3] and additional literature searches done in order to identify relevant new studies on health effects of cadmium, published in 2017-2020. The SCOEL report has been integrated into this report with main parts of the text elaborated with the new data where relevant. The SCOEL report is available at the link below[3] and in Appendix 1. Furthermore, this report is updated with current information on for example, uses, exposure, existing OELs, analytical methods and published approaches to establishing OELs and BLVs.

The SCOEL (2017) document was based on SCOEL (2010) document, completed by existing compilations by ATSDR (2012), IARC (2012), Hartwig (2013a), BAuA (2014), NTP (2016) and on a literature search by SCOEL in January 2017. SCOEL (2017) considered that the core database relevant for grouping of cadmium as a carcinogen and for OEL setting (8h-TWA and BLV) had not significantly changed since the time of the SCOEL Recommendation in 2010.

Recommendation

It is recommended to apply the current OEL 0.001 mg Cd/m^3 (1 µg Cd/m^3) (inhalable fraction) together with a BLV of 0.002 mg Cd/g creatinine (2 µg Cd/ g creatinine) for cadmium in urine.

Derived Limit Values

OEL as 8-hour TWA:	0.001 mg/m^3 (inhalable)
STEL:	No proposal
BLV:	0.002 mg/g creatinine
BGV:	No proposal

Notations

Notations:	None

[3] SCOEL Opinion available at https://op.europa.eu/en/publication-detail/-/publication/3325374b-0a14-11e7-8a35-01aa75ed71a1/language-en

1. Chemical Agent Identification and Physico-Chemical Properties

Cadmium (Cd) was first isolated in 1817 in Germany.

Metallic cadmium is a white silvery metal with a low melting point (321°C). It is soft, malleable, ductile and similar in many respects to zinc. The most common oxidation state of Cadmium is +2. There is a great variety of inorganic cadmium compounds which are typically white or colourless crystalline compounds with the marked exception of sulfur, selenium and tellurium compounds which are coloured. For the identification of physical and chemical properties, reference can be made to ATSDR (2012).

Cadmium's identification and physico-chemical properties are described in Table 1 and Table 2:

Table 1: Substance identification

Substance name	CAS No	EINECS/EC -list No.	Description	Molecular formula
Cadmium	7440-43-9	231-152-8		Cd
cadmium oxide	1306-19-0	215-146-2		CdO
cadmium hydroxide	21041-95-2	244-168-5		CdH2O2
Silicic acid, zirconium salt, cadmium pigment-encapsulated	102184-95-2	310-077-5		
cadmium sulphide	1306-23-6	215-147-8		CdS
cadmium telluride	1306-25-8	215-149-9		CdTe
cadmium sulfoselenide		701-229-5		CdS(1-x)Se(x)
cadmium sulphate	10124-36-4	233-331-6		Cd.H2O4S
cadmium zinc sulfide (hexagonal)		701-227-4		(Cd1-x.Znx)S
cadmium carbonate	513-78-0	208-168-9		CH2O3.Cd
Indium, cake	69029-48-7	273-794-1	Product from the pH-adjustment of indium-rich solutions causing the precipitation of indium, ammonium and cadmium hydroxides and sulfates and zinc sulfate.	
cadmium nitrate	10325-94-7	233-710-6		Cd.2HNO3
Cadmium, dross	69011-69-4	273-707-7	A scum formed on the surface of molten cadmium.	

Substance name	CAS No	EINECS/EC -list No.	Description	Molecular formula
Zircon, cadmium yellow	72968-34-4	277-135-9		
cadmium selenide	1306-24-7	215-148-3		CdSe
Dicadmium tin tetraoxide	12185-56-7	700-126-2		Cd2O4Sn
cadmium chloride	10108-64-2	233-296-7		CdCl2

Table 2: Physical and chemical properties[4]

Name	EC / list number	Density [g / cm³]	WaterSolubility	Melting
Cadmium	231-152-8	8.6	ca. 5 mg/L	>=321.0<326.0°C
Cadmium oxide	215-146-2	8.26	2.1 mg/L	(ca.950.0°C - SublimationTemp)
Cadmium hydroxide	244-168-5	4.73	69.5 mg/L	(186.0°C - DecompTemp)
Silicic acid, zirconium salt, cadmium pigment-encapsulated	310-077-5	4.7	3.13 µg Cd/L	>1000.0°C
Cadmium sulphide	215-147-8	4.81	1.3 mg/L (h)	(>=871.0<=890.0°C - SublimationTemp)
Cadmium telluride	215-149-9	5.83	0.8 mg/L	ca.1042.0°C
cadmium sulfoselenide	701-229-5	5.15	0.19 µg Cd/L	>=593.0<=672.0°C
Cadmium sulphate	233-331-6	4.691 (h)	755 g/L (h)	1000 °C (h)
cadmium zinc sulphide yellow	701-227-4	4.7	1.48 µg Cd/L	(>=892.0<=916.0°C - DecompTemp)
Cadmium carbonate	208-168-9	4.44	3.2 mg/L	(ca.343.0°C - DecompTemp)

[4] Values obtain from corresponding registration data except values marked with (h) which are taken from: D. R. Lide (Ed.), *CRC Handbook of Chemistry and Physics*, 75th Edition, CRC Press, Boca Raton, Ann Arbor, London, Tokio, **1995**.

Name	EC / list number	Density [g / cm³]	WaterSolubility	Melting
Indium, cake	273-794-1	3.158	<1.0mg In /L	>1100.0°C
Cadmium nitrate	233-710-6	2.52 (.4H2O)[5]	2150 g/L (.4H2O)[5] (h)	>=48.0<=62.0°C (.4H2O)[5]
Cadmium, dross	273-707-7	4.77	49.0 mg/L	308.0°C
Zircon, cadmium yellow	277-135-9	4.42	66.7 µg Cd /L	(ca.949.0°C - DecompTemp)
Cadmium selenide	215-148-3	5.571	5.7 µg/L	>1350.0°C (h)
Dicadmium tin tetraoxide	700-126-2	Nan	<=0.1mg/L	(>900.0<=1000.0°C - DecompTemp)
Cadmium chloride	233-296-7	3.91	1400 g/L	>=553.0<=560.0°C

2. EU Harmonised Classification and Labelling - CLP (EC) 1272/2008

Information about the EU harmonised classification and labelling for cadmium and some of its inorganic compounds is included in Table 3 below. Cadmium and most of the cadmium containing substances are classified as Carc. 2 or Carc. 1B.

Table 3: EU classification: Summary of harmonised classifications

Index No	International Chemical Id	EC No	CAS No	Hazard Class and Category Code	Hazard Statement Code
048-001-00-5	cadmium compounds, with the exception of cadmium sulphoselenide (xCdS.yCdSe), reaction mass of cadmium sulphide with zinc sulphide (xCdS.yZnS), reaction mass of cadmium sulphide with mercury sulphide (xCdS.yHgS), and those specified elsewhere in this Annex[6]			Acute Tox. 4* Acute Tox. 4* Acute Tox. 4* Aquatic Acute 1 Aquatic Chronic 1	H332 H312 H302 H400 H410

[5] The indicated values are for the tetrahydrate $Cd(NO_3)_2.4H_2O$

[6] This refers to Annex VI to the CLP Regulation (EC) 1272/2008

Index No	International Chemical Id	EC No	CAS No	Hazard Class and Category Code	Hazard Statement Code
048-002-00-0	cadmium (non-pyrophoric) [1] cadmium oxide (non-pyrophoric) [2]	231-152-8 [1] 215-146-2 [2]	7440-43-9 [1] 1306-19-0 [2]	Carc. 1B Muta. 2 Repr. 2 Acute Tox. 2 * STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H341 H361fd H330 H372 ** H400 H410
048-003-00-6	cadmium diformate; cadmiumformate	224-729-0	4464-23-7	Carc. 2 Acute Tox. 3 * Acute Tox. 3 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H351 H331 H301 H373 ** H400 H410
048-004-00-1	cadmium cyanide	208-829-1	542-83-6	Carc. 2 Acute Tox. 1 Acute Tox. 2 * Acute Tox. 2 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H351 H310 H330 H300 H373 ** H400 H410
048-005-00-7	cadmiumhexafluorosilicate(2-); cadmium fluorosilica	241-084-0	17010-21-8	Carc. 2 Acute Tox. 3 * Acute Tox. 3 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H351 H331 H301 H373 ** H400 H410
048-006-00-2	cadmium fluoride	232-222-0	7790-79-6	Carc. 1B Muta. 1B Repr. 1B Acute Tox. 2 * Acute Tox. 3 * STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H360FD H330 H301 H372 ** H400 H410
048-007-00-8	cadmium iodide	232-223-6	7790-80-9	Carc. 2 Acute Tox. 3 * Acute Tox. 3 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H351 H331 H301 H373 ** H400 H410
048-008-00-3	cadmium chloride	233-296-7	10108-64-2	Carc. 1B Muta. 1B Repr. 1B Acute Tox. 2 * Acute Tox. 3 * STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H360FD H330 H301 H372 ** H400 H410

Index No	International Chemical Id	EC No	CAS No	Hazard Class and Category Code	Hazard Statement Code
048-009-00-9	cadmium sulphate	233-331-6	10124-36-4	Carc. 1B Muta. 1B Repr. 1B Acute Tox. 2 * Acute Tox. 3 * STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H360FD H330 H301 H372 ** H400 H410
048-010-00-4	cadmium sulphide	215-147-8	1306-23-6	Carc. 1B Muta. 2 Repr. 2 Acute Tox. 4 * STOT RE 1 Aquatic Chronic 4	H350 H341 H361fd H302 H372 ** H413
048-011-00-X	cadmium (pyrophoric)	231-152-8	7440-43-9	Pyr. Sol. 1 Carc. 1B Muta. 2 Repr. 2 Acute Tox. 2 * STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H250 H350 H341 H361fd H330 H372 ** H400 H410
048-012-00-5	cadmium carbonate	208-168-9	513-78-0	Carc. 1B Muta. 1B Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H332 H312 H302 H372 (kidney, bone) H400 H410
048-013-00-0	cadmium hydroxide; cadmium dihydroxide	244-168-5	21041-95-2	Carc. 1B Muta. 1B Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H332 H312 H302 H372 (kidney, bone) H400 H410
048-014-00-6	cadmium nitrate; cadmium dinitrate	233-710-6	10325-94-7	Carc. 1B Muta. 1B Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H332 H312 H302 H372 (kidney, bone) H400 H410

3. Chemical Agent and Scope of Legislation - Regulated uses of cadmium and its inorganic compounds in the EU

3.1 Directive 98/24/EC and Directive 2004/37/EC

Cadmium and its inorganic compounds are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and fall within the scope of this legislation.

Cadmium and its inorganic compounds are also carcinogens or mutagens for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and fall within the scope of this legislation.

3.2 REACH Registrations

There are 17 substances for cadmium and its compounds considered registered under REACH[7]. For these substances tonnage information is available as part of a REACH registration. These include, 15 substances with full registrations, and 2 substances registered only as an intermediate. Information on the registrations is available on the ECHA website[8]. Chemical Safety Reports are only available for those with a full registration.

Error! Reference source not found. gives a summary of the registrations with tonnage, for the registered substances referred to in this report.

Table 4: REACH Registrations and tonnage

Substance(s)		Tonnage (tonnes / annum)	
Name	EC number	Intermediate registration	Full registration
Cadmium	231-152-8	10-1000 (<5 reg)	1000-10 000 (21 reg)
cadmium oxide	215-146-2		1000-10 000 (7 reg)
cadmium hydroxide	244-168-5		1000-10 000 (<5 reg)
Silicic acid, zirconium salt, cadmium pigment-encapsulated	310-077-5		10-1000 (15 reg)
cadmium sulphide	215-147-8	10-1000 (<5 reg)	10-1000 (<5 reg)
cadmium telluride	215-149-9		10-1000 (<5 reg)
cadmium sulfoselenide	701-229-5		10-1000 (<5 reg)
cadmium sulphate	233-331-6	10-1000 (<5 reg)	

[7] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396 of 30 December 2006, p. 1; corrected by OJ L 136, 29.5.2007, p. 3)

[8] ECHA https://echa.europa.eu/information-on-chemicals/registered-substances

Substance(s)		Tonnage (tonnes / annum)	
Name	EC number	Intermediate registration	Full registration
cadmium carbonate	208-168-9	10-1000 (<5 reg)	10-1000 (<5 reg)
cadmium zinc sulfide (hexagonal)	701-227-4		10-1000 (<5 reg)
Indium, cake	273-794-1		10-1000 (<5 reg)
cadmium nitrate	233-710-6		10-1000 (<5 reg)
Cadmium, dross	273-707-7	10-1000 (<5 reg)	
Zircon, cadmium yellow	277-135-9		10-1000 (6 reg)
cadmium chloride	233-296-7		<10 (<5 reg)
cadmium selenide	215-148-3		<10 (<5 reg)
Dicadmium tin tetraoxide	700-126-2		<10 (<5 reg)

3.3 Authorised uses under Annex XIV of REACH

Cadmium and its compounds are not listed in Annex XIV of REACH ("Authorisation List"). Therefore there are no authorised uses for cadmium and its compounds. .

3.4 Restricted uses under Annex XVII of REACH

REACH Restriction entry 23[9]:

- Mixtures and articles produced from plastic material (as listed) shall not be placed on the market if the concentration of cadmium (expressed as Cd metal) is equal to or greater than 0.01 % by weight of the plastic material.
- Shall not be used or placed on the market in paints with codes [3208] [3209] in a concentration (expressed as Cadmium metal) equal to or greater than 0,01 % by weight
- Shall not be used for cadmium plating metallic articles or components of the articles used in certain sectors/applications
- Shall not be used in brazing fillers in concentration equal to or greater than 0.01 % by weight.
- Shall not be used or placed on the market if the concentration is equal to or greater than 0,01 % by weight of the metal in:
  - metal beads and other metal components for jewellery making;
  - metal parts of jewellery and imitation jewellery articles and hair accessories

[9] https://echa.europa.eu/documents/10162/3bfef8a3-8c97-4d85-ae0b-ac6827de49a9

3.4.1 Other EU restrictions

EU RoHS 2[10] restricts cadmium and its compounds in all electrical and electronic products. The limit is 0.01%. The limit applies to each homogeneous material in a product rather than a product or a part itself.

3.5 Plant Protection Products Regulation (EC) 1107/2009

There are no plant protection products authorised under Regulation (EC) No 1107/2009 which are based on or include cadmium or its compounds. Cadmium or its compounds are not listed as active substances in Annex I to Directive 91/414/EEC.

3.6 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

There are no authorisations for use of cadmium or its compounds in human or veterinary medicines.

3.7 Biocidal Products Regulation (EU) 528/2012

There have been no biocidal products authorised under Regulation (EU) No 528/2012 which are based on or include cadmium or its compounds, nor has there been an active substance evaluation on cadmium or its compounds. Cadmium or its compounds are not listed as active substances in Annex I of Regulation (EU) No 528/2012.

4. Existing Occupational Exposure Limits

A binding occupational exposure limit value of 0.001 mg/m^3 was set for cadmium (inhalable fraction) in 2019 under the Carcinogens and Mutagens Directive (Directive (EU) 2019/983). Member States must bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 11 July 2021. During a transition period, until 11 July 2027, the limit value for the inhalable fraction is 0.004 mg/m^{3}and,in Member States with an implemented biomonitoring system, a biological (urine) limit value of ≤0.002 mg Cadmium/g creatinine with an air limit value is 0.004 mg/m^3 for the respirable fraction can be used.

Currently, occupational exposure limits for cadmium and its inorganic compounds exist in a number of countries. These may be for inhalable (or total) and/or respirable fraction. STEL values have also been established by some Member States. Those are presented in Table 5, but the list should not be considered as exhaustive.

[10] https://ec.europa.eu/environment/waste/rohs_eee/legis_en.htm

Table 5: Existing Occupational Exposure Limits (OELs) indicated as 8-h Time-Weighted Average (TWA) for cadmium and its inorganic compounds……

Country/ Organisation	Cadmium and inorganic compounds TWA -8 hrs mg/m^3	Cadmium and inorganic compounds Short term mg/m^3	Comments
Austria	0.015 (I) 0.03 (I)	0.06 (I) 0.12 (I) 0.002 (R)	TRK value[1] (based on technical feasibility) Battery production, thermal zinc, lead and copper recovery, welding of alloys containing cadmium
Belgium	0.01 (I) 0.02 (R)		
Denmark	0.005	0.010	Total dust
Finland	0.004 (I)		
France	0.004 (I)		Indicative statutory limit value Alveolar fraction if biological monitoring makes it possible to ensure compliance with a maximum biological value of 2 µg Cd / g of creatinine in the urine.
Germany (AGS)	0.00016 (R)	0.008 (I)	Workplace exposure concentration corresponding to the proposed preliminary acceptable cancer risk. (long term value) Workplace exposure concentration corresponding to the proposed tolerable cancer risk (short term value)
Hungary	0.015	0.015	Except CdO, $CdCl_2$, CdF_2 Total dust
Ireland	0.01 (I)	0.002	except CdO fume and CdS pigments
Italy			
Latvia	0.01	0.05	Total dust

Country/ Organisation	Cadmium and inorganic compounds TWA -8 hrs mg/m³	Cadmium and inorganic compounds Short term mg/m³	Comments
Netherlands			
Poland	0.01 (R)		Fumes and dusts
Romania	0.05		Total dust
Spain	0.01 (I) 0.002(R)		
Sweden	0.02 0.005 (R)		Total dust
Switzerland	0.015 (I) 0.004 (R)		
United kingdom	0.025		
USA-NIOSH	0.01		Total dust Corresponds to minimal feasible concentration For fume and dust
USA-OSHA	0.005 (total dust)		Total dust
ACGIH	0.01 (I) 0.002 (R)		

Notes:

(1): (Technische Richtkonzentration trans. Technical Approximate Concentration)

(I) Inhalable fraction

(R) Respirable fraction

Source: Gestis database (searched August 2020): International limit values for chemical agents (Occupational exposure limits, OELs) (https://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp); ACGIH (2001).

Biological limit values

Some Member States have also published biological limit values (BLV) for cadmium in blood and/ or urine. The (non-exhaustive) tables below shows the list of biological limit values.

The tables also show reference values for the non-occupationally exposed population. They represent the upper concentration of the chemical agent or one of its metabolites in any appropriate biological medium corresponding to a certain percentile (generally the 90th or 95th percentile) in a defined reference population.

