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Call for Evidence: Occupational Exposure Limit for Cadmium and its Inorganic Compounds

PART 3

SUBMISSION OF INFORMATION ON HEALTH EFFECTS

REPEATED DOSE TOXICITY AND CARCINOGENICITY OF CADMIUM AND ITS INORGANIC COMPOUNDS

Document prepared by EBRC Consulting GmbH, Germany in collaboration with the *International Cadmium Association*

For further information, please contact:
Noömi Lombaert, Manager Regulatory Toxicology of ICdA
nlombaert@cadmium.org

Table of Contents

1 Updating literature search for cadmium

1.1 Aim

The aim of the updating literature review is to address specific questions:

A. Is the kidney still the critical organ (systemic) after repeated exposure? And what is the effect level?
B. Are other systemic endpoints (bone, ED) covered by this effect level?
C. Is lung function impairment still the critical effect after inhalation exposure and what is the effect level? (Consequently can 4 µg/m³ respirable fraction still be retained as protective for this end point)?
D. Is an OEL-only based approach protective against renal effects?

1.2 Documentation of search

A targeted literature search has been conducted to identify additional toxicological data that has been published after the SCOEL review in 2010 and 2017 [SCOEL 2010, 2017]. The search was targeted but not limited to information on the endpoints repeated dose toxicity and carcinogenicity.

The literature search has been conducted via the database provided by STN international. The following databases have been selected based on a trial search and previous experience with similar search topics: TOXCENTER BIOSIS CABA HCAPLUS EMBASE ESBIOBASE FSTA MEDLINE PQSCITECH SCISEARCH. The search was restricted, to exclude patent literature and to publications since the year 2010 (up to those entered into databases as of the date of the search, 2020-04-27). Only articles in English, French or German language were considered.

The effort required for the evaluation of the literature search was estimated by aid of an orientating search, conducted with the key word “cadmium” being in the title and/or abstract. This resulted in 70.000 hits for cadmium in title and abstract or 40.000 hits for cadmium in title.

Due to the large number of hits, it was decided to follow a step-wise approach by first targeting the search by using general key terms, as follows:

Repeated dose toxicity

=> (toxicity and (repeated or sub-acute or chronic or subchronic or sub-chronic) or bioassay or NOEL or NOEC or LOEL or LOEC or NOAEL or NOAEC or LOAEL or LOAEC)

Carcinogenicity

=> (carcinogen? or cancer or carcinom? or adenom? or melanom? or sarcom? or tumor or tumour or neoplas? or malignant)

The retrieved titles for Repeated dose toxicity (n= 1829) and Carcinogenicity (n=2103) were reviewed and selected manually for potential relevance. In a second step, the full bibliographic data (such as author, source, abstract) were retrieved for the 480 potentially relevant references identified in the first step (261 for Repeated dose toxicity and 219 for Carcinogenicity). The abstracts were again screened manually for potential relevance. Hard copies were obtained for those references considered relevant for the purpose of hazard and risk assessment (131 for Repeated dose toxicity and 119 for Carcinogenicity).

Strict selection criteria were applied to titles, abstracts and full references as follows:

1. exclude all non-relevant species, such as goat, sheep, chicken, catfish, etc.
2. low relevance was given to in vitro studies, in vivo studies (i) with mixed exposure (e.g. Cd and Pb co-exposure), (ii) investigating the ameliorating effect of substances/diets after Cd intoxication or

(iii) purely in vivo mechanistic investigations on isolated biomarkers (iv) human data following a cross-sectional design, especially when using low number of participants

3. medium relevance was given to (i) animal studies which followed generally a guideline compliant study design but with limitations, such as targeted investigation of selected organs/biochemical parameters, (ii) human studies (cohort or case-control design) for which a significant influence of confounders could not be excluded or with limited numbers of participants
4. high relevance was given to in vivo studies where cadmium and its substances were administered repeatedly via physiological route and the study design was similar or in accordance with accepted guidelines.

2 Repeated dose toxicity

2.1 Animal data

A total of 59 references on repeated dose toxicity in animals were summarised (endpoints, test substance, study design, toxicological effects, effect dose) and evaluated for quality (low, medium, and high).

In summary, the endpoints addressed in these references are very diverse and comprise effects on the kidney (n=21), liver (n=18), lung/respiration (n=6), gastro-intestinal (GI) tract (n=5), bone (n=4, heart/cardiovascular system (n=8), eyes (n=1), thyroid (n=2), brain/behaviour (n=5), ear/hearing (n=1), pancreas as well as glucose/insulin homeostasis (n=4), spleen and immune system effects (n=2), reproductive organs/fertility/endocrine system (n=12), and development (n=4). The test substances were almost exclusively administered via the oral route (via drinking water, feed, or gavage), except for one aerosol inhalation study using CdO nanoparticles (NPs). In the majority of references, cadmium chloride ($CdCl_2$) was selected as test substance (n=50). However, cadmium oxide (CdO; n=1), cadmium acetate (CdAc; n=2), and cadmium sulphate ($CdSO_4$; n=1) were sporadically tested, as well. In a few cases, the test substance was not further specified and classified as 'Cd-category' (n=5). Moreover, the references comprised data on rats (n=39), mice (n=18), rabbits (n=1), and pigs (n=1).

Notably, the database primarily comprised low quality references (n=48), whereas only eleven references are considered to have a medium (low/medium) quality (summarized in appendix 1). None of the references obtained is of a high quality. It has to be mentioned, that none of the references describes a study which was performed according to any current validated test guideline. Moreover, all references contain analysis focussed on single selected parameters. None of the references contain a comprehensive analysis comparable to guideline studies. The deficiencies of the reviewed were regularly characterised by inclusion of only one dose group, a low number of animals tested per group, reporting deficiencies and unclear methodology, inappropriate dose regimen, analysis of only a few selected parameters without investigating systemic toxicity.

2.1.1 Repeated dose toxicity - inhalation

2.1.1.1 Information on effects after inhalation from low/medium-quality references:

Lebedová, J. et al. (2016) investigated the effects of CdO nanoparticles (NPs) on mice lungs after 1-13 weeks whole body inhalation. The female mice were exposed to daily CdO NP aerosol concentrations of 0, 12.7, and 31.7 µg/m³ for 24 hours per day. The authors observed presence of CdO nanoparticles in the liver, kidney, spleen, brain, and lung via transmission emission microscopy (TEM). The absolute lung weight was significantly increased after CdO NP-exposure. Moreover, histopathological analysis of the lungs revealed damage depending on time and dose. Further, the liver showed increased oxidative stress and histopathological alteration indicating severe liver damage. The kidney, spleen, and brain showed no histopathological alterations. Impact on body weight, clinica l signs, haematology, and mortality is not reported.

2.1.1.2 SCOEL 2017 opinion on inhalation repeated dose toxicity in animals

"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/m3 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/m3 for intermediate exposures; 0.2–2 mg/m3 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/m3 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 haemorrhage, 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/m3 for 30 minutes (Henderson et al. 1979) and in rabbits exposed to cadmium oxide dusts at 4.5 mg/m3 for 2 hours (Grose et al. 1987). Exposures in rats to cadmium chloride at 6.1 mg Cd/m3 1 hour/day for 5, 10, or 15 days resulted in emphysema; a 3-day exposure to 61 mg Cd/m3 for 1 hour/day resulted in pulmonary haemorrhage (Snider et al. 1973).

In sub-chronic 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/m3 for the 2-week studies and 0.025 to 1 mg/m3 for the 13-week studies. In the 2-week studies, all rats and mice at the highest exposure level (10 mg/m3) 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/m3 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/m3) 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/m3 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/m3 levels in mice, lung lesions were minimal and not considered life threatening. A NOAEL in the nasal cavity was 0.05 mg/m3 for rats and mice (NTP 1995).”

2.1.2 Repeated dose toxicity - oral

2.1.2.1 Kidney effects

Medium quality references:

Jacquet, A. et al. (2018) examined sub-chronic effects of $CdCl_2$ on glucose homeostasis and different organs in rats. Nine rats per sex and group were exposed for three months to 0, 5, 50, and 500 µg $CdCl_2$/kg bw/day via drinking water. Rats exposed to $CdCl_2$ at 50 and 500 µg/kg bw/day showed a significant Cd accumulation in the kidney. However, in general, the exposed rats showed no signs of nephrotoxicity as indicated by the absence of statistically significant effects on relative kidney weights or Kim-1 (Kidney injury molecule-1) excretion. Effects on mortality or body weights were not observed.