Table 6 : Overview of existing occupational BLVs and reference values for the general population (not occupationally exposed) for cadmium and inorganic compounds in blood

Country	Cadmium in blood	Specifications	References
France (ANSES)	4 µg/L	VLB sampling time not relevant	ANSES (2018)
France (ANSES)	0.7 µg/for non-smokers (3 µg/L for smokers)	VBR (general population) sampling time not relevant	ANSES (2018)
Finland	50 nmol/L (5.6 µg/L)	BAL sampling time not relevant	FIOH (2019)
Finland	5 nmol/L (0.56 µg/L) for non-smokers 18 nmol/L (2.9 µg/L) for smokers	Reference value (general public)	FIOH (2019)
Germany	1 µg/L for non-smokers	BAR (1)	DFG (2010)
ACGIH	5 µg/L		ACGIH 2016
US CDD	1.35 µg/L (95ème percentile)	general population	NHANES (2018)
Spain	5 µg/l	VLB	INSST (2019)

VLB: Valeurs limite biologiques (Biological limit value for workers)

VBR: Valeurs biologiques de reference (Reference values for the non-occupationally exposed general population)

BAL: Biological Action Levels

BAR: Background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to this substance

VLB: Valor límite biológico (Biological limit value for the workers)

Table 7 : Overview of existing occupational BLVs and reference values for the general population (not occupationally exposed) for cadmium and inorganic compounds in urine

Country	Cadmium in urine	Specifications	References
France (ANSES)	5 µg/g. creatinine 2 µg/g creatinine (	VLB For an assessment with an 8 h OEL of 0,004 mg/m^3 for cadmium and inorganic compounds	ANSES (2018)
France (ANSES)	0,8 µg/g. creatinine for non-smokers 1 µg/g. creatinine for smokers	VBR (general population) sampling time not relevant	ANSES (2018)
Finland	20 nmol/L (2,2 µg/L)	BLV sampling time not relevant	STM (2018)
Finland	5 nmol/L (0.56 µg/L) for non-smokers 10 nmol/L (1.1 µg/L) for smokers	Reference value(general public)	FIOH (2019)
Germany	0,8 µg/L for non-smokers	BAR (1)	DFG (2010)
ACGIH	5 µg/g. creatinine		ACGIH 2016
Switzerland	5 µg/g creatinine 5,03 nmol/mmol creatinine		SUVA (2016)
Spain	2 µg/g creatinine	VLB	

VLB: Valeurs limite biologiques (Biological limit value for workers)

VBR: Valeurs biologiques de reference (Reference values for the non-occupationally exposed general population)

BAR: Background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to this substance

VLB: Valor límite biológico (Biological limit value for the workers)

Source: Biotox database (http://www.inrs.fr/publications/bdd/biotox.html)

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

Cadmium makes up about 0.1 ppm of Earth's crust. It is much rarer than zinc, which makes up about 65 ppm. No significant deposits of cadmium-containing ores are known. The only cadmium mineral of importance, greenockite (Cadmium Sulphide), is nearly always associated with sphalerite (Zinc Sulphide). This association is caused by geochemical similarity between zinc and cadmium, with no geological process likely to separate them. Thus, cadmium is produced mainly as a byproduct of mining, smelting, and refining sulphidic ores of zinc, and, to a lesser degree, lead and copper. Small amounts of cadmium, about 10% of consumption, are produced from secondary sources, mainly from dust generated by recycling iron and steel scrap (coal can contain significant amounts of cadmium, which ends up mostly in flue dust). A significant amount of cadmium is also recovered from spent nickel cadmium batteries.

5.2 Occupational exposure

In an occupational setting the highest risk of cadmium exposure comes from processes involving heating cadmium containing materials such as smelting and electroplating. Risk will vary depending on the workplace, but occupations with the highest potential levels of exposure include smelting zinc and lead ores, welding or remelting cadmium-coated steel, working with solders that contain cadmium, and producing, processing, and handling cadmium powders. Recycling of scrap metal and Ni-Cd batteries may also involve some exposure.

In industrial settings, airborne exposure levels typically have been reported to range from 5 to 50 µg/m³; with extreme values up to 400 µg/m³ (European Chemical Bureau, 2007). More recent data from industrial monitoring indicates that the majority of workers (76%) are exposed to <4 µg/m³, and 99% or workers are exposed to <10 µg/m³. More information on the monitoring programme is in Section 5.4.1.

5.3 Production and Use Information

The following information is extracted from the U.S. GEOLOGICAL SURVEY MINERALS YEARBOOK (2017):

Primary Production (2017) - Global cadmium production, excluding U.S. production, decreased slightly to an estimated 25,400 t. The two leading producers were China and the Republic of Korea, accounting for 32% and 22%, respectively, of global production. Most (65%) of the world's refined cadmium was produced in Asia and the Pacific (Australia, China, India, Japan, and the Republic of Korea), followed by Europe and Central Eurasia (Bulgaria, Germany, Kazakhstan, the Netherlands, Norway, Poland, Russia, and Uzbekistan) with 20%; North America (Canada and Mexico), 12%; and South America (Argentina, Brazil, and Peru), 4%.

Major sites in Europe include:

Country	Location of main facilities
Bulgaria	Plovdiv, Plovdiv.
Netherlands	Budel, Noord Braban
Norway	Odda, Hordaland
Poland	Miasteczko Slaskie, Silesia

Secondary Production (2017) - Most secondary metal was recovered at NiCd battery recycling facilities in Asia, Europe, and the United States. In Europe, NiCd battery recycling took place in Germany, Sweden, and France.

Consumption (2017) - Based on production and trade data within Europe, Belgium and Sweden are the two biggest consumers. In Belgium, cadmium is used to produce cadmium compounds, including cadmium chloride, nitrate, and oxide, and cadmium powder. Those cadmium compounds and powder were used mainly in coatings, NiCd batteries, paint pigments, PVC stabilizers, surface treatments, and thin-film solar panels. Information from registrants in Sweden indicates the same uses, plus a use in the nuclear industry (alloys for moderator bars).

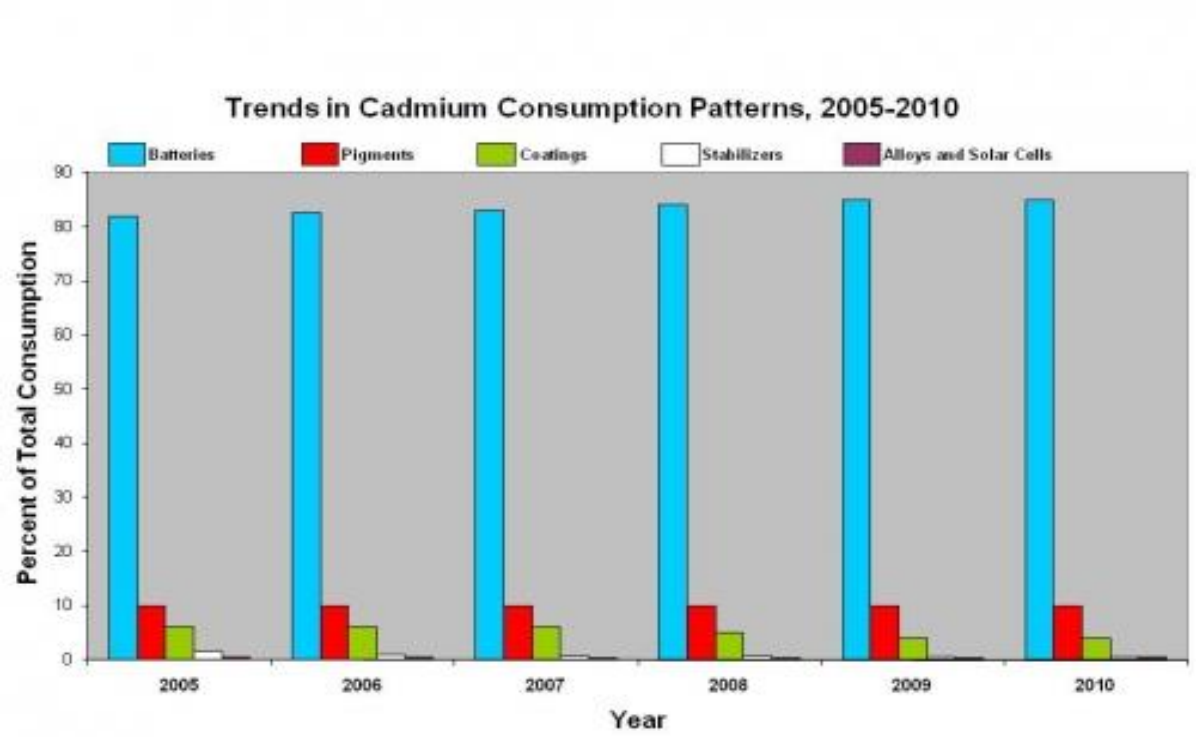
The following substances, listed in order of registration tonnage, account for 99% of cadmium and compound usage (*not including frits[11]).

Name	EC number	Uses
Cadmium	231-152-8	Batteries, coatings, alloys, intermediate, stabilisers
Cadmium oxide	215-146-2	Batteries, coatings, intermediate, lab reagent
Cadmium hydroxide	244-168-5	Batteries, lab reagent
Silicic acid, zirconium salt, cadmium pigment-encapsulated	310-077-5	Pigment
Cadmium sulphide	215-147-8	Pigment, intermediate, photovoltaic agent
Cadmium telluride	215-149-9	Intermediate, photovoltaic agent
Cadmium sulfoselenide	701-229-5	Pigment, lab reagent
Cadmium sulphate	233-331-6	Intermediate, lab reagent
Cadmium zinc sulphide yellow	701-227-4	Pigment, lab reagent
Cadmium carbonate	208-168-9	Intermediate
Indium, cake	273-794-1	Intermediate

[11] Frits can contain a variety of cadmium compounds (normally as pigments) in different concentration ranges. It is not possible from the registration information to know exactly how much of the different cadmium compounds are in the frits as they are presented as ranges.

The main industrial uses of cadmium and its compounds are for the production of:
- active electrode materials in batteries (about 85 % of its uses in 2010, mainly cadmium oxide (CdO)),
- pigments in ceramics, plastics and glasses (10%, $Cd_{(1-x)}$ Zn_xS and $CdS_{(1-x)}Se_x$)),
- stabilisers in PVC and related polymers (1%, mainly organic salts),
- constituents of coating for steel and non-ferrous metals (4%, Cadmium metal), and
- alloys and other uses (1%, Cd metal) (International Cadmium Association).

The Figure below is copied from the International Cadmium Association, showing Trends in Cadmium Consumption Patterns from 2005 through 2010:[12]



Batteries

The primary use of cadmium, in the form of cadmium hydroxide, is in electrodes for Ni-Cd batteries. In 2010, about 85% of cadmium was used in batteries, predominantly in rechargeable nickel-cadmium batteries. Nickel-cadmium cells have a nominal cell potential of 1.2 V. The cell consists of a positive nickel hydroxide electrode and a negative cadmium electrode plate separated by an alkaline electrolyte (potassium hydroxide). A number of types of cell construction are possible. These variations in cell construction lie mostly in the nature of electrode support utilised. For the positive electrode three principal types are recognised - pocket plate, sintered plate and fibre plates. An electrode support is necessary because the active material (nickel hydroxide) is usually in powder form and held in pocket plates or mixed with gel or paste and placed in sintered or fibre electrodes. Also, graphite or iron oxide needs to be added to improve the conductivity of both nickel and cadmium hydroxide.

[12] https://www.cadmium.org/introduction

Nickel-cadmium batteries are characterised by their resistance to electrical abuse, high cycle lives, reliability and versatility and have found a wide range of application. The several types of cell construction are manufactured in a wide range of size, capacity and shape and the choice of a particular battery will depend upon the application and its current load requirements. These applications are principally of two types: industrial and portable batteries.

(a) Industrial nickel-cadmium batteries are of the vented (or open) or semi-sealed type, and may be of pocket plate, sintered plate or fibre structured construction. Applications include railway uses such as locomotive starting, emergency braking, coach lighting and air conditioning, trackside power for signalling and warning lights and others. Other uses include standby power for alarm systems, emergency lighting, military communications, solar energy storage, navigation equipment, military equipment, hospital operating theatres and many others. Semi-sealed industrial batteries are used in aeronautical applications where they are used to start engines and also to provide stand-by power for aircraft systems when the principal power source fails. After long periods of operation most vented or semi-sealed cells may require electrolyte maintenance by topping up with distilled water.

(b) Portable nickel-cadmium batteries are of the sealed type and are generally of sintered plate construction. They may be of cylindrical, button or prismatic design. Sealed nickel-cadmium batteries are in strong demand for use in consumer electronic equipment such as cellular telephones, portable tools, toys, camcorders and other domestic cordless appliances. They are also used for memory back-up in computing equipment, military and civil communications, emergency lighting and many other similar applications. Sealed cells require no maintenance and may be recharged up to 2000 times.

Another type of battery based on cadmium is the silver-cadmium battery, using cadmium metal as its negative terminal, silver oxide as the positive terminal, and an alkaline water-based electrolyte. It produces about 1.1 volts per cell on discharge, and about 40 watt-hours per kilogram specific energy density. A silver-cadmium battery provides more energy than a nickel-cadmium cell of comparable weight, however, the high cost of silver and the toxicity of cadmium restricts its applications.

NiCd batteries had been favoured for use in less expensive consumer appliances and electronics owing to their cost advantage over other battery chemistries. Lithium-ion batteries, however, have significantly replaced NiCd batteries in some electronics, particularly power tools, and substitution is expected to continue. NiCd batteries are expected to continue to be used in certain industrial applications because of their superior reliability and stability compared with the other rechargeable battery technologies. NiCd batteries power some battery-powered electric vehicles and are also used in a limited number of hybrid electric vehicles. NiCd batteries also are used as buffers in transportable, renewable hybrid-power systems developed to generate electricity in remote locations and in underdeveloped regions. Industrial-sized NiCd batteries potentially could be used to store energy produced by certain on-grid solar or wind systems. Excess energy generated during periods of low electricity demand could be stored in batteries, from which it would later be dispatched during periods of high electricity demand. NiCd may be a favoured battery chemistry for this use owing to its stability in offshore and harsh weather environments. Cadmium-containing residues will continue to be produced as a by-product from zinc smelting, regardless of cadmium demand. Although there is growth potential in certain end uses, if applications for and consumption of cadmium continue to decline, excess by-product residues may need to be permanently stockpiled and managed.

Pigments

Various cadmium salts are used in paint pigments, with Cadmium sulphide (CdS) as a yellow pigment being the most common, used in a wide variety of applications, including engineering plastics, glass, glazes, ceramics, rubber, enamels, artists' colours, and fireworks.

a) Plastics

Most cadmium pigments are used in plastics. These pigments disperse well in most polymers to give good colouring and high opacity and tinting strength. The pigments are insoluble in organic solvents, have good resistance to alkalis and in most cases will remain colour fast for the life of the plastic. As a result, cadmium pigments have been used in a wide range of plastic products. Nowadays, their greatest application is in complex polymers which are processed at higher temperatures and require the unique durability and technical performance of a cadmium pigment. Pigments are usually incorporated in plastics in proportions of 0.01 to 0.75 per cent by weight.

(b) Specialist and industrial paints

To painters who work with the pigments, cadmium provides the most brilliant and durable yellows, oranges, and reds — so much so that during production, these colours are significantly toned down before they are ground with oils and binders or blended into watercolours, gouaches, acrylics, and other paint and pigment formulations. Cadmium yellows and reds can have service temperatures well above 300C and are used in coatings for process chemical and steam pipes. They can also be incorporated in latex and acrylic coatings. Cadmium pigments are usually incorporated in these paints in proportions of 10 to 15 per cent by weight.

(c) Ceramics and glasses

The unique abilities of highly stable cadmium pigments to withstand high processing and service temperatures make them the main choice for glasses, ceramic glazes and vitreous and porcelain enamels. In transparent glasses the cadmium pigment particles are colloidally dispersed to produce the colours by selective absorption and scattering. The addition of 0.5 percent by weight of cadmium pigment produces bright transparent glasses with colour ranging from intense yellow through to ruby red depending upon the composition.

(d) Miscellaneous uses

Cadmium pigments have a number of other minor uses in rubber, paper and inks although these are small in terms of cadmium consumption.

Coatings/Electroplating

Cadmium and cadmium alloys are used as engineered or electroplated coatings on iron, steel aluminium, and other non-ferrous metals. Cadmium coatings are particularly useful in the electrical, electronic, aerospace, mining, offshore, automotive and defence industries where they are applied to bolts and other fasteners, chassis, connectors and other components. Electroplating accounts for over 90 per cent of all cadmium used in coatings but mechanical plating, and vacuum and ion deposition have some commercial significance[13]. The coating is normally specified in thickness' between 5 and 25 µm depending on the severity of the atmosphere. Chromate post-treatment of the coating can increase coating life.

(a) Electroplating

Cadmium is electrodeposited on the metal article from an electrolyte solution of cadmium salts in barrels or vats. These electrolyte solutions are nearly always based on the alkaline cyanide system. Other solution types are used, such as those based on fluoroborates, but these have not proved popular as they lack the excellent combination of brightness, covering power, throwing power and wide operating parameters of the alkaline cyanide system. When a current is passed through the electrolyte, cadmium is electrodeposited on

[13] https://www.cadmium.org/cadmium-applications/cadmium-coatings

the metal article at the cathode and cadmium from the anode goes into solution. Large or delicate articles are attached to racks and vat-plated whilst small components, such as bolts, washers, nuts, springs and clips can be vat-plated in drum cages or plated in a rotating barrel.

(b) Mechanical plating

This process uses mechanical energy to deposit metal coatings on small components by the impact of glass beads. Either cadmium or mixed-metal coatings of cadmium-tin or cadmium-zinc can be applied when glass beads, proprietary chemicals, water and metal powder are tumbled with the components in a rotating barrel. The process is suited to components such as fasteners and clips which are small enough to be plated in a barrel.

(c) Vacuum and ion deposition

Conventional thermal vapour deposition involves heating of cadmium in a vacuum until it vaporises. Cadmium atoms then condense on the substrate to form a thin high quality coating of cadmium. Ion deposition in argon atmospheres adds more energy to this coating process and uses 'sputter cleaning' to clean the substrate surface. As a result, ion deposition is said to give improved coating adhesion, density and uniformity. Components such as undercarriage legs of transport aircraft, helicopter rotor parts and other high strength steel components have been successfully coated using this method.

PVC Stabilisers

Cadmium salts of organic acids were widely used in the past as heat and light stabilisers for flexible vinyl chloride polymers and other plastics (IARC 2012, NTP 2016).

Cadmium-bearing stabilisers are used to retard the degradation processes which occur in polyvinylchloride (PVC) and related polymers on exposure to heat and ultra violet light (sunlight). These stabilisers consist of mixtures of barium, lead and cadmium organic salts, usually cadmium stearate or cadmium laurate, which are incorporated into the PVC before processing and which arrest any degradation reactions as soon as they occur. They ensure that PVC develops good initial colour and clarity and allow high processing temperatures to be employed. They also ensure a longer service life for the PVC. Cadmium-bearing stabilisers also allow higher temperature processing for some PVC resins and impart dynamic and thermal stability to resins processed in calendering (sheet rolling) operations.

Barium/cadmium stabilisers typically contain between 1 and 15 per cent cadmium and usually constitute about 0.5 to 2.5 per cent of the final PVC compound. No alternative stabilisers offer all of the advantages of barium/cadmium formulations and they are incorporated into PVC used, for example, in rigid profiles for window and door frames, water and drain pipes, hoses and electrical insulation.

Outlook

Cadmium use is generally decreasing because it is toxic (it is specifically listed in the European Restriction of Hazardous Substances[14]) and nickel-cadmium batteries have been replaced with nickel-metal hydride and lithium-ion batteries. One of its few new uses is in cadmium telluride solar panels. Solar cell manufacturing may become a significant market for cadmium in the future. Cadmium telluride thin-film photovoltaics are an alternative to the traditional silicon-based solar cells and are a preferred photovoltaic technology for commercial rooftop applications and for large-scale, ground-mounted utility systems. There are also other minor/niche uses including in nuclear fission, QLED TVs, anticancer drugs and lab uses.

[14] https://echa.europa.eu/documents/10162/3bfef8a3-8c97-4d85-ae0b-ac6827de49a9

5.4 Routes of exposure and uptake

In humans, uptake of cadmium occurs occupationally *via* inhalation of cadmium containing dusts and fumes in industrial settings (occupational exposure), and for the general population *via* the gastrointestinal route through contaminated food (environmental exposure).

An additional source of cadmium exposure is tobacco smoke. Each cigarette contains about 2 µg of cadmium, the amount varying considerably with the origin of tobacco leaves.

5.4.1 Worker exposure

The major routes of occupational exposure are inhalation of dust and fumes and incidental ingestion of dust from contaminated hands, cigarettes, or food (NTP 2016). Exposure can be controlled through the control and reduction of cadmium emissions, good industrial hygiene practices and personal protective equipment.

The International Cadmium Association together with Eurometaux have developed an industry guidance[15] with the purpose of bringing cadmium exposure of all employees at a level which ensures an adequate control of risks to workers. This guidance focuses on 3 pillars to be implemented concurrently:

1. Ensure plant cleanliness,
2. Implement collective and individual hygiene procedures,
3. Conduct medical surveillance of exposed workers, including biomonitoring of both urinary cadmium (Cd-U) and blood cadmium (Cd-B), as a safety net to detect any issue arising in pillars (1) and (2) before any adverse effect is likely to arise.

5.4.2 General population

Cadmium is mined and then released into the environment mainly through the air during smelting. Once in the environment, cadmium moves easily through the soil and is taken up into the food chain. Certain plants, such as tobacco, rice, other cereal grains, potatoes, and other vegetables, take up cadmium from the soil[16].

The general population may be exposed through consumption of food and drinking water, inhalation of cadmium-containing particles from ambient air or cigarette smoke, or ingestion of contaminated soil and dust. Tobacco smokers are exposed to an estimated 1.7 µg of cadmium per cigarette. Food is the major non-occupational source of cadmium exposure for non-smokers; average cadmium levels in the U.S. food supply range from 2 to 40 ppb. Smokers typically have cadmium blood and body burdens more than double those of non-smokers (Waalkes et al., 2003). In general, smokers will have higher urinary cadmium than non-smokers (Mannino et al., 2004).

According to EFSA (2009), the mean estimated dietary exposure to cadmium is 2.3 µg/kg bw/week (range 2.3-3.0 µg/kg bw/week). The weekly dietary cadmium exposure of vegetarians may be higher, around 5.4 µg/kg bw/week, due to higher consumption of cereals, nuts, oilseeds and pulses. Also high intake of bivalve molluscs or wild mushroom may increase the weekly intake of cadmium. EFSA estimated that in order to limit the cadmium body burden and keep the urinary cadmium level below 1 µg/g creatinine at the

[15] https://www.cadmium.org/doc/news_18/2018-2-icda-guidance-document.pdf

[16] https://www.atsdr.cdc.gov/csem/cadmium/docs/cadmium.pdf

age of 50 years, a tolerable weekly intake (TWI) of 2.5 µg/kg bw was established (EFSA 2009).

6. Monitoring Exposure

6.1 External exposure

Cadmium and its inorganic compounds as contained in particulates can be monitored in the workplace air using a number of official methods.

The principle of most of the methods is trapping the sample on a suitable filter by using a particle sampler (for inhalable or respirable fraction). The cadmium compounds are then extracted and further analysed using a suitable technique. The LOQ is given as mass of cadmium

The methods (included in Table 8) have validation data that show compliance with the requirements of the standard EN 482 "Workplace exposure. General requirements for the performance of procedures for the measurement of chemical agents" or potential to meet these requirements for the proposed OEL.

The table states whether the method is relevant for sampling of inhalable, respirable fraction or both as reflected in the sample and analysis methods. When a specific particulate sampler (and its associated flow rate) has been recommended the calculations of the sampling time have used the maximum flowrate recommended by the method. However, the latter does not exclude that the methods have the potential to use other sampler at different flowrates that may allow to achieve lower LOQ or to collect a different aerosol fraction. The methods appearing under "similar methods" have a similar methods principle and analytical technique and may differ in the sample preparation or in details such as the filter, or the sampler used.

Table 8: Overview of sampling and analytical methods for monitoring cadmium and cadmium compounds (as cadmium) in workplace air based on digestion of the loaded filter

METHOD/ Fraction	Analytical technique	LOQ and sampling volume ad time	Similar methods/ comments
DFG 2017 (Inhalable or respirable fraction)	ICP-AES (Inductively coupled plasma atomic emission spectroscopy)	0.007 µg/m^3 for a 1200 l sample (2 hours) Flow rate: 10 l/min	
ISO 11174	FAAS (Flame Atomic Absorption Spectroscopy)	0.25 µg/m^3 for a 480 l sample (less than 1 hour)[1]	MDHS 10/2, MétroPol Fiche 003, BGI 505-54, INSHT MA-025, OSHA ID-121, OSHA ID-189, NIOSH 7078
	ETAAS (Electrothermal Atomic Absorption Spectrometry)	0.05 µg/m^3 for a 480 l sample (less than 1 hour)[1]	

METHOD/ Fraction	Analytical technique	LOQ and sampling volume ad time	Similar methods/ comments
ISO 15202	ICP-AES (Inductively coupled plasma atomic emission spectroscopy)	5 µg/m^3 for a 480 l sample (less than 1 hour)[1]	Métropol 003, NIOSH 7300, NIOSH 7301, NIOSH 7303, OSHA ID-125G, OSHA ID-206

(1) Sampling time calculated for the maximum flow of 10 l/min (maximum flow rate for common inhalable and respirable fraction samplers)

6.2 Biomonitoring of exposure (internal exposure)

6.2.1 Background levels

Exposure to cadmium via the environment, diet or smoking results can be detected when measuring urinary cadmium levels. According to EFSA (2009), studies presenting data on background levels of cadmium indicate concentrations (95th percentiles) between 0.6 and 1.2 µg Cd/g creatinine in non-smokers. If smokers were included, the levels varied between 0.6 and 1.8 µg Cd/g creatinine. Women normally have higher concentrations of cadmium in urine than men, most likely due to increased cadmium absorption and a lower creatinine excretion. (EFSA, 2009)

Established reference values for the non-occupationally exposed population are presented in Chapter 4. The values are in the range of 0.6-0.8 µg Cd/g creatinine for non-smokers and 1 µg Cd/g creatinine for smokers.

6.2.2 Biomonitoring analytical methods

Biomonitoring of exposures to cadmium and cadmium compounds in the workplace can be carried out by the measurement of total cadmium in blood and urine (**Table 9**). The level can be quantitated either by atomic absorption spectroscopy (AAS) or by inductively coupled plasma quadrupole mass spectrometry (Q-ICP-MS). For none of the three methods a limit of quantification (LOQ) was presented, only a limit of detection (LOD).

Table 9: Overview of the available methods for biomonitoring of occupational exposures to cadmium and cadmium compounds*

Method	Matrix	Analysis	Within series imprecision	Between-day imprecision	Various	Detection limit	References
DE-DFG 1981	Blood	Flameless AAS	0.65-5.5 µg/L: *s*=12.3–5.5% *u*=27.8–12.3%	5.5-31.9 µg/L: *s*=8.4-6.6% *u*=18.1-14.7%	0.7-2.0 µg/L: *s*=16-8% ***	0.2 µg/L	DFG (1981)
DE-DFG 1984	Urine	Electro-thermal AAS	2.6-5.5 µg/L: *s*=3.7–4.0% *u*=8.1–9.5%	2.9-41.2 µg/L: *s*=10.5-6.8% *u*=22.0–14.1%	*r* = 106% **	0.2 µg/L	DFG (1984)
DE-DFG 1998	Urine	Q-ICP-MS	0.21 or 2 µg/L: *s*=4.8 or 0.9% *u*=9.0 or 1.5 %	1 µg/L: *s*=2.4% *u*=4.2%	*r* = 95% **	0.020 µg/L	DFG (1999b)

* *s* = standard deviation (rel); *u* = prognostic range; *r* = recovery rate; AAS = atomic absorption spectroscopy; Q-ICP-MS = inductively coupled plasma quadrupole mass spectrometry

** Inaccuracy; recovery rate

*** Between-laboratory imprecision

7. Health Effects

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

7.1.1 Human data

Absorption

Cadmium is absorbed by the respiratory route at rates varying between 2 and 50% depending on the cadmium compound involved (water soluble or insoluble), the size of the particles (dusts or fumes), the deposition pattern in the respiratory tract and the ventilation rate. The gastrointestinal (GI) absorption of cadmium is usually less than 5% but varies with the composition of the diet [e.g. absence of Zn in rice increases cadmium GI absorption; (Chaney et al., 2004)], and the individual iron and/or calcium status. High GI absorption rates (up to 20%) have been observed in women with lowered iron stores (serum ferritin <20 µg/l) (Flanagan et al., 1978; Berglund et al., 1994).

Distribution

Cadmium is a cumulative toxicant. It is transported from its absorption site (lungs or gut) to the liver, where it induces the synthesis of metallothionein, which sequestrates cadmium. The cadmium-metallothionein complex is then slowly released from the liver and transported in the blood to the kidneys, filtrated through the glomerulus, and reabsorbed in the proximal tubule where it may dissociate intracellularly. There, free cadmium again induces the synthesis of metallothionein, which protects against cellular toxicity until saturation. However, while protecting from acute toxicity, metallothionein binding may promote chronic toxicity in the kidney: Due to a very long half-life of cadmium in the kidney of several decades, gradual release of cadmium ions during storage may contribute to the particular susceptibility of this organ towards cadmium.

In non-occupationally exposed individuals, the cadmium concentration in the kidneys is generally between 10 and 50 mg/kg wet weight, with smokers showing 2-5 fold higher values than non-smokers (Nilsson et al., 1995).

In humans, average cadmium concentrations in liver and kidney are near zero at birth, and rise roughly linearly with age to peak values of around 40-50 mg/kg in the kidney between ages 50 and 60 (after which kidney levels plateau or decline), and 1-2 mg/kg in the liver by age 20-25 (and increase only slowly thereafter). After “normal” exposure to background cadmium levels, about 50% of the cadmium body burden is found in the kidneys, about 15% in the liver, and about 20% in the muscles (ATSDR 2012). Kjellström (1979) describes that after long-term low level exposure, about half the cadmium body burden is stored in the liver and kidneys where the major part is located in the cortex (). The ratio between cadmium tissue concentrations in the kidney and the liver decreases with the intensity of exposure and is, for instance, lower in occupationally exposed workers [7-8 fold ratio (Ellis et al., 1981; Roels et al., 1981)] than in the general population [10-30 fold ratio (Elinder, 1985)]. The distribution of cadmium in the kidney is of particular importance as this organ is one of the critical targets after long-term exposure.

Studies in the general population without occupational exposure after year 2000 have shown typical kidney concentrations of cadmium of 10 – 20 mg/kg, increasing with age, higher in women than in men, and higher in smokers than in never-smokers. Concentrations above 50 mg/kg also occur (Barregard et al., 2010). Clear positive associations have been demonstrated between cadmium in the kidney and cadmium in blood and urine (Akerstrom et al., 2013).

Cadmium can cross the placenta, but at a low rate (Lauwerys et al., 1978; Lagerkvist et al., 1992). The placenta is therefore only a partial barrier to foetal exposure (Baars et al., 2001).

Excretion

Most of the absorbed cadmium is excreted very slowly, with urinary and fecal excretion being approximately equal in quantity (<0.02% of the total body burden per day) (Kjellström et al., 1985). The biologic half-life of cadmium has been estimated to be between 10-30 years in kidney and between 5-10 years in liver (Ellis et al., 1985). The half-life in both organs, particularly the kidneys, is markedly reduced with the onset of renal toxicity when tubule loss of cadmium is accelerated.

In a recent study of the elimination constant in healthy adults, based on paired samples of cadmium in the kidney and urine, the elimination half-life varied between 18 and 44 years. A kidney concentration of 25 mg Cd/kg corresponded to cadmium in urine of 0.42 µg/g creatinine (Akerstrom et al. 2013).

In blood, most cadmium is localised in erythrocytes (90%) and values measured in adult subjects with no occupational exposure are generally lower than 1 µg/l in non-smokers. Blood cadmium values are 2-5 fold higher in smokers than in non-smokers (Staessen et al., 1990; Järup et al., 1998b). In the absence of occupational exposure, the mean urinary cadmium concentration (Cd-U) is generally below 1 µg/g creatinine in adults. While Cd-B is influenced by both recent exposure and cadmium body burden, Cd-U is mainly related to the body burden (Lauwerys and Hoet, 2001). Smokers excrete more cadmium than non-smokers, and their Cd-U is on average 1.5-fold higher than in non-smokers (ATSDR 2012).

7.1.2 Animal data

Absorption

Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. In mice, 0.27–3.2% of an oral dose of cadmium chloride was retained after 3–5 days (Bhattacharyya et al. 1981; Engström and Nordberg 1979), and in rats, 2–3% of a single oral dose of cadmium chloride was retained (Moore et al., 1973; Schäfer et al., 1990). Following 30 days of oral exposure, 0.2–0.3% of an administered dose was retained in rats (Müller et al., 1986). After 4 weeks of dietary exposure to cadmium, absorption of cadmium was reduced to one-third the absorption of rats without pre-exposure to cadmium (Schäfer et al., 1990). Cadmium pigments (cadmium sulfide and cadmium sulfoselenide) appear to be absorbed much less than cadmium chloride in rats (ATSDR 2012). Increases in cadmium absorption have been observed during gestation and lactation, 0.37 and 0.35% of cadmium administered via gavage was absorbed in mice on gestation days 8 and 15 and 0.56, 0.60, and 0.30% on lactation days 10, 17, and 24, as compared to 0.27% in non-pregnant controls; absorption was only significantly different from non-pregnant controls on lactation days 10 and 17 (Bhattacharyya et al., 1981). Similar findings were observed in mice continuously exposed to cadmium during pregnancy and/or lactation (Bhattacharyya et al., 1981, 1986). For details of these studies, see ATSDR (2012).

7.1.3 *In vitro* data

Wester et al., (1992) evaluated the percutaneous absorption of cadmium ($^{109}CdCl_2$) from water and soil into and through human skin using *in vitro* skin cells. Dermal absorption was very low.

7.1.4 Toxicokinetic modelling

Several models have been reported to describe the kinetics of cadmium in mammalian systems. Of these models, the Shank et al., (1977) and Matsubara-Khan (1974) models

provide insights into the absorption, distribution, and compartmentalization of cadmium in laboratory animals. The Nordberg-Kjellström model (Kjellström and Nordberg 1978; Nordberg and Kjellström 1979) has been used for cadmium risk assessment in humans. Although the Nordberg-Kjellström model has its limitations, it is considered to provide the best overall description of cadmium toxicokinetics, as it is largely based on human data. For details and a critical comparison of the modellings, reference can be made to ATSDR (2012).

7.1.5 Biological monitoring

Blood cadmium levels are principally indicative of recent exposure(s) to cadmium rather than of whole body-burden. In workers occupationally exposed to cadmium by inhalation blood cadmium levels ranging up to 50 µg/L have been noted (Roels et al., 1981). By contrast, urine cadmium levels primarily reflect the total body burden of cadmium, although urine levels do respond somewhat to recent exposure. Therefore, the sampling time is largely non-critical (DFG 2008). When the critical level for renal damage has been reached, urinary cadmium levels rise sharply because of the release of intra-renal cadmium along with decreased renal reabsorption of cadmium (Roels et al., 1981). In environmentally-exposed individuals, Buchet et al., (1990) report that abnormal values of various biomarkers are found in 5% of the population with urinary excretion of cadmium above the 2–4 µg Cd/24 hour level (approximately 1–3 µg/g creatinine). Significant correlations between total cadmium exposure, urinary cadmium levels and renal effects have been found in environmentally exposed populations. See Section 7.3.1.