Liu, Q. et al. (2019) examined on kidney effects in rats after $CdCl_2$ exposure. The male rats received daily gavages of 0, 1.0, 2.5, and 5.0 mg/kg $CdCl_2$ for 60 days. The $CdCl_2$-exposed mice showed dose dependent glomerular and tubular renal damage as evidenced by histopathology renal function markers, and increased apoptosis-related protein expression. Further, the 24-h urine volume was statistically significantly reduced in the two highest dose groups. Moreover, increased oxidative stress levels were evidenced by statistically significantly increased ROS levels and statistically significant and dose dependent alteration of antioxidant enzyme expression. The effects were observed in presence of systemic toxicity, as indicated by statistically significantly reduced body weights (>-20% terminal body weights) and clinical signs, including loss of appetite, rough fur, and irritable mood.

Chen, S. et al. (2018) investigated the toxic effect of $CdCl_2$ on rat kidney via a metabolic analysis of the rat urine. Ten male rats per group received $CdCl_2$ doses of 0, 0.13, 0.8, and 4.9 mg/kg bw for 24 via drinking water. The high dose group animals showed signs of renal damage as indicated by a statistically significantly altered urine metabolite profile (increased levels of guanidinosuccinic acid (GSA), 4-pyridoxic acid, 4-aminohippuric acid (PAH),and 4-guanidinobutanoic acid (GBA)), altered renal function markers as well as increased oxidative stress. Systemic toxicity was not evident (no changes in body weight).

Buha, A. et al. (2019) primarily investigated bone effects in rats after sub-acute oral $CdCl_2$ exposure. Daily oral gavages at doses of 0, 0.3, 0.6, 1.25, 2.5, 5.0, and 10 mg $CdCl_2$/kg bw were given to seven male rats per group. The test animals showed a statistically significantly increased serum creatinine level (10 mg/kg bw/day) and urea level (5 and 10 mg/kg bw/day) as well as a dose dependent and statistically significant decrease of the serum albumin level (all doses). Systemic toxicity was restricted to statistically significant decreases body weight gain in at dose up to and greater than 1.5 mg/kg bw/day.

Low quality references:

Carlson, K. et al. (2018) exposed 6-16 mice for 12 weeks to 0, 3, 11, and 27 mg $CdCl_2$/L via drinking water. Histopathological analysis as well as the analysis of kidney function serum markers indicated no obvious nephrotoxicity under any condition tested. No systemic toxicity was evident.

Cobbina, S.J. et al. (2015) examined the effects of $CdCl_2$ low dose exposure on several organs of mice. Five mice per sex were treated for 1-4 months with 0 and 0.005 mg $CdCl_2$/L via drinking water. The kidneys showed neither histopathological alterations nor significant alterations in the relative and absolute organ weights. Moreover, the oxidative stress markers analysed showed no significant alteration.

Dhir, V. and Gupta, S.K. (2011) investigated Cd-toxicity in rats after sub-chronic exposure. Female rats received $CdSO_4$ at doses of 0 and 50 mg/kg bw/day via gavage for 90 days. The examination of kidney effects was restricted to the analysis of acid and alkaline phosphatase levels. In Cd-exposed rats, both markers were significantly increased indicating cellular damage.

Erdem, O. et al. (2015) investigated the oxidative stress status in several rat organs after $CdCl_2$ exposure. Twenty to thirty male rats were exposed for eight weeks to 0 and 15 ppm $CdCl_2$ via drinking water. The authors observed statistically significantly increased MDA levels, whereas SOD activity was significantly decreased in kidneys. Moreover, the levels of zinc (Zn) and copper (Cu) were significantly altered after $CdCl_2$ exposure. The authors concluded that increased oxidative stress in the kidney is indicated based on altered MDA and essential mineral levels.

Ivanova, J. et al. (2014) investigated the effect of CdAc on renal and cardiac function in mice. Six male mice were exposed for 2 weeks to 0 and 20 mg CdAc/kg bw via drinking water. Cadmium-exposed mice, sacrificed after a two-week post-exposure period, showed effects on the kidney characterised by a statistically significantly increased Cd burden, relative organ weight, and serum creatinine level. Effects on systemic toxicity are not reported.

Kouadria, M. et al. (2019) analysed effects of Cd exposure on biochemical markers and behaviour of rats. The rats (n=5 per dose group) were exposed for 45 days to 0 and 15 mg $CdCl_2$/kg/L via drinking water. Renal dysfunction was indicated by statistically significantly increased blood urea and creatinine levels. The only effect on systemic toxicity reported were statistically significantly reduction in body weight gain.

Lee, Y.-J. et al. (2016) examined on apoptosis and p53 expression in several tissues. Five to six female mice were fed for 12 months with 0 and 300 ppm with an unspecified Cd substance. In the kidney, increased apoptosis and p53 protein accumulation, as evidenced by immunohistochemical staining, were noted. Information on systemic toxicity is not provided.

Lovasova, E. et al. (2013) examined on selected biochemical and antioxidant parameters after Cd-exposure. Eight rats per sex and group were exposed to 0 and 4.8 mg CdCl2/L for one year via drinking

water. Renal dysfunction was not indicated, since serum creatinine and urea levels were not statistically significantly changed. The only parameters changed were a statistically significantly decreased total protein level (only in females), SOD activity, GPx activity (only in males), and total antioxidant capacity (only in females). Effects on systemic toxicity are not reported.

Markiewicz-Gorka, I. et al. (2019) examined on inflammatory processes, oxidative stress, and bone metabolism disorders in rats exposed to $CdCl_2$. Six male rats per group were fed for 3 months with standard diet or diet containing 30 ppm $CdCl_2$. Examination of the kidney revealed an affected renal function, as indicated by serum BUN level, creatinine level and BUN/creatinine ratio, and oxidative stress, as indicated by statistically significantly increased TBARS level and SOD activity as well as a statistically significantly decreased GSH level and GPx activity. These changes were observed in presence of systemic toxicity as indicated by a statistically significantly body weight gain and altered haematological markers. Moreover, oxidative stress and inflammation were indicated by increased levels of serum TBARS level and C-reactive protein level, respectively.

Nai, G.A. et al. (2015) investigated the effect of water pH on the induction of cancer induced by $CdCl_2$ exposure. Fifteen male rats per group were exposed for six months to water (at pH 5, 7, and 8) only and water containing $CdCl_2$ (at pH 5, 7, and 8) at a concentration of 400 mg/L both. The kidneys of $CdCl_2$-exposed rats showed no hyperplastic changes, precancerous lesions, and benign or malignant neoplasms.

Santoyo-Sánchez, M.P. et al. (2013) examined mechanisms leading to proteinuria after Cd exposure. Nine to ten female rats were received daily gavages of 0 and 3.0 mg $CdCl_2$/kg for eight weeks. Kidneys of $CdCl_2$-exposed mice showed a statistically significant Cd accumulation and microalbuminuria. Moreover, statistically significantly increased Kim-1 expression indicated proximal tubule injury and decreased cubilin protein expression suggested an impaired endocytosis. However, urinary flow rate, plasma creatinine, creatinine clearance, urinary glucose, urinary NAG, megalin, and oxidative stress parameters were unaffected after administration of $CdCl_2$. Description of systemic toxicity was restricted to body weights, which were not significantly altered in $CdCl_2$ dose group.

Siddiqui, M.F. (2010) investigated on kidney effects in rats after sub-acute $CdCl_2$ exposure. Four male rats per group were exposed for 30 days to 0 and 0.6 mg $CdCl_2$/kg bw/day via drinking water. According to the authors, the findings of the study indicated damage in the renal cortex, proximal tubules membrane, distal tubules membrane, cell nuclei, and blood vessels. Moreover, the author observed cytosolic bodies and swelling in glomeruli. Systemic toxicity is not reported.

Tokumoto, M. et al. (2011) investigated on Cd-induced nephrotoxicity and its mechanisms. Five to six female mice pre group were exposed for 12 months to 0 and 300 ppm Cd (not further specified) via feed. The Cd-exposed mouse showed statistically significantly increased Cd levels in the kidney. Moreover, mild nephrotoxicity as indicated by mild histopathological changes as well as by a statistically significantly increased relative organ weight, serum BUN level, increased apoptosis in renal tubules. However, serum creatinine was not statistically significantly altered. The expression of Ube2d gene was statistically significantly lower, whereas the p53 protein level was statistically significantly increased. Systemic toxicity was only insufficiently described and only restricted to the documentation of statistically significantly impaired body weight gain.