Liver and kidney tissues preferentially accumulate cadmium. In workers exposed to cadmium by inhalation, values up to 300 µg/g wet weight in kidney and 100 µg/g wet weight in liver can be found (Roels et al., 1981). Because kidney cadmium content begins to decline after the onset of cadmium-induced renal dysfunction, liver cadmium may be a better indicator of cadmium exposure than kidney cadmium, and it has been suggested that kidney dysfunction is likely to appear at liver cadmium concentrations between 30 and 60 µg/g wet weight (Roels et al., 1981). Studies in cadmium workers suggest that metallothionein levels may also be a biomarker of cadmium exposure. Elevated levels of metallothionein gene expression were observed in peripheral blood lymphocytes in highly exposed workers. The level of metallothionein gene expression was significantly correlated with blood and urinary cadmium levels (Lu et al., 2001). Urinary metallothionein correlates with cadmium concentrations in liver, kidney, and urine (Shaikh et al., 1987). Relatively strong correlations have been found between urinary metallothionein and urinary cadmium levels in exposed humans (Kawada et al., 1989), and a dose-related increase in urinary metallothionein was found in rats exposed to cadmium in drinking water for up to 2 years (Shaikh et al., 1989).

Excess urinary excretion of low-molecular-weight proteins and solutes is associated with decreased tubular reabsorption (Hoet et al., 2012). Increased excretion of high-molecular-weight proteins or decreased serum clearance of creatinine reflects glomerular dysfunction, which is generally associated with progressive renal damage (Roels et al., 1989).

Urinary β_2-microglobulin, a low molecular weight protein, has been widely used as an indicator of tubular renal dysfunction. However, tubular renal dysfunction can be caused by exposures and diseases other than cadmium, so β_2-microglobulin is not a specific marker of cadmium-induced effects. Practical considerations in using urinary β_2-microglobulin as a marker of tubular renal dysfunction include the need to control the pH of samples to prevent the rapid degradation that occurs at pH values below 5.5 (Shaikh and Smith 1984), and the fact that urinary β_2-microglobulin excretion normally rises with age (Roels et al., 1989).

Urinary retinol-binding protein is also considered to be a sensitive indicator of decreased tubular reabsorption, but it also is not specific for cadmium-induced damage in the kidney (Shaikh and Smith 1984; Topping et al., 1986). Retinol-binding protein is more stable in

urine than β_2-microglobulin (Bernard and Lauwerys 1981) and appears to be of approximately equal sensitivity and specificity for detecting tubular proteinuria in cadmium-exposed populations (Topping et al., 1986). Levels of both proteins fluctuate over time, so regular, repeated sampling may be necessary to establish abnormal levels (Ormos et al., 1985).

Human complex-forming glycoprotein (pHC, also referred to as α1-microglobulin) is another sensitive marker of tubular renal dysfunction (Moriguchi et al., 2005). As with retinol binding protein, pHC is more stable in urine than β_2-microglobulin at room temperature and low urinary pH levels.

Urinary N-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme present in high concentrations in the proximal tubule, has been shown to correlate with urinary cadmium levels in occupationally and environmentally exposed subjects and has a better correlation with urinary cadmium levels than does β_2-microglobulin at low cadmium exposure levels (urinary cadmium <10 µg/g creatinine). However, increased urinary NAG activity can result from effects other than nephrotoxicity (Bernard and Lauwerys 1989).

There is no single biological indicator for cadmium toxicity that is entirely adequate when considered alone. Measurement of cadmium levels in various biological materials can provide an indication of recent or total cadmium exposure, but the probability of adverse effects cannot be reliably predicted except at high exposure levels. Measurement of a variety of markers of renal dysfunction can provide a sensitive measure of early kidney toxicity, but cannot establish whether cadmium exposure was the cause (ATSDR 2012).

7.1.6 Summary

The absorption of cadmium varies depending on the solubility of the cadmium compound. Absorbed cadmium is excreted slowly, resulting in an accumulation in the body. The half-life of cadmium has been estimated to be between 10-30 years in kidney and between 5-10 years in liver. Urinary cadmium levels correlate with long-term cadmium exposure, whereas blood cadmium levels reflect recent exposure.

7.2 Acute toxicity

7.2.1 Human data

Cadmium fumes (mainly consisting of CdO) when inhaled at a sufficiently high concentration are toxic to the epithelial and endothelial cells of the alveoli and cause acute pulmonary edema. Compared to elements with which it is found, such as zinc, and with which it is alloyed, such as copper, the boiling point of cadmium (765°C) is low. Cadmium oxide fumes are therefore generated in potentially toxic concentrations in

- the smelting, melting, and refining of metals that contain cadmium,
- in cadmium alloy production and welding,
- during oxyacetylene cutting of cadmium-coated steel and rivets.

In these occupational settings, the presence of CdO fumes is often unsuspected. Moreover, the acute effects induced by cadmium fumes on the lungs do not appear before a delay of 4-10 hours, and the toxicity usually remains unrecognized by those exposed, who therefore can accumulate increasing doses. Early symptoms are predominantly respiratory and similar to those of metal fume fever (shortness of breath, chest tightness, and cough that can be associated with flu-like symptoms such as chills, fever, and muscle pains). When exposure is sufficiently intense, evidence of pneumonitis and pulmonary edema develops within 1 or 2 days, which can be fatal in severely affected victims. The diagnosis of acute cadmium poisoning can be confirmed by the measurement of Cd-U (Ando et al., 1995). The dose that is sufficient to cause pulmonary oedema is not exactly known. In one fatal case, the average airborne concentration was estimated to be 8.6 mg/m³ during 5 hours, or approximately an 8-hour time-weighted average (TWA) of 5 mg/m³ (Barrett

et al., 1947). This estimate was based on lung cadmium content at postmortem examination, which may have been greater than the dose necessary to cause death, and the atmospheric concentration necessary to cause pneumonitis may therefore be considerably less. It has been estimated that an 8- hour exposure to 1 mg/m³ is immediately dangerous for life (Friberg et al., 1986).

7.2.2 Animal data

Acute inhalation of cadmium oxide fumes led to death in rats, mice, rabbits, guinea pigs, dogs, and monkeys, with the mortality rate apparently being directly proportional to the product of the duration of exposure and the concentration of inhaled cadmium (Barrett et al., 1947). The most reliable LC_{50} (after 7 days) established by this study was 500 minute-mg cadmium oxide/m^3 for rats, equivalent to a 15-minute exposure to 30 mg Cd/m^3 (Barrett et al., 1947). Rusch et al., (1986) demonstrated high mortality rates in the Sprague-Dawley rat from a 2-hour exposure to cadmium fumes at 112 mg Cd/m^3 (25 of 32 died within 1 week). A 2-hour exposure to a different form of cadmium, cadmium carbonate, at 132 mg Cd/m^3 resulted in considerably lower mortality (3 of 22 died by day 30). No deaths resulted from a 2-hour exposure to cadmium sulfide at 99 mg Cd/m^3 or cadmium selenium sulfide (cadmium red pigment) at 97 mg Cd/m^3. Grose et al., (1987) reported 2 out of 36 rats died from a 2-hour, nose-only inhalation exposure to only 0.45 mg Cd/m^3 of cadmium oxide dusts, but the statistical significance of this low rate of mortality was not reported. A 3-day, 1-hour/day exposure to cadmium chloride aerosol at 61 mg Cd/m^3 resulted in the death of 17 of 18 rats exposed (Snider et al., 1973). In another study, no deaths were observed in rats from a cadmium yellow (cadmium sulfide) pigment exposure 6 hours/day for 10 days at 6.29 mg Cd/m^3 (Klimisch 1993). Thus, it appears that in acute exposures, the relatively more soluble cadmium chloride, cadmium oxide fume, and cadmium carbonate compounds are more toxic than the relatively less soluble cadmium sulfide compounds (Klimisch 1993; Rusch et al., 1986). Rusch et al., (1986) attribute this difference to higher lung absorption and retention times for the more soluble compounds, and greater mucociliary clearance for the less-soluble pigments. Glaser et al., (1986), however, demonstrated that toxicity does not strictly correlate with solubility, and that solubility of cadmium oxide in biological fluids may be greater than its solubility in water. In hamsters, Henderson et al., (1979) reported that a 30-minute exposure to 10.1 mg Cd/m^3 from cadmium chloride resulted in the death of 3 of 30 animals by day 6 postexposure. In rabbits, Friberg (1950) reported an LC_{50} (by day 14) from a 4-hour exposure to cadmium metal dusts at 28.4 mg Cd/m^3. Barrett and co-workers (Barrett and Card 1947; Barrett et al., 1947) reported LC_{50} values for cadmium oxide fume of 940 mg Cd/m^3 for a 14-minute exposure in the monkey, 46.7 mg/m^3 for a 15-minute exposure in the mouse, 204 mg Cd/m^3 for a 15-minute exposure in the guinea pig, and 230 mg Cd/m^3 for a 15-minute exposure in the dog. However, the authors noted that these LC_{50} values are only approximations because of insufficiencies in the data or the small numbers of animals used (ATSDR 2012).

Oral LD_{50} values are presented in Table 10.

Table 10: Oral LD50 values

	CAS number	Oral LD_{50} (mg Cd /kg bw)
Cadmium oxide	1306-19-0	2330
Cadmium chloride	10108-64-2	225

Source: ECHA dissemination website

https://echa.europa.eu/information-on-chemicals/registered-substances

7.2.3 Summary

Cadmium fumes when inhaled at a sufficiently high concentration are toxic to the epithelial and endothelial cells of the alveoli and cause acute pulmonary edema. Soluble cadmium compounds are more toxic than soluble ones, as seen in animal studies.

7.3 Specific target organ toxicity/Repeated dose toxicity

7.3.1 Human data

Chronic toxicity of cadmium, both at work and in the general environment, includes effects on the kidneys (in particular tubular function), and on bone. In occupational settings, inhalation exposure may locally affect the respiratory system.

Respiratory system

Early reports indicated that anosmia was a common finding in workers often exposed to high airborne cadmium levels (Friberg, 1950; Adams and Crabtree, 1961). A study in workers exposed to lower levels (mean Cd-B, 3.7 µg/L and Cd-U, 4.4 µg/g creatinine) has confirmed that olfactory neurons are sensitive to cadmium, as demonstrated by an elevation of the olfactory threshold in these workers (Mascagni et al., 2003). Similar olfactory alterations have been reported among Polish workers from a nickel-cadmium production plant, although with much higher exposure (mean Cd-B, 35 µg/l and Cd-U, 86 µg/g creatinine) (Rydzewski et al., 1998).

Long-term inhalation exposure to cadmium and cadmium compounds may also affect lung function and is associated with the development of emphysema. Surveys of workforces exposed to cadmium published in the 1950s already indicated that protracted occupational exposure to cadmium could cause emphysema (Friberg, 1950; Lane and Campbell, 1954). Mortality studies in cadmium workers in the United Kingdom found that those who had experienced high exposure had an increased mortality rate from "bronchitis" (Armstrong and Kazantzis, 1983). In copper-cadmium alloy producers, a marked excess of deaths from chronic non-malignant respiratory diseases has also been found related to cadmium exposure (Sorahan et al., 1995). The respiratory impact of occupational cadmium exposure has also been reported in more recent studies able to collect detailed lung function measurements, good exposure assessment and to control for confounding such as other industrial exposures and tobacco smoking. In a copper-cadmium alloy factory, it was found that the cadmium-exposed workforce had evidence of airflow limitation (reduced FEV_1 and Tiffeneau ratio), hyperinflated lungs (increased RV and TLC), and reduced gas transfer (reduced DL_{CO} and KCO), an overall pattern of functional abnormalities consistent with emphysema. Regression analysis identified a significant relationship between the reduction in FEV_1, FEV_1/FVC ratio, DL_{CO}, and KCO, and both estimated cumulative cadmium exposure (years * µg/m³), and liver cadmium content measured by neutron activation analysis (Davison et al., 1988). A moderate increase in residual volume (+7% compared to controls matched for smoking habits) has also been reported in workers exposed to cadmium fumes in a factory producing silver-cadmium-copper alloys for brazing, already at cumulative exposure levels below 500 years * µg Cd/m^3 (mean Cd-U, 3 µg Cd/l) (Cortona et al., 1992). Other studies, however, have shown no cadmium-related impairment of respiratory function (Stanescu et al., 1977; Edling et al., 1986) presumably because of differences in the intensity of exposure, the species of cadmiuminvolved, variable diagnostic criteria or incomplete control for confounding factors, including tobacco smoking.

Kidneys

Numerous studies in rats, mice, rhesus monkeys and rabbits have indicated that exposure to cadmium compounds administered orally or by inhalation causes kidney damage including modifications of relative kidney weight, histological (necrosis of the proximal

tubules, interstitial fibrosis) and functional changes (reduced glomerular filtration rate, proteinuria) (European Chemical Bureau, 2007).

The first manifestation of cadmium nephrotoxicity in occupationally-exposed subjects is usually a tubular dysfunction resulting in a reabsorption defect and, hence, an increased urinary excretion of low molecular weight (LMW) proteins such as the human complex protein (HC) also called α1-microglobulin, ß$_2$-microglobulin (ß$_2$M) and/or retinol-binding protein (RBP), but also calcium and amino-acids (Lauwerys et al., 1979a,b; Elinder et al., 1985b; Jakubowski et al., 1987; Mason et al., 1988; Chia et al., 1989; Roels et al., 1993; Järup et al., 1994). Other biomarkers of tubular toxicity such as urinary alanine aminopeptidase (AAP), gamma-glutamyltranspeptidase (γGT), and the lysosomal enzyme N-acetyl-beta-D-glucosaminidase (NAG) have been used to demonstrate the tubular effects associated with occupational exposure to cadmium (Mueller et al., 1989; Bernard et al., 1995; Hoet et al., 2012; Hambach et al., 2013a,b). A cadmium body burden corresponding to a urinary excretion (Cd-U) of 5-10 µg Cd/g creatinine constitutes a threshold at or above which these tubular effects have been observed (LOEL). *Table 11* gives a compilation of relevant studies showing renal adverse effects of cadmium exposure in humans, related to biological cadmium exposure parameters. Studies examining the dose-response relationship between Cd-U and renal effects in workers are summarised in Table 12. Some of these cross-sectional studies may have underestimated the true LOEL because of the inclusion of aged workers with previously much higher exposure having probably lost a significant portion of their kidney cadmium burden when the study was conducted, resulting in a left shift of the dose-response relationship (Bernard et al., 1997).

Table 11: Dose-effect relationships between biological parameters of cadmium exposure and effects on kidneys.

Dose measure		Exposure	Effect	Reference
Cd-U (µg/g creat)	Cd-B (µg/l)			
≤1		E	increased urinary N-acetylglucosaminidase and alanine aminopeptidase activity	Noonan et al. 2002
1 – 3		E	renal tubular effects (microproteinuria)	Buchet et al. 1990, Hotz et al. 1999 Järup et al. 2000
	5.6 – 8.4	O	glomerular damage (reduced GFR)	Roels et al. 1989, Roels et al. 1991, Järup and Elinder 1994
> 4	> 6.7	O	kidney stones	Järup and Elinder 1993

E : environmental; O : occupational exposure

Table 12: Thresholds for renal effects in studies in occupational settings.

	Type of industry	n	Glomerular effect	Tubular effect	Threshold
Lauwerys et al. 1979b	Electronic workshop Ni-Cd storage battery factory Cd-producing plants	-	HMW proteins β2M-S creatinine-S	ß2M-U	Cd-U : 10 µg/g creatinine (G and T)

	Type of industry	n	Glomerular effect	Tubular effect	Threshold
Jakubowski et al 1987	alkaline battery factory	102		ß2M, RBP	Cd-U : 10-15 µg/g creat
Shaikh et al. 1987	Cd smelter	53		ß2M	Cd-U : 13.3 µg/g creat
Verschoor et al. 1987	secondary Cd users	26		ß2M, RBP, NAG	Cd-U : 5.6 µg/L
Kawada et al. 1989	Cd pigment factory	29		ß2M, NAG	Cd-U : < 10 µg/g creat (NAG)
Bernard et al. 1990	non-ferrous smelter	58	albumin, transferrin, serum β2M	ß2M, RBP, protein-1, NAG	Cd-U : 10 µg/g creat
Roels et al. 1991	Zn-Cd smelter	108	GFR decline		Cd-U : 10 µg/g creat
Toffoletto et al, 1992	Cd alloy factory	105		ß2M	Cd-U : 10 µg/g creat
Roels et al. 1993	Zn-Cd smelter	37	albumin, transferrin	ß2M, RBP and other markers	Cd-U : 4 µg/g creat (G) Cd-U : 10 µg/g creat (T)
van Sittert et al. 1992	Zn-Cd refinery	14		ß2M	Cd-U : 7 µg/g creat
Järup and Elinder 1994	battery factory	561		ß2M	Cd-U : 1.5 µg/g creat (>60 y) Cd-U : 5 µg/g creat (<60 y)
Chaumont et al. (2011)	battery factory	599		ß2M	Cd-U: 5.5-6.6 µg/g creat

G :glomerular effects, T : tubular effects

Tubular changes observed above 5-10 µg/g creatinine are generally irreversible (Roels et al., 1997; Trzcinka-Ochocka et al., 2002) and the association with further renal alteration, including a reduction of the glomerular filtration rate (GFR) (Roels et al., 1989; Roels et al., 1991; Järup et al., 1993) support the health significance of this threshold (LOAEL).

An effect on the glomerulus may also be observed in cadmium-exposed workers, as indicated by increased urinary excretion of high molecular weight (HMW) proteins including albumin, immunoglobulins G or transferrin (Bernard et al., 1990; Roels et al, 1993).