Nephrotoxicity in rats induced by $CdCl_2$-epxosure was investigated by Tsutsumi, T. et al. (2014). Nine to ten male rats pre group were exposed for 114 days to 0 and 300 ppm $CdCl_2$ via drinking water. The authors observed mild nephrotoxicity as indicated by histopathological alterations as well as statistically significantly increased plasma urea nitrogen levels, increased LPA1 gene expression, and decreased relative weight of peri-renal fat. Plasma creatinine level, ATX expression, aSMA expression, SPHK1 expression, SPHK2 expression, and S1P1 expression remained unchanged. The Cd-exposed rats showed statistically significantly reduced body weight gain and feed consumption.

Wu, X. et al. (2012) examined on kidney effects in pigs after $CdCl_2$ exposure. Four pigs per group were fed with 0, 0.5, 2, 8, and 32 mg $CdCl_2$/kg (actual doses: 0.181, 0.430, 2.171, 8.192, and 31.543 mg/kg) for 100

days. Pigs exposed to $CdCl_2$ showed dose and time dependent increased of blood and urine Cd. Moreover, a dose and time dependent increase of markers of renal damage (urinary levels of β2-microglobulin, N-acetyl-β-D-glucosaminidase, cadmium-metallothionein, and retinol binding protein) was observed. Description of systemic toxicity is restricted to the body weights, which show no meaningful alteration.

Yamanobe, Y. et al. (2015) examined on kidney effects in mice after CdCl2 exposure. Two mice per sex and group were exposed for 11 weeks to 0 and 32 mg $CdCl_2$/L via drinking water. The kidney of Cd-exposed test animals showed significant Cd accumulation, which was statistically significantly higher in females than in males. However, the kidney showed no obvious adverse effects as evidenced by histopathological examinations. The only significant alteration reported were decreased protein expression levels of glutathione S-transferase A1 and A2.

2.1.2.2 Liver effects

Medium quality references:

Chen, S. et al. (2018) investigated the toxic effect of $CdCl_2$ on rat liver via a metabolic analysis of the rat urine. Ten male rats per group received $CdCl_2$ doses of 0, 0.13, 0.8, and 4.9 mg/kg bw for 24 via drinking water. The high dose group animals showed indications for an affected lipid metabolism and liver injury is indicated by significantly increased PAG (phenylacetylglycine) and LysoPC metabolite urine levels. Systemic toxicity was not evident (no changes in body weight).

Jacquet, A. et al. (2018) examined sub-chronic effects of $CdCl_2$ on glucose homeostasis and different organs in rats. Nine rats per sex and group were exposed for three months to 0, 5, 50, and 500 µg $CdCl_2$/kg bw/day via drinking water. Rats exposed to $CdCl_2$ at 50 and 500 µg/kg bw/day showed a significant Cd accumulation in the liver. However, no hepatotoxicity was evident as indicated by unaltered levels of liver function markers (ASAT and ALAT activity) and relative liver weight. Effects on mortality or body weights were not observed. Effects on mortality or body weights were not observed.

Liu, L. et. al. (2015) investigated on hepatic oxidative stress and inflammatory responses in mice after Cd exposure. Seven males per group were exposed for 7 or 21 days to 0, 3, 10, and 30 mg $CdCl_2$/L (about 0, 0.43, 1.29, and 4.3 mg/kg bw) via drinking water. Mice exposed to $CdCl_2$ showed inflammatory responses and oxidative stress in the liver as indicated by histopathological alterations, altered oxidative stress marker levels and activity (MDA, SOD, CAT, and GST), as well as by increased cytokine mRNA (tumour necrosis factor α (TNFα), interleukin 6 (IL6), interleukin 1α (IL1α),), inducible nitric oxide synthase (INOS), and interferon γ (INFγ)) expression levels. Most of the changes were only evident in the high dose group and only after 21 days of exposure. The high-dose group animals showed a statistically significantly decreased relative liver weight. Moreover, the serum levels of TNFα, IL6, and, IL1β were statistically significantly increased in the high-dose group after the 21-day exposure. Description of systemic toxicity is restricted to the effect on body weight, which did not show a statistically significant alteration.

Low quality references:

Banni, M. et al. (2010) examined on the effect of sub-acute Cd exposure on the liver and liver metallothionein expression in rats. Eight male rats per group were exposed to 0 and 200 ppm $CdCl_2$ via drinking water for 35 days. Rats exposed to $CdCl_2$ showed a statistically significant Cd accumulation in the liver. Moreover, the metallothionein protein and mRNA levels were significantly increased, indicating oxidative stress. However, no effect on the relative organ weight was observed. The Cd exposure had no effect on body weight gain.

Carlson, K. et al. (2018) primarily investigated on ototoxicity induced by Cd exposition but included examination of the liver. Six to sixteen mice per group were exposed to 0, 3, 11, and 27 mg $CdCl_2$/L for 12 weeks via drinking water. Histopathological examination of the liver as well as the analysis of liver function markers indicated no obvious hepatotoxicity under any condition tested. No systemic toxicity was evident.

Cobbina, S.J. et al. (2015) examined the effects of $CdCl_2$ low dose exposure on several organs of mice. Five mice per sex were treated for 1-4 months with 0 and 0.005 mg $CdCl_2$/L via drinking water. The effects observed in the Cd-exposure group are restricted to transiently altered ALT, AST, and AP levels, indicating liver cell injury, as well as sporadically decreased levels of oxidative stress markers (SOD activity and GPx level). Moreover, no statistically significant alterations were observed for the absolute and relative organ weight as well as other oxidative stress markers (MDA level, CAT level, NOS activity). Systemic toxicity as evidenced by clinical sings, body weight, food consumption, and haematopoietic parameters was not observed.

Dhir, V. and Gupta, S.K. (2011) investigated Cd-toxicity in rats after sub-chronic exposure. Female rats received $CdSO_4$ at doses of 0 and 40-50 mg/kg bw/day via gavage for 90 days. The examination of liver effects was restricted to the analysis of levels of AST, ALT, acid phosphatase, and alkaline phosphatase. In Cd-exposed rats, all markers were significantly increased indicating liver damage. Systemic toxicity was not evaluated.

Erdem, O. et al. (2015) investigated the oxidative stress status in several rat organs after $CdCl_2$ exposure. Twenty to thirty male rats were exposed for eight weeks to 0 and 15 ppm $CdCl_2$ via drinking water. The authors observed statistically significantly increased hepatic MDA levels and GPx activity, whereas SOD activity was significantly decreased. Moreover, the levels of zinc (Zn) and copper (Cu) were significantly altered after $CdCl_2$ exposure. The authors concluded that increased oxidative stress in the liver is indicated based on altered MDA and essential mineral levels.

He, X. et al. (2020) evaluated the effects of chronic Cd exposure on energy metabolism and liver toxicity. Eight male mice per group were exposed for 26 weeks to 0 and 150 µg $CdCl_2$/L via drinking water. The Cd level in liver of $CdCl_2$-exposed mice was statistically significantly increased. Histopathological examinations revealed hepatocellular necrosis and inflammation. Moreover, a statistically significant increase was observed for the number of Kupffer cells, as evidenced by CD68 immunohistochemical staining. Further, increased oxidative stress was indicated by increased hepatic MDA level and decreased mRNA levels of HO-1 and GPx. According to the authors chronic Cd exposure had a profound effect on transcriptional regulation of the energy metabolism, as evidence by multivariate data analysis of transcription factor expression. Information on systemic toxicity is not provided.

Kouadria, M. et al. (2019) analysed effects of Cd exposure on biochemical markers and behaviour of rats. The rats (n=5 per dose group) were exposed for 45 days to 0 and 15 mg $CdCl_2$/kg/L via drinking water. Hepatic damage was indicated by statistically significantly increased activity of ALT and AST in Cd-exposed rats. Moreover, Cd-exposure resulted in statistically significantly decreased body weights. No further information on systemic effects is provided.

Lee, Y.-J. et al. (2016) examined on apoptosis and p53 expression in several tissues. Five to six female mice were fed for 12 months with 0 and 300 ppm with an unspecified Cd substance. The liver function markers ALT and AST were increased (ca. 3.2- and 3.4-fold, respectively) in Cd-exposed animals. Moreover, the authors noted a slightly increased apoptosis rate, as evidenced by TUNEL staining. Further, *Ube2d3* (involved in p53 ubiquitination) mRNA expression was statistically significantly increased after Cd-exposure. Protein levels of p53, however, remained unchanged. Further information on hepatic or systemic toxicity were not provided.

Lovasova, E. et al. (2013) examined on selected biochemical and antioxidant parameters after Cd-exposure. Eight rats per sex and group were exposed to 0 and 4.8 mg CdCl2/L for one year via drinking water. No hepatic damage was indicated, since serum ALT and AST levels were not statistically significantly changed. The only parameters changed were a statistically significantly decreased total protein level (only in females), SOD activity, GPx activity (only in males), and total antioxidant capacity (only in females). Effects on systemic toxicity are not reported.

Markiewicz-Gorka, I. et al. (2019) examined on inflammatory processes, oxidative stress, and bone metabolism disorders in rats exposed to $CdCl_2$. Six male rats per group were fed for 3 months with standard

diet or diet containing 30 ppm $CdCl_2$. Liver biomarkers (activities of AST, ALT, and LDH) were statistically significantly increased in rats exposed to $CdCl_2$. Moreover, a statistically significantly increased TBARS level, SOD activity, and GPx activity as well as a statistically significantly decreased GHS levels indicated increased hepatic oxidative stress. These changes were observed in presence of effects on systemic toxicity as indicated by a statistically significantly body weight gain and altered haematological markers. Moreover, oxidative stress and inflammation were indicated by increased levels of serum TBARS level and C-reactive protein level, respectively.

Nai, G.A. et al. (2015) investigated the effect of water pH on the induction of cancer induced by $CdCl_2$ exposure. Fifteen male rats per group were exposed for six months to water (at pH 5, 7, and 8) only and water containing $CdCl_2$ (at pH 5, 7, and 8) at a concentration of 400 mg/L both. The liver of $CdCl_2$-exposed rats showed no hyperplastic changes, precancerous lesions, and benign or malignant neoplasms. Except for two premature deaths due to acute pulmonary oedema, no information on systemic toxicity is provided.

Treviño, S. et al. (2015) examined on effects on the pancreas and insulin resistance in multiple peripheral tissues in Cd-exposed rats. Ten to twenty male rats per group were exposed to 0 and 32.5 ppm $CdCl_2$ via drinking water for 60, 90, and 120 days. Rats exposed to $CdCl_2$ showed a statistically significantly Cd accumulation in the liver. Moreover, Cd-exposed test animals showed a decreased hepatic insulin sensitivity (HIS index) and a statistically significantly increased hepatic insulin resistance as indicated by the HIRI and LIRI indices. The Cd treatment had no obvious effect on body weight, body mass index, and fat tissue. However, the basal levels of circulating glucose and insulin were statistically significantly increased indicating that rats were hyperglycaemic and hyperinsulinemic. The peripheral insulin resistance was increased (HOMA-IR index) and insulin sensitivity was statistically significantly decreased (HOMA-S% index; QUICKI; Matsuda-DeFronzo index). Moreover, the serum lipid profile was statistically significantly altered (increased free fatty acids (FFA, total cholesterol, LDL, and VDL as well as decreased HDL).

Yamanobe, Y. et al. (2015) examined on liver effects in mice after $CdCl_2$ exposure. Two mice per sex and group were exposed for 11 weeks to 0 and 32 mg $CdCl_2$/L via drinking water. Rats exposed to $CdCl_2$ showed an accumulation of Cd in the liver. The histopathological examination revealed no obvious effects on hepatocytes. The only statistically significant alteration was restricted to a decreased protein levels of glutathione S-transferase Mu2, Mu4, and Mu7. Systemic toxicity was not evident.

The effects of Cd on hepatic inflammation and hypoxia-inducible factor-1α (HIF-1α) gene expression in rats were investigated by Yazihan, N. et al. (2015). Ten male rats per group received doses of 0 and 15 ppm $CdCl_2$ via drinking water for eight weeks. Rats exposed to $CdCl_2$ showed a 150-fold increased hepatic Cd burden. Histopathological examination revealed dilatation and congestion of sinusoids, inflammatory cell infiltration, focal necrosis, pyknotic nuclei, and an increased mitosis rate. Moreover, inflammation was further indicated by statistically significantly increased cytokine levels (IL-1β, TNF-α, and IL-8) and increased galectin-3 protein level. Moreover, a statistically significantly increased cytochrome C level indicated apoptosis. Information on systemic toxicity is not provided.

2.1.2.3 Lung effects

Medium-quality references:

No medium-quality references containing relevant information on lung effects were obtained.

Low-quality references:

Effects of Cd on the lung and respiration in mice were investigated by Chandler, J.D. et al. (2016). Mice were exposed to 10 mg $CdCl_2$ for 20 weeks via drinking water. A pure water control group was run concurrently. Mice exposed to $CdCl_2$ showed statistically significantly increased Cd levels in the lung. Moreover, the exposure to $CdCl_2$ resulted in an increased airway hyperresponsiveness (after methacholine challenge) and impacted neuronal pathways regulating bronchial tone, as evidenced by gene enrichment

analysis and neurotransmitter metabolite analyses. Metallothionein expression was not affected in Cd-exposed mice. Effects on body weight and clinical signs were not evident under the conditions tested.

Go, Y.M. et al. (2019) investigated the effects of Cd on nutritional metal homeostasis in mice lung. The mice were exposed to 0, 1.0, 3.3, and 10 mg $CdCl_2$/L via drinking water for 16 weeks. The levels of cobalt, vanadium, copper, and molybdenum were positively correlated with Cd levels. Moreover, the correlation of vanadium and copper were increased in lung mitochondria. Further information on lung or systemic effects is not provided.

Hu, X. et al. (2019) investigated on lung effects after sub-chronic Cd exposure. Eight male mice per group were exposed for 16 weeks to $CdCl_2$ concentrations of 0, 0.2, 0.6, and 2.0 mg/L in drinking water. The Cd lung burden was statistically significantly increased in rats exposed to 2 mg $CdCl_2$/L and showed a positive dose-response relationship. Lung histopathology revealed significant inflammation in high-dose group animals, characterised by interstitial inflammatory cell infiltration und accumulation of inflammatory cells around the airway and blood vessels. A metabolome wide association study of lung Cd burden showed an enrichment in lipid metabolism, which was most prominent in the highest dose group. Moreover, rats from the high-dose group showed statistically significantly increased lipid levels in the lung. The authors stated that Cd caused a disruption of the mitochondrial metabolome and redox proteome at the highest Cd dose. Effects on systemic toxicity were not investigated by the authors.

Kulas, J. et al. (2019) examined on effects on pulmonary inflammation and immune reactivity in rats after sub-acute Cd exposure. In two independent experiments, four male rats per group were exposed to 0, 5, and 50 mg $CdCl_2$/L (0, 0.35±0.04, and 3.51±0.29 mg/kg bw, respectively) via drinking water for 30 days. Sub-acute oral exposure to $CdCl_2$ resulted in statistically significantly increased pulmonary Cd levels. Histopathological examination of lung from $CdCl_2$ treated mice revealed dose dependent damage of pulmonary tissue and inflammatory cell infiltration. The oxidative stress markers, SOD and CAT activity, were statistically significantly increased in the high-dose group and in both dose groups, respectively. Increased activity of lung leukocytes was indicated by a statistically significantly increased MOP activity. Further, inflammation was indicated by statistically significantly altered cytokine levels (increase of TNF-α and dose-dependent increase of IL-1β), whereas IL6 showed contradictory results (stimulation at low and inhibition at high dose). Furthermore, leukocytes showed a change in the production of ROS and NOS as well as altered cytokine levels. The relative lung weight was, however, unchanged in the $CdCl_2$ treatment groups. Body weights were not statistically significantly different between groups.

Wang, C. et al. (2019) investigated on lung injury in mice after short-term Cd exposure. Solutions of $CdCl_2$ at doses of 0, 5, and 10 mg $CdCl_2$/kg bw were administered via nasal drips for seven days. Histopathological analysis revealed alveolar hyperaemia and destroyed integrity of the alveoli after Cd exposure. Both treatment groups showed statistically significantly increased neutrophil extracellular traps (NETs) in BAL fluid. Moreover, statistically significantly elevated ROS levels were observed in neutrophils. Further analyses indicated involvement of ERK 1/2 and p38 phosphorylation in NET induction. Systemic toxicity was not investigated.