On the basis of studies conducted in Europe (Buchet et al., 1990; Hotz et al., 1999; Järup et al., 2000), United States (Noonan et al., 2002) and Asia (Jin et al., 2002), it appears that renal effects can be detected in the general population for Cd-U below 5 µg Cd/g creatinine and even from 2 µg Cd/g creatinine or below. These studies detected associations between Cd-U and markers of tubular effect (including urinary calcium excretion and its possible relationship with bone effects (see below)). The largest studies were conducted in Belgium (Cadmibel study) in a population exclusively exposed via the environment (n=1700; geometric mean Cd-U, 0.84 µg/24 h) (Buchet et al., 1990) and in Sweden (OSCAR study) in subjects with environmental and/or occupational exposure (n=1021; Cd-U, 0.18-1.8 µg/g creatinine) (Järup et al., 2000). Both studies had a cross-

sectional design and it may therefore not be excluded that some of the tubular effects observed in these cohorts are the results of previous much higher exposures (particularly in occupationally exposed subjects included in the OSCAR study), which may have contributed to shift the dose-effect/response relationship to the left. In the Cadmibel study, it was found that, after adjustment for age, gender, smoking, use of medications and urinary tract disease, tubular effects (mainly increased urinary calcium excretion) occurred in the general population at Cd-U levels ≥ 2 µg/24 h (roughly equivalent to 2 µg/g creatinine). The association between renal parameters and Cd exposure has been further confirmed in a follow-up study in the most exposed subgroup of the Cadmibel study (Pheecad study) (Hotz et al., 1999). In the OSCAR study, excretion of protein HC was found associated with Cd-U (0.18-1.8 µg/g creatinine) and the prevalence of elevated values (>95th percentile in a Swedish reference population) increased with Cd-U. The exact health significance of tubular changes observed at Cd-U levels < 5µg/ g creatinine is, however, uncertain and subject to contrasting scientific opinions. Some authors believe that these changes represent the earliest dysfunction of the renal tubular cells and should be considered as an adverse effect because the aim of public health is to detect and prevent effects at their earliest stage in the most sensitive groups of the population (Järup et al., 1998). Others, however, believe that these changes most likely reflect benign, non-adverse responses (Hotz et al., 1999; Bernard, 2004). SCOEL (2017) considered that the main arguments to support the latter interpretation are that:

- variations of tubular parameters observed at these Cd-U levels remain within a normal range,
- statistical associations with Cd-U remain weak (r^2 <10 %), and
- similar associations are observed with other non-nephrotoxic metals in urine (e.g. Cu) (Ikeda et al., 2007),
- variations of this amplitude are reversible when exposure decreases timely, and
- such changes are not predictive of an alteration of the renal function.

Mortality studies were not able to detect an excess of end-stage renal diseases in populations environmentally exposed to cadmium compounds. This was confirmed by qualitative systematic reviews, which did not support the contention that human exposure to cadmium leads to progressive chronic kidney disease (Moody et al., 2018; Byber et al. 2016). However, a study conducted in Sweden indicated that cadmium exposure was a determinant of the incidence of renal replacement therapy in a population with occupational/environmental exposure to cadmium (Hellström et al., 2001).

Several studies have also suggested that diabetics may represent a population with an increased susceptibility to the renal effects of cadmium (Buchet et al., 1990; Hellström et al., 2001; Hotz et al., 1999; Åkesson et al., 2005). However, the study by Wu et al. (2017) examined in a systematic review and meta-analysis the relationship between cadmium exposure and diabetes mellitus in two Swedish cohort studies and 9 cross-sectional studies from different countries. The meta-analysis did not show any correlation between high U-Cd levels and increased risk of diabetes mellitus risk (OR = 1.19; 95% CI = 0.83–1.71) or between B-Cd levels and risk of diabetes mellitus (OR = 1.16; 95% CI = 0.84-1.62) in the general population (Wu et al., 2017).

An additional effect on the kidney seen in workers with high cadmium exposures is an increased frequency of kidney stone formation (Friberg, 1950; Scott et al., 1978; Kazantzis, 1979; Falck et al., 1983; Elinder et al., 1985a; Thun et al., 1989; Järup and Elinder, 1993).

Bone

The bone tissue is another target organ for populations exposed occupationally and/or environmentally to cadmium compounds.

Occupational exposure to cadmium dust and fumes by inhalation has been related to the development of osteomalacia and osteoporosis among workers and the general population in different countries. The most severe form of bone disease caused by cadmium intoxication is Itai-Itai disease which was associated with kidney and bone lesions in aged Japanese women in the past (for review, see Friberg *et al.*, 1986; Tsuchiya, 1992).

A follow-up of the population examined in the Cadmibel study (mean Cd-U, approx. 0.5 and 0.8 µg/g creatinine in men and women, respectively) has shown that Cd-U was associated with an increased risk of fracture in women and, possibly, an increased risk of height loss in men. The decline of bone mineral density in postmenopausal women was significantly aggravated by cadmium exposure (Staessen et al. 1999). In the OSCAR study, bone mineral density (g/cm² and Z-score values) has been measured in the forearm of more than 1000 individuals with occupational (Cd-U, 0.06-4.7 µg/g creatinine) and/or environmental (Cd-U, 0.06-3.7 µg/g creatinine) exposure to cadmium. An association between Cd-U and decreased bone mineral density was found in older men, and an increased risk of osteoporosis was noted in men >60 years with a similar tendency in women >60 years. The threshold (LOAEL) for these effects was about 3 µg/g creatinine (Alfven et al. 2000). It has also been shown in the OSCAR cohort that cadmium exposure was associated with an increased risk of forearm fractures in people over 50 years of age (Alfven et al. 2004). The association between cadmium exposure, tubular effects and osteoporosis has been confirmed in a large cross-sectional study in a Chinese population with environmental exposure to cadmium (mean Cd-U in the group with the highest exposure, 11 µg/g creatinine) (Jin et al., 2004). In a population-based health survey conducted in southern Sweden among women with no known historical cadmium contamination [Women's Health in the Lund Area (WHILA)], negative effects of low-level cadmium exposure (median 0.67 µg/g creatinine) on bone, possibly exerted via increased bone resorption, seemed to be intensified after menopause (Åkesson et al. 2006).

Several studies with positive associations between cadmium in urine and blood and osteoporosis fractures have been published later (Zhu et al., 2004; Chen et al., 2009; Nawrot et al., 2010; Engström et al., 2011, 2012; Wallin et al., 2015). Recent reviews and a meta-analysis have indicated that effects on bone mineral density, osteoporosis, and increased fracture risk may occur at Cd-U as low as 0.5–2 µg/g creatinine (Akesson et al. 2014, Cheng et al. 2016, Nordberg et al. 2018).

In the report by Cheng et al. (2016) a meta-analysis of the data of seven studies (reporting 21,941 bone fracture cases; 504,346 participants) was carried out, evaluating the relationship between cadmium exposure and risk of any fracture. The pooled relative risk of any fracture for the highest versus lowest category of cadmium concentration was 1.30 (95% confidence interval = 1.13-1.49) and a high cadmium exposure was considered a risk factor for any fracture. However, the authors noted that the result needs to be ”interpreted cautiously because of the heterogeneity among studies and existence of publication bias”. They concluded that there is a need for further extensive prospective studies to evaluate the association between cadmium exposure and the risk of development of fracture.

In the risk assessment by Nordberg et al. (2018), it was concluded that “based on available evidence, it seems reasonable to consider long term (decades) cadmium exposures with urinary cadmium of 5 µg g^{-1} creatinine (5 nmol $mmol^{-1}$ creatinine) or higher (or blood cadmium of 5 µg L^{-1} or higher) as related to an increased risk of adverse bone effects in terms of osteoporosis and (or) decreased BoneMD” [bone mineral density]. At such exposure levels there are consistent observations of this kind of effects. As mentioned, upon cadmium exposure at lower concentrations there are several studies reporting a relationship between bone effects and exposure resulting in urinary cadmium levels < 5 µg/g creatinine. However, some other studies do not present any statistically significant

associations between bone effects and urinary cadmium (Horiguchi et al. 2015, Rignell-Hydbom et al. 2009, Trzcinka-Ochocka et al. 2009, Wallin et al. 2005).

In workers exposed to cadmium compounds, clinical bone disease has been described but the number of cases is limited. One cross-sectional study reported results compatible with a role of cadmium in the genesis of osteoporosis in exposed workers who were also included in the OSCAR study mentioned above (Järup et al. 1998a). The dose-effect/response relationship between cadmium body burden and bone effects has not been defined.

In humans, the mechanism of bone toxicity is not fully elucidated and types of bone lesions associated with cadmium exposure are not clearly identified. One likely mechanism is direct disturbance of bone metabolism but another explanation is that cadmium-induced kidney damage and/or hypercalciuria might promote osteoporosis and osteoporotic fractures. Also other potential mechanisms have been suggested, for example that the hypercalciuria may be due to nutritional imbalances resulting in a higher combined uptake of cadmium and calcium. Nordberg et al. (2018) considered that more information is needed on toxicodynamics associated with tissue levels of cadmium, on the toxicokinetics of cadmium in bone and on the relationship between biomarkers and effects.

Cardiovascular

Dozens of studies in the 2000s have demonstrated associations between cadmium in blood or urine and atherosclerosis and cardiovascular disease as presented in reviews and meta-analyses by for example Tellez-Plaza et al. (2013), Chowdhury et al. (2018), and Tinkov et al. (2018). These associations have been demonstrated in the US, Europe, and Asia and have been reported for many cardiovascular outcomes: myocardial infarction, stroke, atherosclerosis in carotid arteries and legs, and aortic aneurysm. Associations have been demonstrated also in never-smokers and suggest increased cardiovascular risk already at cadmium concentrations around 1 µg/g creatinine in urine or 1 µg/L in blood. In the systematic review and meta-analysis of Larsson and Wolk (2016) an association between cadmium exposure and increased cardiovascular disease mortality was observed.

A recent review by Sjögren et al. (2020) identified occupational mortality studies examining the risk of cardiovascular disease among cadmium-exposed workers (quantitative exposure data lacking) (Järup et al., 1998a; Virtanen and Notkola, 2002; Kazantzis et al., 1988; Sorahan et al., 1995; Binks et al., 2005; Marsh et al., 2009).. None of the studies reported an increased risk of cardiovascular disease. The review also identified 11 studies on the general population, which supported a relationship between blood or urine cadmium concentrations and the occurrence of cardiovascular disease, ischaemic heart disease, arterial disease or hypertension. An association with stroke was supported by four of the studies in the general population (Sjögren et al.2002). The risk of CVD was increased among the general population for subjects having blood cadmium levels of 0.26–0.50 µg/L compared to subjects with levels <0.17 µg/L (Tellez-Plaza et al., 2013) and at urinary cadmium levels of 0.62–0.92 µg/g creatinine compared to those with levels ≤0.61 µg/g creatinine (Barregård et al., 2016). Sjögren et al. (2002) concluded that "the evidence from general population studies for a relationship between cadmium exposure and CVD is strong". However, they noted that the relationship is weakened by the lack of positive findings in occupational studies and by confounding from smoking.

Other

A possible effect of long-term cadmium exposure to promote the occurrence of polyneuropathy in exposed workers has been suggested (Viaene *et al.* 1999).

7.3.2 Animal data

7.3.2.1 Inhalation

Early animal studies confirm that renal damage occurs following inhalation exposure to cadmium. Rabbits developed proteinuria after a 4-month inhalation exposure to cadmium metal dust at 4 mg/m^3 for 3 hours/day, 21 days/month; histologic lesions were found after an additional 3–4 months of exposure (Friberg 1950). Friberg (1950) noted that the degree of proteinuria was not especially pronounced. Most subsequent studies using inhalation exposure have not found proteinuria primarily because the levels of exposure and durations of follow up (e.g., 1–5 mg/m^3 for intermediate exposures; 0.2–2 mg/m^3 for chronic exposures) that produce serious respiratory effects have not been sufficient to produce a critical concentration of cadmium in the kidney (ATSDR 2012).

Studies in animals are in accordance with human experience that inhalation exposure to cadmium can lead to respiratory injury (ATSDR 2012). Single acute exposures in rats to 5–10 mg Cd/m^3 as cadmium oxide dust, cadmium oxide fume, or cadmium chloride for 1–5 hours resulted in moderate to severe, multifocal interstitial pneumonitis, diffuse alveolitis with hemorrhage, increased lung weight, inhibition of macrophages, focal interstitial thickening, oedema, and necrosis of alveolar type 1 cells leading to type 2 cell hyperplasia and fibroblasts (Boudreau et al. 1989; Buckley and Bassett 1987; Bus et al. 1978; Grose et al. 1987; Hart et al. 1989; NTP 1995). Similar results (i.e., severe pneumonitis) were seen in hamsters exposed to cadmium chloride at 10 mg/m^3 for 30 minutes (Henderson et al. 1979) and in rabbits exposed to cadmium oxide dusts at 4.5 mg/m^3 for 2 hours (Grose et al. 1987). Exposures in rats to cadmium chloride at 6.1 mg Cd/m^3 1 hour/day for 5, 10, or 15 days resulted in emphysema; a 3-day exposure to 61 mg Cd/m^3 for 1 hour/day resulted in pulmonary hemorrhage (Snider et al. 1973).

In subchronic inhalation toxicity studies reported by NTP (1995) male and female F344/N rats and B6C3F1 mice were exposed to cadmium oxide aerosol (MMAD=1.1-1.6 mm) for 6 hours per day, 5 days per week, for 2 or 13 weeks. Exposure levels were 0.1 to 10 mg/m^3 for the 2-week studies and 0.025 to 1 mg/m^3 for the 13-week studies. In the 2-week studies, all rats and mice at the highest exposure level (10 mg/m^3) died from respiratory toxicity characterised by inflammation, necrosis, and fibrosis of the lung. Toxicity to the nasal cavity and tracheobronchial lymph nodes was also observed in the 10 mg/m^3 groups. At the lower exposure levels, treatment-related toxic lesions were not life threatening, and all body weights were within 10% of controls. In the 13-week studies, all rats and mice (with the exception of one control mouse) survived to the end of the studies. The final mean body weight of rats in the highest exposure groups (1 mg/m^3) was 93% of the control value. For all other exposed rat and mouse groups, final mean body weights corresponded to those of the respective controls. For rats and mice in the 13-week studies, the major toxicity was to the respiratory system. Treatment-related lesions were observed in the lung, tracheobronchial lymph node, larynx, and nose. The no-observed-adverse-effect concentration (NOAEC) in the lungs was 0.025 mg/m^3 for rats. A NOAEC was not found in the lungs or larynx of mice or in the larynx of rats. At the 0.025 and 0.05 mg/m^3 levels in mice, lung lesions were minimal and not considered life threatening. A NOAEL in the nasal cavity was 0.05 mg/m^3 for rats and mice (NTP 1995).

7.3.2.2 Oral exposure

Numerous oral studies indicate that the kidney is the primary target organ of cadmium toxicity following extended oral exposure, with effects similar to those seen following inhalation exposure. A notion that a critical concentration of approximately 200 µg/g in the renal cortex must be reached before proteinuria develops is generally supported by the available animal data (for details, see ATSDR 2012).

In animals, cadmium has been shown to affect bone metabolism, manifested as osteomalacia and/or osteoporosis (Buha et al., 2019; Brzoska et al., 2010; Brzoska et al., 2004; Brzoska et al., 2005a; Brzoska et al., 2005b; Brzoska et al., 2005c). In most experimental studies, bone effects were accompanied or preceded by renal damage induced by cadmium treatment; these studies do therefore not allow an understanding of whether cadmium bone toxicity occurs in parallel to or as a consequence of nephrotoxicity. Young age (growing bones), gestation, lactation, and ovariectomy (used as an animal model of menopause) appeared to exacerbate cadmium induced bone toxicity.

7.3.2.3 Dermal exposure

No relevant data on dermal exposure were retrieved.

7.3.3 *In vitro* data

In vitro studies regarding to the chronic toxicity of cadmium were primarily focussed on the mode of action of carcinogenicity (see 8.9). At the cellular level, cadmium affects cell proliferation, differentiation, apoptosis and other cellular activities. Current evidence suggests that exposure to cadmium induces genomic instability through complex and multifactorial mechanisms. Most important seems to be cadmium interaction with DNA repair mechanism, generation of reactive oxygen species and induction of apoptosis. For details, reference can be made to reviews by Hartwig (2013a,b) and Rani et al. (2014).

In vitro studies have demonstrated that cadmium compounds exert a direct effect on bone metabolism, affecting both bone resorption and formation, and inducing calcium release (Miyahara et al., 1988; Wilson et al., 1996; Litchfield et al., 1998; Romare and Lundholm, 1999).

7.3.4 Summary

Kidney toxicity is a well-known effect related to prolonged cadmium exposure. Other important target organ effects include local lung effects upon inhalation of cadmium fumes/particles, bone effects (for example osteoporosis) and cardiovascular effects.

7.4 Irritancy and corrosivity

7.4.1 Human data

Dermal or ocular toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported dermal or ocular effects following acute or chronic exposure (ATSDR 2012).

Routine patch tests on patients with dermatitis and eczema yielded evidence of skin irritation after application of 2 % cadmium chloride solutions (European Chemical Bureau 2007, DFG 2006).

7.4.2 Animal data

7.4.2.1 Skin

No study was located that specifically examined dermal toxicity in animals following inhalation exposure to cadmium (ATSDR 2012).

7.4.2.2 Eyes

No study was located that specifically examined ocular toxicity in animals following inhalation exposure to cadmium (ATSDR 2012).

7.4.3 *In vitro* data

No relevant studies were retrieved.

7.4.4 Summary

Cadmium and its compounds are not known to cause irritation or corrosion.

7.5 Sensitisation

7.5.1 Human data

Regarding skin sensitisation, some studies report on positive patch tests with 1-2% cadmium chloride or sulfate preparations. However, the clinical relevance is questionable, and an involvement of irritation is uncertain (see 8.4.1). For details, it may be referred to DFG (2006). There are no data available for sensitization of the respiratory tract in humans caused by cadmium and its inorganic compounds (DFG 2006).

7.5.2 Animal data

No relevant data were retrieved.

7.5.1 *In vitro* data

No relevant data were retrieved.

7.5.2 Summary

Cadmium and its compounds are not known to cause sensitisation.

7.6 Genotoxicity

In the first IARC Monograph (1993), the genotoxicity core data on cadmium and its compounds, published up to 1992, were comprehensively presented. The data on the genotoxicity of cadmium published up to 2002 have been summarized and evaluated by Verougstrate et al. (2002) and in the report of the European Commission (European Chemical Bureau 2007). Data up to 2012 were compiled by ATSDR (2012). For details, reference can be made to these exhaustive compilations.

7.6.1 Human data

With regard to human exposure to cadmium and compounds, data are conflicting but seem to indicate a genotoxic potential, at least in occupational settings, but it is unclear whether these effects are solely attributable to cadmium. An informative human study was conducted by Forni et al. (1992) in a group of 40 cadmium workers with a wide range of cumulative exposure and 40 controls. An increase in chromosome-type aberrations was recorded only in the subgroup of workers with the highest cumulative exposure to Cd (>1000 µg/m³ x years, Table 13, or Cd-U>10 µg/L, Table 14). Chromosomal aberrations have also been reported in occupationally exposed persons in a more recent study (Abrahim et al., 2011). There are however also several studies with negative or ambiguous results.