2.1.2.4 GI tract effects

Medium-quality references:

No medium-quality references containing relevant information on GI tract effects were obtained.

Low-quality references:

He, X. et al. (2020) examined on structural and functional alterations of the gut microbiome after sub-chronic Cd exposure. Ten mice per group were exposed for 20 weeks to 0, 10, and 50 ppm $CdCl_2$ via drinking water. Histopathological examination of the gut revealed a dose related damage of the intestinal gut barrier. Moreover, mRNA expression levels of intestinal tight junction genes *Occludin* and *Claudin-1* were

decreased in the small bowel of both treatment groups. Further, the mRNA level of the cytokine TNF-α was significantly increased in the high dose group. Analysis of the microbiome indicated decreased gut microbial richness after Cd exposure. Short chain fatty acid (SCFA)-producing were predominantly inhibited accompanied by dose dependent reduction of major faecal SCFAs (acetate, propionate, and butyrate). Furthermore, KEGG analysis revealed downregulation of the majority of differently regulated metabolic functions after Cd exposure. The Cd treatment groups showed a dose dependent decrease in body weight. No further effect on systemic toxicity is reported.

He, X. et al. (2020) evaluated the effects of chronic Cd exposure on energy metabolism and liver toxicity. Eight male mice per group were exposed for 26 weeks to 0 and 150 µg $CdCl_2$/L via drinking water. The Cd level in liver of $CdCl_2$-exposed mice was statistically significantly increased. The analysis of the faeces of $CdCl_2$-exposed mice revealed an accumulation of Cd. The microbial composition in the gut was statistically significantly changed as evidenced by 16S rRNA gene sequencing. The proportion of six bacterial families were statistically significantly changed. Moreover, KEGG analysis indicated functional differences between the microbiome of treated vs. untreated mice. Furthermore, according to the authors, the energy metabolism is impacted based on evidently increased serum triglyceride levels and changed urinary metabolite levels (phosphocreatine, creatinine, glutamine, 2-oxoglutarate, citrate, phosphorylcholine, choline, and TMAO). Information on systemic toxicity is not provided.

The effect of $CdCl_2$ on the gut microbiota in mice was investigated by Liu, Y. et al. (2014). Ten female mice per group were exposed to 0, 20, and 100 ppm $CdCl_2$ in drinking water for three weeks. Mice exposed to $CdCl_2$ via drinking water showed a dose and time related increased of the Cd burden in the colon. Moreover, biopsied bacterial cultures of Cd-exposed mice showed a statistically significant and dose related decrease in the growth rate. The gut mucus layer thickness was statistically significantly decreased in an apparently dose-related manner. Further, the TNF-α cytokine level was statistically significantly increased. The overall gut microbial census was statistically significantly decreased accompanied by a significantly altered microbiota composition (Lactobacilli and Bifidobacteria ratio). This data was linked to a dose dependent decrease of major faecal SCFAs (acetate, butyrate, and propionate). Simultaneously, genes, involved in butyrate and acetate synthesis, were statistically significantly less expressed in $CdCl_2$-treated mice. Systemic toxicity was not investigated.

Nai, G.A. et al. (2015) studied the influence of the water pH in the initiation of gastro-intestinal tract injury after Cd exposure. Fifteen male rats per group were exposed to water and $CdCl_2$ solutions each at pH 5, 7, and 8. The test animals received the test material for 6 months via drinking water. Rats exposed to $CdCl_2$ solutions at different pH values showed no histopathological alterations in the small intestine, large intestine, and oesophagus. However, the mild dysplasia of the gastric mucosa was observed in Cd-treated rats. Systemic toxicity is not reported.

Ninkov, M. et al. (2015) investigated on the effect of sub-acute Cd exposure on gut immunity in rats. In at least two independent experiments, four to six male rats per group were exposed to 0, 5, and 50 ppm $CdCl_2$ (actual intake: 0, 0.511, and 4.236 mg/kg) via drinking water. The Cd burden in the duodenum and mesenteric lymph nodes was statistically significantly increased in Cd-exposed rats. The intestinal showed dose dependent histopathological alteration including morphological alteration and necrosis of villi, inflammatory cell infiltration, and goblet-cell like vacuoles. Moreover, the gut microbiome was affected as indicated by a statistically significantly decreased number of Lactobacilli, which were decreased in a dose related manner. Further, intestinal inflammation was indicated by increased oxidative stress markers (high mobility group box 1 (HMGB1 molecules), SOD, and CAT activity) and increased proinflammatory cytokine levels (TNF-α, IL-1β, IFN-γ, and IL-17). Increased mesenteric lymph node (MLN) GSH and metallothionein mRNA levels and stimulation of both adaptive (cellularity, proliferation, proinflammatory (IFN-γ and IL-17) MLN cell cytokine responses) and innate immune activity (increased NK and CD68+ cell number, oxidative activity and IL-1b level) indicated MLN stress response. Description of systemic toxicity is restricted to effects on body weights, which showed no statistically significant difference at study termination.

2.1.2.5 Bone effects

Medium-quality references:

Brzóska, M.M. et al. (2010) investigated on bone integrity and susceptibility to fractures after chronic exposure to $CdCl_2$. Ten male rats per group were exposed to 0, 1, 5, and 50 mg $CdCl_2$/L (actual test material intake for dose groups: 0.049-0.223, 0.238-0.977, and 2.073-10.445 mg/kg bw) for 12 months via drinking water. Rats exposed orally to $CdCl_2$ showed a statistically significant and dose related Cd accumulation across all dose groups. Moreover, high-dose group animals showed a statistically significant weight reduction of the femur and tibia, accompanied by a reduction of the femur M-L width. Moreover, the bone mineral density was decreased and the vulnerability to fracture at regions of the femur and tibia was elevated in a dose related manner. Systemic toxicity was not investigated.

Buha, A. et al. (2019) examined on the bone mineral composition after sub-acute Cd exposure. Seven male mice per group were gavaged at doses of 0, 0.3, 0.6, 1.25, 2.5, 5, and 10 mg $CdCl_2$/kg bw/day for 28 days. The Cd burden in femur was statistically significantly increased in rats exposed to $CdCl_2$. Analysis of the bone mineral composition revealed statistically significantly decreased levels of Ca, P, and Mg (all three equally decreased across groups), Zn (dose dependent), B (all doses), and Mn (all doses). The levels of Cu and Si were statistically significantly increased in intermediate dose group. But this effect was not observed in the high-dose group animals. Rats exposed to Cd showed statistically significantly decreased body weights (≥1.25 mg/kg bw/day), blood Ca levels (≥1.25 mg/kg bw/day), and increased blood Cd levels. Clinical signs were not observed.

Low-quality references:

Changes on bone structure after sub-chronic Cd exposure were examined by Duranova, H. et al. (2014). Ten rats per group were exposed to 0 and 30 mg $CdCl_2$/L (0.597 mg/kg bw) for 90 days via drinking water. Cadmium-exposed rats showed an accumulation of Cd in the bone. The treatment had no effect on femoral length and cortical thickness, whereas the femoral weight was statistically significantly increased. Moreover, histological examination of the compact bone indicated reduced bone vascularisation and induction of resorption lacunae, which are connected with an early stage of osteoporosis. Further, histomorphometrical analyses revealed effects on primary and secondary osteons, which may impact biomechanical properties. A statistically significant impact on body weight after Cd exposure was not evident. No further information on systemic toxicity is provided.

Markiewicz-Gorka, I. et al. (2019) investigated on inflammatory processes, oxidative stress, and bone metabolism disorders in rats exposed to $CdCl_2$. Six male rats per group were fed for three months with standard diet or diet containing 30 ppm $CdCl_2$. Sub-chronic oral exposure to $CdCl_2$ resulted in a statistically significantly increased Cd accumulation in the bone. Moreover, the bone formation marker vitamin D_3 was statistically significantly decreased in the serum of Cd-exposed rat. Simultaneously, the bone resorption marker C-terminal telopeptide of type I collagen was statistically significantly increased after Cd exposure. These findings indicate a disturbed bone metabolism. These changes were observed in presence of effects on systemic toxicity as indicated by a statistically significantly body weight gain and altered haematological markers. Moreover, oxidative stress and inflammation were indicated by increased levels of serum TBARS level and C-reactive protein level, respectively.