Table 13: Rates of abnormal metaphases (excluding gaps) and of cells with chromosome-type aberrations in cadmium workers, subdivided by cadmium Cd cumulative exposure index, and in the matched controls (Forni et al. 1992)

Cumulative exposure index	% abnormal metaphases		% chromosome-type aberrations	
(µg/m³.y)	Cd workers	Controls	Cd workers	Controls
< 100	1.80	1.60	0.8	0.7
101 – 500	2.61	1.54	0.76	0.15
501 – 1000	2.44	2.33	1.00	0.55
> 1000	3.75	1.37	2.37*	0.50

*different from the other subgroups (p<0.01; Wilcoxon matched pair test)

Table 14: Chromosome-type aberrations in relation to Cd-U (mean values of the last 4 years) (Forni et al. 1992)

Cd workers		Controls		
Cd-U (µg/l)	% Chrom. aberr.	Cd-U (µg/l)	% Chrom. aberr.	
< 10 (N=18)	0.67	nr	0.50	N.S.
> 10 (N=20)	1.55	nr	0.41	P < 0.005

N.S.: not statistically significant; nr: not reported

Several cross-sectional studies investigating micronuclei in occupational settings have been published as well as one longitudinal study (Wegner et al., 2004). The studies by Hamurcu et al. (2001), Palus et al. (2003), and Kasuba et al. (2010 and 2012) showed statistically significant increases in the frequencies of micronuclei, whereas for example Forni (1994), Lison et al. (2019) and Wegner et al. (2004) presented negative results. The only study with data investigating a correlation between induction of micronuclei and biomarkers of exposure is the one of Kasuba et al. (2012), in which a significant association between blood cadmium levels and micronuclei was presented on the basis of a multivariate regression analysis. However, this study did not report any significant difference between blood cadmium levels of workers and control persons. No dose-response relationship could be established for micronuclei in a recent, well-conducted study by Lison et al. (2019), involving markedly exposed workers with blood cadmium levels up to 12.5 µg/L and urinary cadmium up 20 µg/L.

Cadmium levels in blood and urine of workers correlated significantly with sister chromatid exchange in two studies (Abrahim et al., 2011; Wegner et al., 2004) but not in the study by Palus et al. (2003).

Occupational exposure to cadmium was shown to correlate with increased levels of DNA damage in several studies (Hengstler et al., 2003; Palus et al., 2003; Iarmarcovai et al., 2005; Botta et al., 2006; Kasuba et al., 2012).

Studies performed in environmentally-exposed populations do not allow the identification of the type of cadmium compound(s) to which subjects were exposed. But it cannot be excluded, based on the available data, that cadmium might exert genotoxic effects in populations exposed *via* the oral route (Verougstraete et al. 2002).

7.6.2 Animal data

Experimental studies indicate that cadmium, in certain forms, has genotoxic properties (Filipic et al. 2006). In experimental systems (*in vivo*) increased DNA damage, chromosomal aberrations, micronuclei, as well as gene mutations have been reported. Cadmium oxide did not induce micronuclei in erythrocytes of mice exposed by inhalation for 13 weeks (NTP 1995).

Gene mutations were observed in the lymphocytes of rats exposed to cadmium chloride (Jianhua et al., 2006). Moreover, chromosome aberrations have been reported in bone marrow of mice (Fahmy and Ali, 2000, Mukherjee et al, 1988; El-Habit and Moneim, 2014) and in male and female germ cells (Fahmy and Aly, 2000; Miller and Adler, 1992; Watanabe et al, 1979, Watanabe et al 1982). Increases of erythrocyte micronuclei have been reported in several studies (e.g., Mukherjee et al., 1988; Jagetia and Adiga, 1994; Fahmy and Aly, 2000; Viswanadh et al., 2010; El-Habit and Moneim, 2014; Celik et al., 2009; Kasuba et al., 2002). Dose-dependent increase in sister chromatid exchanges have been reported by Fahny and Aly (2000) and Mukherjee et al. (1998). DNA damage in somatic cells has been observed several times (e.g., Valverde et al., 2000; Devi et al., 2001; Kasuba et al., 2002; Breton et al., 2013; Wada et al., 2015; Ghosh and Indra, 2018). The study by Nava-Hernandez et al. (2009) reported dose-dependent increase of DNA damage in rat germ cells.

7.6.3 *In vitro* data

In bacterial systems cadmium, like several other metals, does not induce genotoxicity. Cadmium does not induce DNA damage in cell extracts or on isolated DNA, indicating that its genotoxic activity is mediated by indirect mechanisms. Cadmium oxide was not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537, with or without exogenous metabolic activation (NTP 1995).

Increased DNA damage (Jianhua et al., 2006; Ustundag et al., 2014; Gobrecht et al., 2017; Li et al., 2017), chromosomal aberrations (Deaven and Campbell, 1980; Howard et al., 1991; Wang and Lee, 2001; Rozgaj et al., 2002, Gateva et al., 2013), micronuclei (Ustundag et al., 2014; Gobrecht et al., 2017; Turkez et al., 2012; Seoane and Dulout 2001), and gene mutations (Ochi and Ohsawa, 1983; Jianhua et al., 2006; Gobrecht et al., 2017; Oberly et al., 1982) have been reported in several studies performed with cultured mammalian or human cell lines or human peripheral blood lymphocytes, although there are also some studies showing negative results for genotoxicity. The studies have mainly been conducted with soluble cadmium compounds like cadmium chloride or cadmium sulfate.

7.6.4 Summary

Numerous animal studies and in vitro studies have indicated a genotoxic potential of cadmium compounds. Human data, on the other hand, shows conflicting results. Cadmium and several cadmium compounds have a harmonised classification under the CLP regulation as mutagens (see Chapter 2).

7.7 Carcinogenicity

7.7.1 Human data

The concern that cadmium might cause cancer in humans was raised in the 1960s, before any experimental evidence of carcinogenicity in laboratory animals was available. The first suspicion started with four men who had worked in a factory of cadmium-nickel battery in UK who were reported to have died from prostate cancer although, compared to national rates, less than one case would have been expected (Potts, 1965). Subsequently, three additional studies conducted in small cohorts of workers employed in the production of batteries (Kipling and Waterhouse, 1967), alloys (Kjellström et al., 1979), and cadmium metal (Lemen et al., 1976) reported an association between cadmium exposure and an increased mortality from prostate cancer. However, later studies (Sorahan and Waterhouse, 1983; Thun et al., 1985; Kazantzis et al., 1988) failed to confirm this hypothesis.

A statistically significant increase in mortality from lung cancer has initially been reported in studies involving cadmium recovery (Lemen et al., 1976; Thun et al., 1985), nickel-

cadmium battery (Sorahan, 1987) and cadmium processing workers (Ades and Katzantzis, 1988; Kazantzis et al., 1992). Based on these studies, IARC (1993) concluded that there was sufficient evidence to classify cadmium and its compounds as human carcinogens (category 1). However, the epidemiological data that have been used to support this classification have been criticised because of the lack of control for confounding exposures (mainly arsenic) and smoking habits. Studies conducted after this evaluation by IARC (1993) have tried to address these difficulties. In particular, the dose-response relationship between cadmium exposure and lung cancer mortality rates, previously reported by Thun et al. (1985) and uptated by Stayner et al. (1992) and Park et al. (2012) has not been confirmed with a refined exposure assessment methodology. A significant positive trend between cumulative exposure to cadmium and mortality from lung cancer was found after adjustment for age, year of hiring and ethnicity but only in the presence of concomitant exposure to arsenic (Sorahan and Lancashire, 1997; Sorahan and Esmen 2012). In two .cohorts of workers from a nickel-cadmium battery plant (where arsenic was not a confounder), a globally-increased mortality from lung cancer was observed but the dose-response relationships were not consistent with a causal role of cadmium (Järup et al., 1998a; Sorahan and Esmen, 2004). In the latter cohort, 926 male workers from a Ni-Cd battery factory were followed up for a very long period of time (1947-2000). Significantly increased mortality was observed for pharynx cancer, diseases of respiratory system and diseases of genitourinary system. For lung cancer, the mortality was modestly increased (SMR=111, 95%CI=81-148) and without any definite pattern or trend by time variables and cumulative exposure to cadmium. Interestingly, indications exist in this cohort of increased risks from other known adverse effects associated with exposure to cadmium compounds, specifically, a significantly increased mortality (although without dose-response trend) from non-malignant respiratory diseases (SMR=142, 9%CI=109-182), and an increase of diseases of the genitourinary system (SMR=243, 9%CI=116-446) possibly reflecting late effects of kidney toxicity. These studies indicate that, in the absence of arsenic co-exposure, cadmium does not seem to induce an excess of lung cancers at exposure levels, however, sufficient to cause renal and respiratory toxicity.

In a cohort of copper-cadmium alloy workers for whom individual cumulative exposure indexes were estimated, a non-significant negative trend between cumulative cadmium exposure and risks of lung cancer was reported. The dose-response trend was, however, significant for non-malignant diseases of the respiratory system (Sorahan et al. 1995).

These recent studies do, therefore, not support the hypothesis that cadmium compounds act as lung carcinogens in humans (Verougstraete et al., 2003). In a recent review, which integrates the latest epidemiological studies, IARC has, however, reaffirmed its previous assessment and confirmed the group 1 classifiation of cadmium and its compounds as "human carcinogens for the lung" (Straif et al., 2009; IARC, 2012).

Some epidemiological studies suggest an association between occupational exposure to cadmium and the occurrence of renal cancer (reviewed by Il'yasova and Schwartz, 2005) and urothelial cancer (reviewed by Feki-Tounsi and Hamza-Chaffai, 2014). The meta-analysis by Song et al. (2015) of eight occupational epidemiological studies and one study with environmental exposure showed increased risk of renal cancer (OR = 1.47, 95% CI = 1.27-1.71) at high cadmium exposure.

Studies conducted in environmentally-exposed populations (*i.e., via* the diet) do not provide strong arguments for an increased risk of cancer (Verougstraete et al., 2003). A prospective study conducted in a region of Belgium with historical industrial pollution by heavy metals found an excess of lung cancer cases. The risk of lung cancer was positively associated with Cd-U measured during the Cadmibel study (1985-89), suggesting a possible impact of inhalation exposure to cadmium, but the role of other associated pollutants cannot be excluded (Nawrot et al., 2006). A statistically significant association between dietary cadmium intake (calculated from a food frequency questionnaire) and the risk of endometrial cancer has been reported in a cohort of post-menopausal women in Sweden followed during 16.0 years (484,274 person-years) (Åkesson et al. 2008).

The association between cadmium and prostate cancer has been analysed in a number of studies. The meta-analysis of Chen et al. (2016) covered three studies in the general population and six studies in occupational settings. No significant association was observed between cadmium exposure and prostate cancer.

A meta-analysis focusing on dietary cadmium intake (based on food frequency questionnaires) and breast cancer was published by Van Maele-Fabry et al. (2016). The analysis covered five prospective cohort studies and one case control study. The authors did not reach any firm conclusions due to several inconsistency factors. No statistically significant positive association between dietary cadmium exposure and breast cancer was found in another meta-analysis of one case-control and five cohort studies (Wu et al., 2015).

7.7.2 Animal data

Experimental studies have indicated that several cadmium compounds ($CdCl_2$, $CdSO_4$, CdS and CdO) caused lung cancer (mainly adenocarcinomas) in long-term inhalation experiments in the rat (Takenaka *et al., 1983; Glaser et al., 1990), but not in other species (Heinrich et al., 1989; Kazantzis et al., 1992). The lowest concentration inducing primary lung carcinoma in rats (15 versus 0 % in controls) was 12.5 µg Cd/m³ (23 h/day, 7 days per week for 18 months exposure to $CdCl_2$ aerosols with a mean mass aerodynamic diameter of 0.55 µm) (Takenaka et al. 1983). In a subsequent experiment, no lung tumors were induced when the rats were exposed continuously for 18 months to CdO fumes at a concentration of 10 µg Cd/m³, whereas 21 % of the animals developed tumors when exposed to 30 µg Cd/m³ (Glaser et al.* 1990). While these studies indicate that lung tumors can be induced at very low cadmium concentrations in the rat, it should be considered that tumours were induced under an unusual exposure regimen (23 h/day, 7 days per week).

For details of these studies, see IARC (1993, 2012).

7.7.3 Summary

IARC has concluded that there is sufficient evidence to classify cadmium and its compounds as human carcinogens (category 1), and human and animal studies report tumours upon exposure to cadmium. Cadmium and several of its compounds have a harmonised classification as carcinogens under the CLP regulation (see Chapter 2).

7.8 Reproductive toxicity

7.8.1 Human data

Epidemiological studies do not indicate an association between exposure to cadmium and relevant effects on fertility or reproductive organs (European Chemical Bureau, 2007). Recently, studies presenting an association between non-occupational maternal cadmium exposure and developmental toxicity have been published.

A connection between maternal cadmium exposure and reduced birth weight of girls was reported by Kippler et al. (2012). This prospective cohort study was conducted among environmentally exposed persons in Bangladesh, and involved 1616 mothers. Adjustment was made for maternal age and socioeconomic status. None of the mothers reported smoking during pregnancy, but 38% reported betel chewing. Multiple linear regression analyses showed that maternal urinary cadmium (median 0.63 µg/L) was significantly negatively associated with birth weight and head circumference of new-born girls. An increase in maternal urine cadmium concentration of 1 µg/L was associated with a 45 g decrease in birth weight. In new-born boys, there was little evidence of such connections. No association was seen between urinary cadmium concentration and birth length or gestational age. The authors concluded that "the magnitude of the estimated effects is not necessarily of clinical importance for individual children but may have considerable public

health relevance given the high prevalence of elevated exposure to cadmium, mainly through the diet".

A meta-analysis was conducted on data from 11 studies (10 birth cohorts and one cross-sectional study) focusing on maternal cadmium levels (urine and blood) and correlation with birth weight (Huang et al., 2019). All studies considered exposure of the general population (urinary cadmium normally < 1 µg/g creatinine) and not related to occupational cadmium exposure. The results of the analysis indicated that a 50% increase of maternal urinary cadmium level would be associated with a decrease in neonatal birth weight. The association was more pronounced in female new-borns. In particular, the results involving increased urine concentrations during the first trimester were statistically significantly, indicating that the first trimester may be a critical window. A statistically significant decrease in birth weight was observed for female new-borns of mothers with 50% increased urinary cadmium levels, as compared with mothers with lower urinary cadmium concentration. Furthermore, elevated urinary cadmium was associated with a higher rate of low birth weight (defined as a birth weight ≤ 2499 g). In addition, a 50% increase of maternal blood cadmium level was associated with an 11.57 g decrease in birth weight. There was no evidence of substantial publication bias (analysed by Begg's and Egger's tests), but the authors indicated that the test results should be interpreted by caution as less than 20 studies were included in the meta-analysis.

A systematic review and meta-analysis of epidemiological studies focusing on associations between maternal cadmium exposure and neonatal effects, was presented by Khoshhali et al. (2019). Based on extensive literature searches, 22 studies were selected for the meta-analysis. Using the random-effects model for the analysis of pooled data from the different sources, the authors identified a weak, but still significant association between maternal urinary cadmium levels and birth weight. No correlation was observed between urine cadmium levels and birth length or birth head circumference. There was no evidence of substantial publication bias (analysed by Begg's and Egger's tests). Mean maternal age, mean maternal body-mass index, mean gestational age, or sample size of studies did not contribute to the heterogeneity of meta-analysis (all p values > 0.05).

In a study on the NICE birth cohort in Sweden (covering 655 pregnancies), an association between maternal blood concentrations of cadmium and reduced birth weight and length was reported at blood concentrations >0.20 µg Cd/L. In general, the maternal cadmium concentrations were low (median maternal blood concentration 0.11 µg/L), and mainly related to dietary exposure (Gustin et al., 2020).

Some (weak) indications of effects of cadmium exposure on the development of children have been reported in some studies. The reports focus on effects related to the development of bones (Igra et al., 2019), cognitive development (Gustin et al., 2018; Chatzi et al., 2019; Tian et al., 2009) and neurodevelopment (Rodriguez-Barranco et al., 2013) .

7.8.2 Animal data

While effects on reproductive organs and fertility have been noted in experimental studies at high doses of cadmium compounds (oral LOAEL 1 mg/kg/d, effect on seminiferous tubules in rats, and inhalation NOAEL 0.1 mg/m^3, increased length of oestrus cycle), further information is needed to better understand the possible effect of low doses of cadmium on the developing brain suggested in experimental animals.

In studies by NTP (1995), sperm-positive Sprague-Dawley rats and Swiss (CD-1(R)) mice were exposed to 0, 0.05, 0.5, or 2 mg/m^3 cadmium oxide 6 hours per day, 7 days per week, on gestation day 4 through 19 (rats) or gestation day 4 through 17 (mice). Maternal toxicity was observed in Sprague-Dawley rats exposed to 2 mg/m3 cadmium oxide for 16 days and included body weights lower than those of the controls and clinical signs of toxicity (dyspnea and hypoactivity). There was no evidence of embryolethality in rats at any exposure level. However, in rats exposed to 2 mg/m^3, developmental toxicity was

evidenced by lower fetal weights and a significant increase in the incidence of reduced skeletal ossifications. Maternal toxicity was also observed in Swiss (CD-1(R)) mice exposed to 2 mg/ m^3 cadmium oxide for 14 days. Clinical signs were dyspnea, hypoactivity, lower body weight, and a lower pregnancy rate (30% vs. 97% in the control group). The total number of resorptions per litter was increased at the 2 mg/m^3 level. Developmental toxicity was evidenced by lower fetal weights in the 0.5 and 2 mg/ m^3 groups and an increase in the incidence of reduced sternebral ossification in the 2 mg/ m^3 group. Reproductive toxicity was observed in the 1 mg/ m^3 groups of rats and was evidenced by a reduced number of spermatids per testis and an increase in the length of the estrous cycle. Reproductive toxicity was not observed at any exposure level in mice (NTP 1995).

7.8.3 In vitro data

No relevant in vitro data on reproductive toxicity were retrieved.

7.8.4 Summary

Cadmium compounds can cause developmental effects. This has been observed in epidemiological studies in the general population (environmentally exposed) and in animal studies.

8. Other considerations

8.1 Mode of action (MoA) considerations

8.1.1 Kidney, bone and cardiovascular effects

The kidneys (and possibly bone) are the most sensitive targets of systemic cadmium toxicity following occupational exposure (critical target organs). Cadmium is a cumulative toxicant; the systemic manifestations associated with chronic exposure are related to the body burden of the element (liver and kidney content). Biological markers such as Cd-U (cadmium excretion in urine) allow the assessment of body burden, and to integrate all sources of cadmium exposure, including contaminated food and smoking. The use of such biomarkers of exposure in most epidemiological studies conducted in occupational settings has allowed researchers to document dose-effect/response relationships.