2.1.2.6 Heart/cardiovascular system effects

Medium quality references:

Jacquet, A. et al. (2018) examined sub-chronic effects of $CdCl_2$ on glucose homeostasis and different organs in rats. Nine rats per sex and group were exposed for three months to 0, 5, 50, and 500 µg $CdCl_2$/kg bw/day via drinking water. The relative heart weight was not significantly changed in any of the $CdCl_2$ dose groups. Effects on mortality or body weights were not observed.

Low-quality references:

Afolabi, O.K. et al. (2012) investigated on plasma lipid levels and inflammatory response in rats exposed to Cd. Eight male rats per group were exposed to 0, 50, and 100 ppm $CdCl_2$ for seven weeks via drinking water. Rats exposed to Cd showed altered plasma lipid contents as indicated by statistically significantly increased plasma total cholesterol, triglyceride, and LDL-/VLDL-cholesterol levels. Hypertriglyceridemia was evident in both Cd treatment groups. Moreover, the plasma phospholipid level was statistically significantly increased in high-dose group animals. Proinflammatory cytokine levels (IL-2, IL-6 and TNF-α) were statistically significantly increased at both Cd doses. Plasma lipid hyperoxide concentrations and oxLDL levels were statistically in Cd-exposed rats, whereas paraoxonase activity was shown to be statistically significantly reduced. The authors associated the altered lipid profile and inflammation with atherosclerosis and cardiovascular diseases. Effects on systemic toxicity are not reported.

Erdem, O. et al. (2015) investigated the oxidative stress status in several rat organs after $CdCl_2$ exposure. Twenty to thirty male rats were exposed for eight weeks to 0 and 15 ppm $CdCl_2$ via drinking water. Cadmium-exposed rats showed a statistically significantly cardiac Cd level, whereas Zn and Cu were statistically significantly decreased. Moreover, oxidative stress markers SOD and GPx activity were statistically significantly decreased and increased, respectively. Body weights of Cd-exposed rats remained unchanged compared to control animals.

Ferramola, M.L. et al. (2011) examined on myocardial oxidative stress after different short-term exposure periods to $CdCl_2$. Five male rats per group were exposed to 0 (only for a period of 60 days) and 15 ppm (for 15, 30, and 60 days) $CdCl_2$ via drinking water. Oral exposure of $CdCl_2$ resulted in a statistically significantly increased Cd levels in the heart and serum. Moreover, rats exposed to $CdCl_2$ showed an altered antioxidant/prooxidant ratio, including a statistically significantly increased cardiac TBARS level, increased cardiac carbonyl groups transient, decreased tGSH and GSH levels (transient), increased cardiac CAT activity, decreased cardiac GPx activity, as well as transiently increased cardiac expression of SOD, GPx, and NOX subunits (gp91phox and p47phox). Moreover, serum paraoxonase-1 activity was statistically significantly increased at all time points, whereas serum arilesterase activity was only transiently increased. Further, the serum TBARS level was statistically significantly increased after 60 days. Information on systemic toxicity is not provided.

Ivanova, J. et al. (2014) investigated the effect of CdAc on renal and cardiac function in mice. Six male mice were exposed for 2 weeks to 0 and 20 mg CdAc/kg bw via drinking water. Sub-acute oral exposure to CdAc resulted in a statistically significantly increased cardiac Cd burden. The Cd treatment did not result in a statistically significant change in the relative heart weight. The serum lipid profile remained unaffected. No further information on systemic toxicity is provided.

Oladipo, O.O. (2017) examined on the effects of Cd exposure on lipid profile of blood, oxidative stress, and metal content. Five male rats per group received daily gavages at doses of 0 and 0.01 mg $CdCl_2$/kg bw/day for 15 weeks. Rats exposed to $CdCl_2$ showed no effect on the serum lipid profile, oxidative stress markers (MDA, GPx, metallothionein) and metal levels (Fe and Zn). Thus, no significant cardiovascular effects were observed under the conditions tested. Effects on body weights, clinical signs or mortality are not reported.

Samarghandian, S. et al. (2015) investigated the effect of sub-chronic Cd exposure on serum lipid, lipoprotein, and oxidative stress in rats. Eight male rats were exposed to 0 and 2 mg Cd/L for 13 weeks via drinking water. The test substance was not further specified. Exposure to Cd resulted in increased oxidative stress, as indicated by increased MDA and decreased GSH levels. Moreover, the lipid profile was impacted as indicated by statistically significantly increased levels of serum triglycerides, total cholesterol, and low-density lipoprotein (LDL)-cholesterol as well as a statistically significant decreased in the high-density lipoprotein (HDL)-cholesterol level. Information on systemic toxicity is not provided.

Treviño, S. et al. (2015) examined on effects on the pancreas and insulin resistance in multiple peripheral tissues in Cd-exposed rats. Ten to twenty male rats per group were exposed to 0 and 32.5 ppm $CdCl_2$ via

drinking water for 60, 90, and 120 days. Cardiovascular tissue, of Cd-exposed rats, showed a time related increase in insulin resistance as indicated by the cardiovascular index. The Cd treatment had no obvious effect on body weight, body mass index, and fat tissue. However, the basal levels of circulating glucose and insulin were statistically significantly increased indicating that rats were hyperglycaemic and hyperinsulinemic. The peripheral insulin resistance was increased (HOMA-IR index) and insulin sensitivity was statistically significantly decreased (HOMA-S% index; QUICKI; Matsuda-DeFronzo index). Moreover, the serum lipid profile was statistically significantly altered (increased free fatty acids (FFA, total cholesterol, LDL, and VDL as well as decreased HDL).

2.1.2.7 Eye effects

Medium-quality references:

No medium-quality references containing relevant information on eye effects were obtained.

Low-quality references:

Abd-Elhakim, Y.M. et al. (2018) examined morphological, biochemical, histopathological post-mortem ocular indices in Cd-exposed rabbits. Eighteen male rabbits per group were daily gavaged with 0, and 5 mg $CdCl_2$/kg bw for 30 days. Ocular analysis was performed 0, 4, and 8 hours after sacrifice. The oral exposure to $CdCl_2$ for 30 days resulted in statistically significantly increased ocular GGT activity, urea level, K level, DNA damage and obvious retinal lesions up to eight hours post-mortem. Moreover, the cornea and sclera showed mildly degenerated tissue. Rabbits exposed to $CdCl_2$ showed no effects on body weight and mortality.

2.1.2.8 Thyroid effects

Medium-quality references:

No medium-quality references containing relevant information on thyroid effects were obtained.

Low-quality references:

Janjic, S. et al. (2011) investigated on thyroid effects in rats after sub-chronic exposure to $CdCl_2$. Eleven female mice per group were exposed to 0 and 15 mg $CdCl_2$/kg via drinking water for 13 weeks. Cadmium-exposed rats showed pre-neoplastic changes as indicated by bilateral, strong, diffuse parafollicular C-cell hyperplasia with cells secreting neuron specific enolase (NSE), chromogranin A (ChrA), calcitonin (CT), and calcitonin gene related peptide (CGRP). Moreover, nodular C-cell hyperplasia/C-cell microadenoma was found in five animals (45%) along with diffuse hyperplasia of C-cells. In these cells, secretion was, however, altered and restricted to secretion of only CGRP, indicating a disturbed function of these cells. Effects on systemic toxicity are not reported.

Yamanobe, Y. et al. (2015) examined on thyroid effects in mice after $CdCl_2$ exposure. Two mice per sex and group were exposed for 11 weeks to 0 and 32 mg $CdCl_2$/L via drinking water. Rats exposed to $CdCl_2$ showed an accumulation of Cd in the thyroids, which was statistically significantly higher in females as compared to males. The histopathological examination revealed no obvious effects on follicular epithelial cells. No further effect on the thyroid is reported. Systemic toxicity was not evident.

2.1.2.9 Brain/behaviour effects

Medium-quality references:

No medium-quality references containing relevant information on brain or behaviour effects were obtained.

Low-quality references:

Cobbina, S.J. et al. (2015) examined the effects of $CdCl_2$ low dose exposure on several organs of mice. Five mice per sex were treated for 1-4 months with 0 and 0.005 mg $CdCl_2$/L via drinking water. The brains of Cd-exposed were largely unaffected by Cd treatment as indicated by absence of effects on absolute and relative organ weight, histopathology, and most of the oxidative stress markers tested (MDA level, SOD activity, and NOS activity). The only parameters affected were statistically significantly but only transiently reduced brain CAT level, transiently reduced brain BUN level, as well as reduction of creatinine levels after 30 and 120 days. Further, no effect on spatial learning and memory was evident in the Morris water maze test. The Cd-exposed mice showed no clinical signs, effect on body weight, and haematological parameters. Food consumption was reduced at day 120 but only in males.

Kouadria, M. et al. (2019) analysed effects of Cd exposure on biochemical markers and behaviour of rats. The rats (n=5 per dose group) were exposed for 45 days to 0 and 15 mg $CdCl_2$/kg/L via drinking water. Rats exposed to Cd showed locomotor activity as indicated by the open field test. Moreover, in the elevated plus maze test, the amount of time spent in the closed arms and the number of entries in closed arms was statistically significantly increased, which is indicative of increased anxiety. Moreover, Cd-exposure resulted in statistically significantly decreased body weights. No further information on systemic effects is provided.

Pulido, G. et al. (2019) investigated effects of Cd exposure on brain structure and function. Fifteen male rats were exposed to 0 and 32.5 ppm $CdCl_2$ for 2, 3, or 4 months via drinking water. Rats exposed to $CdCl_2$ showed an altered brain structure as indicated by neuronal hypertrophy and apoptosis (CA1 and C3 neurons and granule cells of the dendrite gyrus). Moreover, in the novel object recognition test, rats treated with $CdCl_2$ showed a statistically significantly decreased short- and long-term recognition memory. The open field test showed no effect on the locomotor activity of Cd-exposed rats. Information on systemic toxicity is not provided.

2.1.2.10 Ear/hearing effects

Medium-quality references:

No medium-quality references containing relevant information on the ear or hearing effects were obtained.

Low-quality references:

Carlson, K. et al. (2018) primarily investigated on ototoxicity induced by Cd exposition but included examination of the liver. Six to sixteen mice per group were exposed to 0, 3, 11, and 27 mg $CdCl_2$/L for 12 weeks via drinking water. No ototoxicity was evident as evidenced by unaltered cochlear hair cell numbers and auditory function (‘Auditory Brainstem Response’ and ‘Distortion Product Otoacoustic Emissions’). No systemic toxicity was evident.

2.1.2.11 Pancreas and glucose/insulin homeostasis effects

Medium-quality references:

Jacquet, A. et al. (2018) examined sub-chronic effects of $CdCl_2$ on glucose homeostasis and different organs in rats. Nine rats per sex and group were exposed for three months to 0, 5, 50, and 500 µg $CdCl_2$/kg bw/day via drinking water. The relative pancreas weight of Cd-exposed rats was not statistically significantly altered. Rats exposed to $CdCl_2$ showed statistically significantly elevated plasma Cd levels in the two highest dose groups. Moreover, the plasma TBARS level was slightly but statistically significantly increased in males of the two highest dose groups. The plasma insulin concentration was statistically significantly increased in both fasted and stimulated females of the two highest dose groups. Further, females showed

a statistically significantly decreased insulin sensitivity as evidenced by the Quantitative Insulin Sensitivity Check Index. These effects suggest an impact on glucose metabolism which was restricted to females. In contrast, glucose level, fasting C peptide levels (suggesting impaired hepatic insulin extraction), and IpGTT (intra-peritoneal glucose tolerance test) were not affected. Further, no effect on GPx level, triglyceride level, total cholesterol level, HDL level, and FFA level was observed. Effects on mortality or body weights were not observed.

Low-quality references:

Nai, G.A. et al. (2015) investigated the effect of water pH on the induction of cancer induced by $CdCl_2$ exposure. Fifteen male rats per group were exposed for six months to water (at pH 5, 7, and 8) only and water containing $CdCl_2$ (at pH 5, 7, and 8) at a concentration of 400 mg/L both. The pancreas of $CdCl_2$-exposed rats showed no hyperplastic changes, precancerous lesions, and benign or malignant neoplasms. Except for two premature deaths due to acute pulmonary oedema, no information on systemic toxicity is provided.

Treviño, S. et al. (2015) examined on effects on the pancreas and insulin resistance in multiple peripheral tissues in Cd-exposed rats. Ten to twenty male rats per group were exposed to 0 and 32.5 ppm $CdCl_2$ via drinking water for 60, 90, and 120 days. The pancreas, of Cd-exposed rats, showed a time dependent Cd accumulation. Histopathological examination of the pancreas revealed no alteration in rats exposed to $CdCl_2$. However, the HOMA-β% index was statistically significantly decreased (indicating impaired β-cell functioning) and the index of insulin generation (IGI) was increased after Cd exposure. Moreover, the insulin level and the available insulin index were statistically significantly increased. Further, the insulin sensitivity was statistically significantly decreased in the liver and muscle. The insulin resistance was statistically significantly increased in the liver as well as in adipose and cardiovascular tissue. The Cd treatment had no obvious effect on body weight, body mass index, and fat tissue. However, the basal levels of circulating glucose and insulin were statistically significantly increased indicating that rats were hyperglycaemic and hyperinsulinemic. The peripheral insulin resistance was increased (HOMA-IR index) and insulin sensitivity was statistically significantly decreased (HOMA-S% index; QUICKI; Matsuda-DeFronzo index). Moreover, the serum lipid profile was statistically significantly altered (increased free fatty acids (FFA, total cholesterol, LDL, and VDL as well as decreased HDL).

The viability of Langerhans islets after Cd exposure was investigated by Treviño, S. et al. (2016). Rats were exposed to 32.5 ppm $CdCl_2$ for 2, 3, or 4 months via drinking water. According to the authors, Cd accumulation in Langerhans islets induced an oxidative environment, however, the enzymatic and non-enzymatic defence antioxidant systems are able of maintain the viability cell, at expense of hyperinsulinemic states which could cause β-cell exhaustion and diabetogenic development. No further information is provided.

2.1.2.12 Spleen/immune system effects

Medium-quality references:

No medium-quality references containing relevant information on the spleen or immune system effects were obtained.

Low-quality references:

Turley, A.E. et al. (2019) investigated on cytokine production by T-cells after sub-chronic Cd exposure. Six male rats per group were exposed to 0 (water pH=4) and 32 ppm $CdCl_2$ (in pH=4 water) for 10 weeks via drinking water. Rats exposed to $CdCl_2$ showed no statistically significant difference in the relative spleen weight. However, haematological examinations revealed a slightly but statistically significantly decreased

RBC count, leukocyte count, and total cell count. The immune cell composition was altered as indicated by a statistically significantly increased proportion of CD4+/CD25+ cells. Further, splenocytes from Cd-exposed rats showed a statistically significantly increased viability, increased mitochondrial membrane potential, and decreased ROS levels. A proinflammatory response was indicated by a statistically significantly increased IL-17a mRNA level, as well as increased IFN-γ and IL-10 levels (after T cell activation). No effects were observed for cytokine induction at early time points following T-cell activation (up to 24 h after activation). The Cd treatment resulted in a slightly but statistically significantly reduced body weights (last two weeks) and sporadically statistically significantly reduced water consumption. Food consumption, clinical signs, and abnormalities were not different between groups.

2.1.2.13 SCOEL 2017 opinion on oral repeated dose toxicity in animals

"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)."

2.1.3 Reproductive toxicity – oral

2.1.3.1 Reproductive organ/fertility/endocrine effects

Medium-quality references:

Nasiadek, M. et al. (2019) investigated the effects of sub-chronic Cd exposure on the reproductive system in female rats. Eight female rats per group received daily gavages of 0, 0.09, 0.9, 1.8, and 4.5 mg $CdCl_2$/kg bw for 90 days. Post-exposure analyses were performed 0, 90, and 180 days after treatment. Rats exposed to $CdCl_2$ showed statistically significant and dose dependent increases blood and uterine Cd levels. The uterine Cd levels decreased not markedly within the exposure periods. The relative and absolute uterus weight was not affected in Cd-exposed females. However, the uterus showed statistically significantly but transiently increased estradiol (E2; only in low dose) and progesterone (Prog) levels, whereas higher dose groups showed a statistically significant and persistent decrease in E2. Moreover, the P/E2 ratio was statistically and significantly increased at all doses, except for the lowest dose. Further, the length of the oestrus phases was disrupted in all dose groups but only transiently at high doses. The endometrial thickness was statistically significantly increased in the low dose group at the end of the dosing period, whereas high dose group showed a decrease at study termination, after 180 days. Ovary histopathology revealed degeneration of the corpus luteum and damaged and less numerous oocytes at the highest dose. Further the uterus of Cd-exposed rats showed statistically significantly and persistently increased MDA levels (1.8 and 4.5 mg/kg bw) and decreased CAT activity (4.5 mg/kg bw). Blood hormone levels (E2 and P/E2 ratio) of Cd-exposed rats were statistically significantly altered. However, these changes were apparently not dose related. Overall, the observed effects indicated interference of Cd with fertility of female rats. The Cd exposure did no impact behaviour, animal appearance, mortality, feed intake, water intake, and body weight.