In workers exposed to cadmium, a cadmium body burden corresponding to a Cd-U (cadmium concentration in urine) of 5 µg/g creatinine is a LOAEL for kidney effects based on the occurrence of low molecular weight proteinuria (see 7.3.1). There is general consensus on the health significance of this threshold (LOAEL) because of the frequent observation of irreversible tubular changes above this value and in view of its association with further renal alteration. Links between kidney and bone effects induced by cadmium strengthen the health significance of these effects.

Based on recent studies, it appears that renal effects can be detected in the general European population (mainly exposed by the oral route) for cadmium body burdens at or even below 2 µg Cd/g creatinine (LOAEL). There is, however, a continuing scientific debate about the health significance of these early changes. This lower LOAEL in the general population compared to that identified in workers is thought to reflect, among other parameters, an interaction of cadmium exposure with pre-existing, concurrent or subsequent renal diseases (mainly renal complications of diabetes) that are less prevalent in healthy individuals in occupational settings. Furthermore, the association between LMW proteinuria and urinary cadmium at concentrations < 2 µg/g creatinine is likely to be confounded by diuresis, and normal physiological variation in renal reabsorption of LMW proteins may result in an increase in urinary cadmium (Nordberg et al., 2018).

In humans, the mechanism of bone toxicity is not fully elucidated and types of bone lesions associated with cadmium exposure are not clearly identified. One likely mechanism is

direct disturbance of bone metabolism but another explanation could be that cadmium-induced kidney damage and/or hypercalciuria might promote osteoporosis and osteoporotic fractures. There is consistent information on dose-response relationships between adverse effects on bones and cadmium exposure causing urinary cadmium levels ≥ 5 µg/g creatinine. At lower cadmium levels, bone effects have been observed in several studies in the general population. For the moment it is difficult to identify a NOAEL for bone effects.

A relationship between cadmium exposure and cardiovascular disease has been observed in studies on the general population. Positive findings in occupational studies have however not been reported. The current data does not identify mechanisms behind cadmium exposure and effects.

8.1.2 Genotoxicity and carcinogenicity

Cadmium is an established human and animal carcinogen. Most evidence is available for elevated risk for lung cancer after occupational exposure; however, associations between cadmium exposure and tumours at other locations including kidney, breast, and prostate may be relevant as well. Furthermore, enhanced cancer risk may not be restricted to comparatively high occupational exposure, but may also occur via environmental exposure, for example in areas in close proximity to zinc smelters. The underlying mechanisms are still a matter of manifold research activities. While direct interactions with DNA appear to be of minor importance, there is interference with distinct cellular signalling pathways (Bishak et al., 2015; Fischer et al., 2016). Thus, elevated levels of reactive oxygen species (ROS) have been detected in diverse experimental systems, presumably due to an inactivation of detoxifying enzymes. Also, the interference with proteins involved in the cellular response to DNA damage, the deregulation of cell growth as well as resistance to apoptosis appears to be involved in cadmium-induced carcinogenicity. Within this context, cadmium has been shown to disturb nucleotide excision repair, base excision repair, and mismatch repair. Particularly sensitive targets appear to be proteins with zinc binding structures, present in DNA repair proteins such as XPA, PARP-1 as well as in the tumour suppressor protein p53. Whether or not these interactions are due to displacement of zinc or due to reactions with thiol groups involved in zinc complexation or in other critical positions under realistic exposure conditions remains to be elucidated. Further potential mechanisms relate to the interference with cellular redox regulation, either by enhanced generation of ROS or by reaction with thiol groups involved in the regulation of signalling pathways. Particularly the combination of these multiple mechanisms may give rise to a high degree of genomic instability evident in cadmium-adapted cells, relevant not only for tumour initiation, but also for later steps in tumour development (for details, see Hartwig 2013a).

In essence, different and *a priori* non-mutually exclusive mechanisms for the carcinogenicity of cadmium have been identified (Joseph, 2009), including oxidative DNA damage (Filipic and Hei 2004), induction of oxidative stress (Liu et al., 2009), inhibition of DNA repair (Hartwig et al. 2002, Kopera et al. 2004) and deregulation of cell proliferation (Beyersmann and Hartwig 2008). All these mechanisms are non-stochastic and characterised by a threshold below which no effect is expected. Cadmium can therefore be considered as a genotoxic carcinogen for which a practical threshold can be identified (Bolt and Huici-Montagud, 2008).

8.2 Correlation between health effects, biological concentrations and air concentrations

In the majority of human studies with data on dose versus health hazard, the dose is expressed as a biological concentration (normally in urine) of cadmium. Information on the relationship between airborne exposures (cadmium concentrations in the air) versus health effects is limited. Therefore, LOAELs/NOAELs are normally identified as urinary concentrations. Unfortunately, robust studies showing a relationship between cadmium

concentrations in the air and urine (or blood) have not been found. Some publications related to air concentrations and health effects are, however, available, and some modelling attempts to have been published.

In the SCOEL (2017) recommendation, which was the basis for the current BOEL, the 8-hour value of 1 µg/m^3 (0.001 mg/m^3) was derived to protect for kidney effects (see Section 9.2.1). SCOEL considered evaluations by WHO (2000) and the German AGS (*Ausschuß für Gefahrstoffe*; BAuA 2014) of published data (primarily the publication of Thun et al. 1991), which indicated for nephrotoxicity a cumulative LOAEC of 100-400 µg/m^3 x years. For 40 years of occupational exposure, this would mean an LOAEC range of 2.5 – 10 µg/m^3. (0.0025-0.01 mg/m^3).

In the WHO (2000) report, the health risk evaluation considered that "some studies suggest that a proportion of workers with cumulative exposures of 100-400 µg/m^3-years might develop tubular dysfunction (prevalences increasing from 2.4% to 8.8%, increase above background from 200 µg/m^3-years)". Although it is not completely clear which studies WHO refers to, it is considered that the article by Thun et al. (1991) is the key source. Thun et al. (1991) analysed pooled data from seven cross-sectional studies presenting data on kidney dysfunction and cumulative occupational cadmium exposure. In addition, they also compared that data with predictions by OSHA and by a published kinetic model (Kjellstrom and Nordberg, 1978). Thun et al. (1991) concluded that the pooled data was well in agreement with the modelling data, particularly at a cumulative exposure level >500 µg/m^3-years. At cumulative exposures <500 µg/m^3-years, the separate studies showed only few cases of tubular proteinuria. When the data from the studies was pooled, the authors interpreted that the "data suggests that prevalence may increase at cumulative exposures between 100 and 499 µg/m^3-years". They were, however, not able to identify a NOAEC, because of the limited sample size, methodological differences between the studies, and imprecision of the exposure data (Thun et al., 1991).

For respiratory effects, SCOEL (2017) referred to the report by Cortona et al. (1992) when identifying a LOAEC of 500 µg/m^3*x*years for changes in residual volume. In an extensive IUPAC Technical Report (Nordberg et al., 2018), a health risk assessment of cadmium was presented. Nordberg et al. (2018) agreed on 500 µg/m^3*x*years as the LOAEC for respiratory effects, and they noted that more recent studies do not report effects at lower cadmium exposure levels.

Nordberg et al. (2018) identified kidney effects as the critical effect, and considered 2 µg/g creatinine as a critical dose level, at which LMW proteinuria may occur in a susceptible subsection of the population. For the derivation of a corresponding air concentration, the authors referred to calculations of ATSDR (2012), who applied toxicokinetic models for the prediction of the relationship between inhalation exposure and cadmium concentrations in the kidney cortex and urine. A cadmium mass fraction of 120 µg Cd/g in the kidney cortex was predicted to correspond to 2 µg/g creatinine, and 84 µg Cd/g (the estimated lower confidence limit on the renal cortex concentration associated with a 10% probability of low molecular mass proteinuria (Diamond et al., 2013)) to correspond to 1.4 µg/g creatinine. The authors estimated that occupational exposure via inhalation of air containing 2.7 µg cadmium sulfide/m^3 (uniform particle size 1 µm) for 40 years (8 h/day, 5 days/week) would result in a kidney cortex mass fraction of 84 µg Cd/g. For cadmium oxide, the corresponding air concentration was calculated as 5.1 µg/m^3.

Recently, a number of epidemiological studies have been published, showing an association between cadmium levels in maternal urine and developmental effects of new-borns after maternal cadmium exposure. The available data shows consistent effects, e.g. reduced body weight of new-borns, but it is not possible to identify any threshold level (LOAEL/NOAEL) based on the available data. Similarly, several studies showing associations between cadmium exposure and bone or cardiovascular effects have been published. Effects have often been reported at low exposure levels. The data does however not provide dose-effect information that could be used to identify LOAEL/NOAEL values for such effects.

8.3 Lack of specific scientific information

Cadmium and its inorganic compounds have been well investigated. This refers to studies both in occupationally-exposed workforce and in experimental systems.

Nevertheless, regarding cadmium-related carcinogenicity in different target organs under low exposure conditions, future research should have a focus on the relevance of underlying mechanisms in experimental animals and in exposed humans (Hartwig 2013a).

8.4 Groups at Extra Risk

Distinct groups of persons at extra risk related to cadmium have not been clearly identified in epidemiological studies. However, based on the established systemic effects of cadmium in humans, persons with pre-existing renal disease or diabetes could be more susceptible than others. This should be taken into account in the medical surveillance of cadmium-exposed workforce.

Women of childbearing age are identified as a group at extra risk because cadmium is accumulating in the body and it can cause developmental effects even at low concentrations.

9. Evaluation and recommendations

9.1 Cancer risk assessment

9.1.1 Published approaches for cancer risk assessment

SCOEL (2017) concluded that based on mechanistic evidence the mode of carcinogenic action of cadmium and its inorganic compounds comprises genotoxic and non-genotoxic elements. The non-genotoxic elements are non-stochastic and characterised by a threshold below which no carcinogenic effect is expected (*i.e.* a genotoxic carcinogen for which a mode of action-based threshold can be identified, also called 'practical threshold'). In consequence, SCOEL proposed OELs (8h OEL / 8h OEL+BLV).

Others have performed linear risk extrapolations from experimental (Takenaka et al 1983) or epidemiological (Thun et al 1985; Park et al 2012) data. Data from the inhalation carcinogenicity bioassay with $CdCl_2$ by Takenaka et al (1983) were considered by EPA (1994) and by the Ausschuß für Gefahrstoffe (BauA 2014). Related to working lifetime exposure, an additional cancer risk of 1:1000 resulted from the EPA procedure at 1 µg Cd/m^3, and of 4:1000 at 1.6 µg Cd/m^3 by the Ausschuß für Gefahrstoffe (BauA 2014). Based on epidemiological data [Park et al. (2012) update of the Thun *et al*. (1985) cohort], Haney (2016) estimated an excess risk level of 1:100000 for a lifetime air concentration of 0.02 µg Cd/m^3 (continuous environmental exposure, corresponding to 1:1000 at 2 µg Cd/m^3) for the general population in the State of Texas.

9.1.2 Cancer risk assessment

The data retrieved for this report does not contradict the conclusions of SCOEL (2017), identifying cadmium as a substance with a practical threshold for carcinogenicity. Therefore there is no need for derivation of dose-response relationships.

9.2 Derived Occupational Exposure Limit (OEL) Values

9.2.1 Published approaches to establishing OELs and BLVs

Several expert groups have made recommendations for OELs and/or BLVs. These are summarised in Table 15, and the justifications for the values are presented in the paragraphs below.

Table 15: Occupational exposure limits and biological limit values for cadmium proposed by expert groups.

Author	OEL (8 h)	Biological limit
SCOEL (2017)	1 µg/m^3 (inhalable fraction) alone or 4 µg/g creatinine if measured together with biological concentration	Urine: 2 µg/g creatinine
SCOEL (2010)	4 µg/m^3 (respirable fraction)	Urine: 2 µg/g creatinine
BAuA (2014)	1 µg/m^3 (inhalable fraction)	--
DECOS (2019)	4 µg/m^3 (respirable fraction)	Urine: 2 µg/g creatinine
ANSES (2016, 2014)	3 µg/m^3 (inhalable fraction)	Urine: 5 µg/g creatinine Blood: 4 µg/L
ACGIH (2016, 2001)	10 µg/m^3 (total particulate fraction) 2 µg/m^3 (respirable fraction)	Urine: 5 µg/g creatinine Blood: 5 µg/L

9.2.1.1 SCOEL (2017)

In the SCOEL recommendation (2017) a BLV (cadmium in urine) and an 8 h OEL for the inhalable fraction were proposed. SCOEL did not propose a STEL or any notations.

SCOEL justified the recommendations as follows:

BLV

"The kidneys (and possibly bone) are the most sensitive target of systemic cadmium toxicity following occupational exposure (critical target organs). Cadmium is a cumulative toxicant; the systemic manifestations associated with chronic exposure are related to the body burden of the element (liver and kidney content). Biological markers such as Cd-U (cadmium excretion in urine) allow the assessment of body burden, and to integrate all sources of cadmium exposure, including contaminated food and smoking. The use of such biomarkers of exposure in most epidemiological studies conducted in occupational settings has allowed researchers to document reliable dose-effect/response relationships. A biological limit value will thus protect workers against systemic toxicity of cadmium, mainly renal and bone effects.

In workers exposed to cadmium, a cadmium body burden corresponding to a Cd-U (cadmium concentration in urine) of 5 µg/g creatinine is a LOAEL based on the occurrence of LMW (low molecular weight) proteinuria […]. There is general consensus on the health significance of this threshold because of the frequent observation of irreversible tubular changes above this value and in view of its association with further renal alteration. Links

between kidney and bone effects induced by cadmium strengthen the health significance of these effects.

Based on recent studies, it appears that renal effects can be detected in the general European population (mainly exposed by the oral route) for cadmium body burdens at or even below 2 µg Cd/g creatinine (LOAEL). There is, however, a continuing scientific debate about the health significance of these early changes. This lower LOAEL in the general population compared to that identified in workers is thought to reflect, among other parameters, an interaction of cadmium exposure with pre-existing, concurrent or subsequent renal diseases (mainly renal complications of diabetes) that are less prevalent in healthy individuals in occupational settings. As workers exposed to cadmium may, however, suffer from such diseases during or, most often, after their occupational career, and considering the long half-life of cadmium in humans and its accumulation with age, it may be prudent to provide a sufficient degree of protection in this respect.

The following considerations are integrated to derive an acceptable biological limit (BLV) for cadmium and its inorganic compounds:

- There is an abundant database on the health effects of Cd and its compounds.
- The mechanisms of the systemic toxicity of Cd are relatively well understood.
- The available dose-effect/response relationships characterising the health hazard of Cd have been extensively and quite reliably documented in a number of human studies.
- Mean Cd-U in European individuals with no occupational exposure to Cd or living in an area with no specific Cd pollution is generally below 1µg Cd/g creatinine.
- The critical systemic effect selected to define the point of departure in epidemiological studies [urinary excretion of LMW proteins reflecting tubular dysfunction] is a relatively early sign occurring before the onset of overt clinical manifestations of kidney disease.
- The point of departure identified from human studies in occupational settings (5 µg Cd/g creatinine) is a LOAEL for renal effects (chapters 8.1.5, *Table 2*; 8.3.1, *Table 3*).
- The point of departure identified from human studies in the general population (2 µg Cd/g creatinine) is a LOAEL for renal effects which is relevant for protecting workers after their occupational career.
- Other points of departure for systemic effects are 3 µg Cd/g creatinine as a LOAEL for respiratory effects in workers and 3 µg/ g creatinine as a LOAEL for bone effects in the general population.
- Cd and its compounds are considered as SCOEL group C carcinogens, and it is seems prudent to recommend limiting the body burden of the workforce to a minimum.

Therefore, a BLV of 2 µg Cd/g creatinine is proposed. As explained […], the sampling time is not critical.

8h OEL

Besides a biological limit (BLV, see above), setting an 8h-TWA limit is necessary to protect workers against long-term local effects of airborne cadmium (and its inorganic compounds) at the respiratory system. Chronic inhalation of cadmium -containing dusts and fumes is associated with the development of local respiratory effects, including lung emphysema and cancer. Cadmium is considered as a lung carcinogen in experimental animals and upon occupational exposure.

- Experimental studies have reported the induction of lung tumours in rats exposed to low concentrations of cadmium (12.5 µg/m³).
- Insufficient epidemiological evidence exists in humans to perform a working-life risk assessment for the cancer risk for exposure to cadmium alone. When an increased risk

was observed in cadmium exposed populations, co-exposures did appear to play a central role.

- The mechanism of the carcinogenic activity of cadmium is not exactly known, but involves, at least in part, non-genotoxic events such as interactions with DNA repair processes and genotoxic events mediated by indirect mechanisms (e.g. oxidative stress), for which a threshold can be identified (Category C, Bolt and Huici-Montagud, 2008).
- A threshold of 1000 µg/m³ *x* years (or 25 µg/m³ Cd over 40 years) has been reported for genotoxic effects in workers exposed to cadmium by inhalation.
- There is also some epidemiological evidence that cadmium does not seem to induce an excess of lung cancers at exposure levels sufficient to cause renal and respiratory toxicity (Sorahan and Esmen, 2004).

Human data have shown that changes in residual volume of the lung occur for a cumulative exposure to CdO fumes of 500 µg Cd/m³ x years, corresponding to 40 years exposure at a level of 12.5 µg Cd/m³ (LOAEL). Applying an extrapolation factor of 3 (LOAEL to NOAEL; Leung, 2002) leads to a value of 4 µg Cd/m³.

An 8h-TWA (8h time-weighted average) of 4 µg/m³ (respirable fraction), based on non-cancer respiratory effects, can therefore be considered as being protective for workers against local respiratory effects of cadmium exposure. Such a 8h-TWA value of 4 µg Cd/m^3 (as derived by SCOEL in 2010) must be seen in close conjunction with the derived BLV, as both refer to and are protective for different toxicity endpoints of relevance (local and systemic). Thus, implementation of both elements of the OEL- TWA and BLV- are of critical importance.

However, an isolated OEL (8-h TWA) of 4 µg/m^3 (not linked with a BLV) would not appear being equally protective against the systemic nephrotoxixity of cadmium. Evaluations by both WHO (2000) and the German AGS (Ausschuß für Gefahrstoffe; BAuA 2014) of published data (primarily by Thun et al 1991) have pointed, for nephrotoxicity, to a cumulative (life-time) lowest-effect exposure of 100-400 µg/m^3 *x* years. For working-life exposure of 40 years, this equals an LOAEC range of 2.5 – 10 µg/m^3. AGS (BAuA 2014) has deduced that nephrotoxic effects could arise in about 1% of the workforce after 40 years of airborne exposure to 4 µg Cd/m^3. Accordingly, an OEL (8h-TWA, not connected with biological monitoring) for cadmium and its inorganic compounds should be 1 µg/m^3.

In this case, an OEL (8h TWA) of 1 µg Cd/m^3 (inhalable fraction) can be proposed."

In its previous recommendation, SCOEL (2010) proposed a BLV of 2 µg Cd/g creatinine, to be used together with an OEL (8 h TWA) of 4 µg/m^3 (respirable fraction).

9.2.1.2 AGS (BAuA 2014)

AGS (BAuA 2014) based its cadmium OEL of 1 µg/m^3 (inhalable fraction) on kidney effects. The value of 1 µg/m^3 was calculated based on an approximate LOAEL of 2.5 µg/m^3 (40 years of exposure) for nephrotoxicity, as identified by WHO (2000). An assessment factor of 3 was used for the extrapolation from LOAEL to NOAEL/NOEL, and thereby the rounded value of 1 µg/m^3 was obtained. AGS noted that uncertainties are related to the WHO assessment, as it was based on an attempt to identify an association between urinary cadmium concentrations, at which kidney effects were observed, with air concentrations of cadmium (see Section 8.2). The tolerable cadmium cancer risk (1:1000) derived by AGS corresponds to a work life-long exposure at 1.6 µg/m^3 (respirable fraction) (see also 9.1.1) (BAuA 2014).

9.2.1.3 DECOS (2019)

In its report from 2019, *Health Council of the Netherlands* (DECOS) evaluated the SCOEL (2017) recommendation on an 8-hour cadmium OEL of 1 µg/ m^3 (inhalable). DECOS had

earlier (2013) published an advisory report, recommending to follow the SCOEL (2010) approach [BLV 2 µg Cd/g creatinine + OEL 4 µg/m^3 (DECOS did not specify the fraction)]. In the recent evaluation, DECOS (2019) concluded that the new value of 1 µg/m^3 (inhalable fraction) is "scientifically insufficiently substantiated". Therefore, DECOS (2019) recommended to apply a BLV of 2 µg Cd/g creatinine to protect workers against systemic cadmium effects and an OEL of 4 µg/m^3 (respirable fraction), to protect against local lung effects. The reasons for not agreeing on the value of 1 µg/m^3 (inhalable fraction) were limitations identified for the studies underlying the SCOEL (2017) recommendation. DECOS (2019) pointed out that those studies covered only a limited number of individuals with exposure levels below 500 µg/m^3 (and it was often not clear which dust fraction was measured), only a few cases of kidney effects were observed in the studies, and the criteria to define kidney dysfunction varied between the studies.

9.2.1.4 ANSES

ANSES (2016) recommended a pragmatic 8h OEL of 3 µg/m^3 (inhalable fraction) for cadmium. Impairment of renal function was identified as the critical effect, and the study by Järup et al. (1988) was selected as the key study for the derivation of an OEL. The study presented dose-response relationships for urinary β2-microglubulin levels and cumulative air cadmium exposure. A threshold concentration of 310 µg Cd/g creatinine was identified for increased urinary β2-microglubulin and according to ANSES a cumulative exposure index of 131 µg/m^3-years was identified as a NOAEL (1% prevalence of exceeding the threshold concentration of β2-microglubulin). Considering 40 years of exposure, an air concentration of 3.257 µg/m^3 was extrapolated. No adjustment factors were considered necessary as the key study covered a large number of workers and long-term exposure, and thus an OEL of 3 µg/m^3 was recommended. Although the Järup et al. (1988) study focused on the respirable fraction, ANSES considered the inhalable fraction appropriate for the proposed OEL, due to the potential to cause lung cancer.

A value of 15 µg/m^3 (5 times the 8h-OEL) was recommended as a 15-minutes STEL, aiming at preventing effects on respiratory function.

As a urinary biological limit value, ANSES (2014) recommended a concentration of 5 µg Cd/g creatinine, based on kidney effects reported in Järup and Elinder (1994) and Chaumont et al. (2011). In addition, 2 µg/g creatinine was identified as a threshold value for additional medical monitoring. A BLV in blood, 4 µg/L, was also recommended. The value was derived on the basis of several studies presenting correlations between blood and urinary cadmium concentrations.

9.2.1.5 ACGIH

The American Conference of Governmental Industrial Hygienists (ACGIH) established in 1993 8-hour TWA values (TLV®) of 10 µg/m^3 (total particulate) and 2 µg/m^3 (respirable particulate matter) (ACGIH 2001). The value for the total dust fraction is set to minimise kidney effects, specifically preclinical kidney dysfunction (detected by a β_2-microglobulin excretion > 290 µg/L). It was derived using data from the study by Mason et al. (1988). The value for the respirable fraction aims at minimising the accumulation of cadmium in the lungs, and thereby the carcinogenicity risk. ACGIH (2001) noted also that the values are below the level associated with a SMR of 100 for lung cancer by Thun et al. (1985). In 1993 (documentation updated in 2016), ACGIH also adopted biological limit values (BEI®) for cadmium in urine (5 µg/g creatinine) and cadmium in blood (5 µg/L) (ACGIH 2016). It was concluded that based on several studies, NAG or β_2-microglobulin excretion will increase at cadmium urine levels > 5 µg/g creatinine. ACGIH considered that the increased excretion is not directly causing clinical effects, but there are indications that the "changes might progress and become clinically significant when combined with effects associated with aging" (ACGIH 2016). Monitoring of urine cadmium levels is recommended as a specific test for chronic cadmium exposure. For the monitoring of acute exposure (e.g. new employees), ACGIH recommends examination of the cadmium blood levels. The limit

value is supported by several studies, which indicate an increase in markers of renal dysfunction at blood concentrations <10 µg/L.

The ACGIH general position framework of setting Threshold limit values and Biological exposure indices (TLVs/BEIs) is acknowledged. More specifically: "ACGIH® formulates a conclusion on the level of exposure that the typical worker can experience without adverse health effects. The TLVs® and BEIs® represent conditions under which ACGIH® believes that nearly all workers may be repeatedly exposed without adverse health effects. They are not fine lines between safe and dangerous exposures, nor are they a relative index of toxicology" [17]. Since ACGIH TLVs and BEIs are based solely on health factors, there is no consideration given to economic or technical feasibility.

9.2.2 Occupational Exposure Limits (OELs) – 8 h TWA

In the third amendment of the Carcinogens and Mutagens Directive (Directive (EU) 2019/983), an OEL (8 h TWA) of 0.001 mg/m^3 (inhalable fraction) was set for cadmium and its inorganic compounds.

During a transition period, until 11 July 2027, the limit value for the inhalable fraction is 0.004 mg/m^3.

The OEL was derived to protect against systemic kidney effects. In addition, SCOEL (2017) also considered that the value would protect against local respiratory effects (see Section 9.2.1).

However, it has been noted that the basis for the derivation of the OEL (see Section 9.2.2) is not very robust, and the limitations of the data used in the key study (Thun et al., 1991, WHO 2000) have been debated (DECOS 2019, BAuA 2014).

9.2.2.1 Identification of critical effects and doses

Kidney effects

Kidney effects are still considered the critical systemic effects of cadmium. In occupational settings, a cadmium body burden corresponding to a cadmium concentration in urine of 5 µg/g creatinine is identified as a LOAEL for kidney effects based on the occurrence of low molecular weight proteinuria. In the general population, renal effects have been linked to cadmium exposure also at lower urine concentrations of cadmium (2 µg/g creatinine or lower), but as discussed in Section 8.1.1, uncertainties are related to these findings.

The calculations of ATSDR (2012), who applied toxicokinetic models for the prediction of the relationship between inhalation exposure and cadmium concentrations in the kidney cortex and urine are considered the most relevant ones for the estimation of an air concentration at which kidney effects may occur. A cadmium mass fraction of 120 µg Cd/g in the kidney cortex was predicted to correspond to 2 µg/g creatinine, and 84 µg Cd/g to correspond to 1.4 µg/g creatinine. The authors estimated that occupational exposure via inhalation of air containing 2.7 µg cadmium sulfide/m^3 (uniform particle size 1 µm; corresponds to 2.1 µg Cd/m^3) for 40 years would result in a kidney cortex mass fraction of 84 µg Cd/g. For a similar situation with cadmium oxide, the corresponding air concentration was calculated as 5.1 µg cadmium oxide/m^3. As the calculations were performed for particles with a size of 1 µm, the outcome can be considered applicable for the respirable fraction. (See Section 8.2).

SCOEL (2017) used the reports of WHO (2000) and the German AGS (BAuA 2014) for the derivation of on OEL. For nephrotoxicity, they considered to a cumulative (life-time)

[17] https://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations/tlv-bei-position-statement

lowest-effect exposure of 100-400 µg/m^3 *x* years. For working-life exposure of 40 years, this would equal an LOAEC range of 2.5 – 10 µg/m^3. As explained in Section 8.2, some level of uncertainty is related to the data (e.g., few cases with kidney effects at exposure levels in the LOAEC range), and it is therefore not considered the best starting point for an OEL.

Respiratory effects

Respiratory effects have been observed in humans exposed to cadmium by inhalation. Such effects include changes in residual volume of the lung and have been estimated to occur upon a cumulative exposure to cadmium oxide fumes of 500 µg Cd/m³ *x* years (respirable fraction), corresponding to 40 years exposure at a level of 12.5 µg Cd/m³ (LOAEL, urinary level reported as 3 µg Cd/g creatinine) (Cortona et al. 1992). Applying an extrapolation factor of 3 (LOAEL to NOAEL) would result in a value of 4 µg Cd/m³ (respirable fraction).

Bone effects

A connection between cadmium exposure and bone effects has been reported in numerous studies focusing both on occupational settings and the general population. The study by Alfven et al. (2000) reported an association between Cd-U and decreased bone mineral density in older men. An increased risk of osteoporosis was noted in men over 60 years with a similar tendency in women of the same age. The identified threshold (LOAEL) for these effects was around 3 µg/g creatinine.

Other studies report effects also at lower exposure levels, but uncertainties and confounding factors make it difficult to identify thresholds (LOAEL/NOAEL) based on that data.

Cardiovascular effects

A clear relationship between cadmium exposure and cardiovascular disease has been observed in studies on the general population. Positive findings in occupational studies have however not been reported. The currently available data cannot be used to derive an OEL.

Developmental toxicity

In studies focusing on pregnant women with an increased environmental cadmium exposure an association with developmental effects on the (unborn) child have been reported. The available data can however not be used to derive an OEL.

Carcinogenicity

Cadmium and its compounds are known carcinogens. It is considered that cadmium causes carcinogenicity via indirect mechanisms. The lowest concentration reported to induce primary lung carcinoma in rats is 12.5 µg Cd/m³ (23 h/day, 7 days per week for 18 months exposure to $CdCl_2$ aerosols with a mean mass aerodynamic diameter of 0.55 µm) (Takenaka *et al.* 1983). Based on this data, BAuA (2014) estimated that work-life long exposure to 1.6 µg Cd/m^3 (respirable fraction) would be related to an increased cancer risk of 4:1000. The current epidemiological data cannot be used to identify a threshold for the carcinogenic effects of cadmium.

9.2.2.2 Proposal for OEL

An OEL needs to protect against both systemic and local effects. As there is a lack of robust data on the correlation between air concentrations and health effects, it is difficult to propose such a value. To protect against systemic effects, it is relevant the value covers total inhalation exposure to cadmium and therefore it needs to be set for the inhalable fraction. For (local) respiratory effects, the respirable fraction is likely to be of higher importance.

As described in Section 9.2.2.1, effects on kidneys, bone, and the cardiovascular system, as well as carcinogenicity and respiratory effects are important hazardous effects. An OEL should provide protection against all these effects.

Renal effects are identified as the critical effects and a BLV of 2 µg/g creatinine is proposed (see Section 9.2.4). Modelling estimates indicate that a urinary concentration of 1.4 µg Cd/g creatinine corresponds to 2.1 µg Cd/m^3. The calculations were made for particles sized 1 µm, but it is assumed that the particle size does not have a major impact on kidney effects. Thus, exposure to 2 µg Cd/m^3 (inhalable fraction) is expected to result in urinary levels below 2 µg/g creatinine, provided that the previous body burden of the worker is at normal background level.

Taking into consideration the available data, the current OEL of 0.001 mg µg Cd/m^3 (1 µg Cd/m^3) inhalable fraction) is likely to protect against systemic effects, as well as local respiratory effects, and is considered conservative. Thus, there is no need to decrease the current OEL.

However, the current OEL does not take into consideration previous (high) exposure to cadmium or indirect exposure via other routes than inhalation. Therefore, the OEL should be applied together with the proposed BLV to ensure that the total body burden is not too high (see Section 9.2.4).

If an OEL of 0.004 mg µg Cd/m^3 (4 µg Cd/m^3) (respirable fraction) was applied together with the BLV, as proposed by SCOEL (2017) that value is considered protective against local respiratory effects like changes in residual volume of the lung. However, lung carcinogenicity is an important "local" effect linked to cadmium exposure. According the estimates of BAuA (2014), exposure at 1.6 µg Cd/m^3 (respirable fraction) is linked to an increased cancer risk of 4:1000. To protect against carcinogenicity, a value of 4 µg Cd/m^3 (respirable fraction) is therefore considered too high, and it is recommended to apply the current OEL 0.001 mg µg Cd/m^3 (1 µg Cd/m^3) (inhalable fraction) together with the BLV.

9.2.3 Short Term Exposure Limits (STELs)

The key effects of cadmium are related to long term exposure. No STEL has been proposed.

9.2.4 Biological Limit Value (BLV)

No EU BLV has been set for cadmium or its compounds. However, in the Carcinogens and Mutagens Directive (Directive (EU) 2019/983) it is specified that during a transition period, until 11 July 2027, in Member States with an implemented biomonitoring system with a biological (urine) limit value ≤0.002 mg Cd/g creatinine, the air limit value is 0.004 mg/m^3 for the respirable fraction. The urinary BLV proposed by SCOEL (2017) was 0.002 mg Cd/g creatinine.

The main scope of this report was to make a comparison of the effectiveness of the health protection of the combination of an OEL and biomonitoring value as proposed in the SCOEL Opinion 336 (2017) compared to the OEL adopted in Directive 2019/983/EU.

Cadmium accumulates in the body and the elimination is slow, which must be considered when setting limit values. Biological limit values are often considered useful for this kind of substances, as biomonitoring can be used to measure the total body burden, covering past exposure and exposure via different routes, whereas OELs for the workplace air reflect current exposure. Typically, in settings with low air concentrations, the main route of exposure can be the oral route, due to personal hygiene issues or working routines. At the workplaces there are currently workers who have been exposed to cadmium for years, at air concentrations significantly higher than the current OEL. As a result, cadmium may have accumulated in their bodies and the urinary cadmium levels may be markedly higher than among occupationally non-exposed persons. In a worst case situation, the urinary concentrations of such workers may already be close to or above the proposed BLV, or may increase during the next years, although the exposure levels would be below the OEL

(1 µg/m^3). In those situations there is a risk for health effects. For an equal protection of all workers, it would thus be important to monitor the cumulative exposure.

In SCOEL (2017) kidneys were identified as critical target organs from a systemic toxicity perspective. A LOAEL of 5 µg/g creatinine was identified as a LOAEL for renal effects from studies in occupational settings, and 2 µg/g creatinine as a LOAEL from studies in the general population.

The following issues are relevant when considering the basis for a BLV for cadmium:

- There is an abundant data base on the health effects of cadmium and its compounds, including human studies, and the mechanisms of the systemic toxicity of cadmium are relatively well understood.
- Kidney effects are still considered the critical effects of cadmium exposure. Several studies indicate a LOAEL of 2 µg/g creatinine in the general population. In occupational settings the LOAEL has been identified as 5 µg/g creatinine. No NOAEL was identified. Some data indicates effects in the general population at concentrations < 2 µg/g creatinine (even as low as 0.5 µg/g creatinine). Diuresis is however likely to cause major confounding effects at such low levels of exposure. The mean urinary cadmium concentration European individuals with no occupational exposure to cadmium, or living in an area with no specific cadmium pollution is generally < 1 µg/g creatinine.
- For respiratory effects in workers, 3 µg Cd/g creatinine is identified as a LOAEL. Bone toxicity has consistently been reported at urinary concentrations > 5 µg/g creatinine. At lower levels, bone effects in the general population have been observed at urinary concentrations 0.5-5 µg/g creatinine, but there are also studies with no effects.

Taking into account all aspects, a BLV is considered important for the protection of workers, in order to ensure that the accumulation of cadmium in the body does not become too high. The concentration of cadmium in the urine is known to reflect long-term exposure better than blood concentrations, which are reflecting recent exposure. Thus, a BLV for cadmium in urine of 0.002 mg Cd/g creatinine (2 µg Cd/ g creatinine) is proposed. As explained in Section 7.1.5, the sampling time is not critical.

9.2.4.1 . Comparison of the effectiveness of the OEL and proposed BLV

The proposed BLV does not necessarily protect against respiratory effects or (lung) cancer on its own, as it is estimated to correlate with a higher air concentration than the OEL (see Section 9.2.2.1). The BLV should be used together with the OEL.

The OEL on its own would protect against systemic and local effects upon current inhalation exposure but not against cumulative effects due to previous exposure and not against indirect (oral) exposure.

The BLV on its own would protect against systemic effects, cumulative effects and effects due to indirect exposure but perhaps not against local respiratory and carcinogenicity effects.

Thus the values used individually may not provide equal protection of workers. The recommendation is to use a combination of both values.

9.2.5 Biological Guidance Value (BGV)

No BGV is proposed.

9.3 Notations

Cadmium has not been reported to cause skin or respiratory sensitisation. There are no indications of systemic toxicity upon dermal exposure to cadmium. No notations are proposed.

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Appendix 1. SCOEL report

The SCOEL Opinion, which was adopted on 8 February 2017, is available at https://op.europa.eu/en/publication-detail/-/publication/3325374b-0a14-11e7-8a35-01aa75ed71a1/language-en