Nasiadek, M. et al. (2018) examined the level of sex hormones, oestrus cyclicity, and endometrial morphology after sub-acute Cd exposure. Ten female rats per group were gavaged with $CdCl_2$ at doses of 0, 0.09, 1.8, and 4.5 mg/kg bw/day for 30 days. Post-exposure analyses were performed 0 and 90 days after treatment. The sub-acute oral treatment with $CdCl_2$ resulted in statistically significant and persistent increased of the blood, brain, and uterine Cd levels. The relative and absolute uterus weight as well as uterine hormone levels were not statistically significantly altered in Cd-exposed rats. However, a statistically significantly reduced plasma E2 level was observed on the post-exposure group, whereas a decreased progesterone level and P/E2 ratio was observed at all doses. The oestrus cyclicity disturbed indicated by statistically significantly and persistently prolonged dioestrus phase in the high-dose group and transiently

increased total cycle length. A statistically significantly increased endometrium thickness, as evidenced by morphometrical analysis, was observed in all dose groups and suggested to be due to endometrial oedema. However, histopathological analysis of the uterus showed no significant alterations. In contrast, ovaries of high-dose group rats were damaged, as indicated by areas of degeneration of corpora luteum and numerical reduction and damage of oocytes. Moreover, some moderate signs of degeneration of granulosa cells were noted in the high-dose group. Overall, the effects observed indicate effects on fertility after Cd exposure. Effects on body weight, water intake, food consumption, and plasma total cholesterol level were not observed.

The effects of sub-acute Cd exposure on the uterus of rats was investigated by Nasiadek, M. et al. (2014). Doses of 0, 0.09, 0.9, 1.8, and 4.5 mg $CdCl_2$/kg bw/day were administered for 28 days to eight female rats per group via gavage. The rats were analysed after 0 and 90 days post-exposure. Rats exposed to $CdCl_2$ showed an accumulation of Cd in the blood and uterus at concentrations greater than 0.009 mg/kg bw/day. The Cd level did not markedly decrease during the post-exposure period. Antioxidant activity and lipid peroxidation were altered in high-dose females as indicated by statistically significantly decreased CAT activities and increased MDA levels. The absolute and relative uterus weight was statistically significantly changed after Cd exposure. Moreover, no effects were observed for plasma TAS level, CAT activity in erythrocytes, water consumption, feed consumption, terminal body weights, as well as liver and kidney weights.

Ren, Y. et al. (2019) examined the effects of Cd exposure on testis structure and function. Six male mice received daily gavages of 0, 2, 4, and 8 mg $CdCl_2$/kg bw for eight weeks. The administration of $CdCl_2$ resulted in a dose dependent increase in testicular damage showing very thin germinal epithelium, seminiferous tubules with aberrant morphology, depressed spermatogenesis, lack of swirling contours, and abnormalities of the testicular stroma at the highest dose. Moreover, the apoptosis rate in testicular tissue was statistically significantly increased at all Cd doses, as evidenced by TUNEL staining. The serum androgen level was statistically significantly increased at lower but not at the higher dose levels. This pattern was also observed for testicular 17α-hydroxylase and luteinizing hormone receptor (LHR) expression showing no clear dose-response relationship. Protein expression of 17α-hydroxylase and LHR was statistically significantly increased in Leydig cells of all dose groups but showed no apparent dose related response. The expression of endothelial nitric oxide (NO) synthase (eNOS) was statistically significantly increased. No effect on body weight was observed after Cd exposure. No further detail on systemic toxicity.

Low-quality references:

Banzato, T.P. et al. (2012) investigated on the sperm quality of male rats exposed to Cd in utero and during lactation. Ten dams per group were exposed to natrium acetate (control) and CdAc at a dose of 10 mg/L via drinking water. The treatment started at GD0 and was terminated on PND21. Ten F1 males (1 individual per litter) pre group were examined on PND90. Cadmium-exposed males from the F1 generation showed a statistically significantly compromised sperm morphology and motility, whereas sperm count and production were not markedly affected. Moreover, the apoptosis rate was increased in the seminiferous tubules (mainly spermatids). However, histopathological examination as well as absolute and relative testis weights showed no alterations after Cd exposure. Further, no effects serum levels of testosterone, LH, and FSH were observed. The epididymis showed a slightly but statistically significantly increased in the relative organ weight. However, histopathological alterations were not observed. The prostate and vas deferens showed no statistically significant changes in the absolute and relative organ weights. The body weight gain of Cd-exposed rats was not affected. No further information on maternal or signs of general toxicity in F1 is not provided.

Dhir, V. and Gupta, S.K. (2011) investigated Cd-toxicity in rats after sub-chronic exposure. Female rats received $CdSO_4$ at doses of 0 and 50 mg/kg bw/day via gavage for 90 days and were afterwards mated with untreated males. Rats exposed to Cd showed in irregular oestrus cyclicity, a reduced fertility rate (ca. -50%) and a high foetal mortality rate. Moreover, the ovaries showed statistically significantly increased

AST, ALT, AP and acid phosphatase levels. Moreover, hepatic and renal cellular damage was indicated by increased biomarker levels. Systemic toxicity was not further evaluated.

Oxidative stress on rat ovaries after sub-acute Cd exposure was investigated by Tribowo, J.A. et al. (2014). Forty female rats per group (control + case group) received gavages of Cd (not further specified) for four weeks. The Cd exposed showed increased ovarian oxidative stress levels as indicated by statistically significantly increased SOD activity, peroxidase activity, CAT activity, hydrogen peroxide levels, and MDA levels. No effects on systemic toxicity were reported.

Adamkovicova, M. et al. (2014) examined effects on testis and epididymis after sub-chronic Cd exposure. Ten male rats were exposed to 0 and 30 mg $CdCl_2$/L for 90 days via drinking water. Rats exposed to $CdCl_2$ showed a statistically significantly increased absolute testis weight. Moreover, morphometric analysis showed a reduction in relative volume and surface area of seminiferous epithelium and tubule lumen as well as increase of relative volume and surface of intraepithelial spaces and blood vessels. Further, histopathology revealed moderate to severe testicular degeneration and distortion which was accompanied by lumen contraction. Blood vessels appeared dilated and more congested. The seminiferous epithelium showed desquamation of immature germ cells with vacuole formation (indicating an impairment in spermatogenesis). Many seminiferous tubules showed germ cell disorganization with necrotic cellular debris, and numerous tubular lumens contained a number of mature sperms. The epididymis showed a statistically significantly increased absolute weight. Morphometric analyses revealed a statistically significantly reduction of the relative volume and surface area of epididymal epithelium and blood vessels but in contrast increased tubule lumen, tubule surface, and tubule diameter. Reduction of the epithelium, necrotic epithelial cells, vasoconstriction, and interstitial oedema together with mononuclear cell infiltration was evidenced by histopathological examinations. Body weight and food consumption were not statistically significantly altered in Cd-exposed rats.

Mouro, V.G.S. et al. (2020) examined potential testicular toxicity after Cd exposure. Five male mice per group were exposed to 0 and 24 mg $CdCl_2$/kg via gavage for 7 and 42 days. The exposure to CdCl2 did not resulted in statistically significantly increased Cd levels in testis. Moreover, testis weight, Albuginea weight, parenchyma weight, gonadosomatic index, and parenchymosomatic index were not affected. However, the testis of $CdCl_2$ exposed mice showed a seminiferous epithelium degeneration and transiently increased germ cell death. Moreover, the Leydig cells showed a statistically significantly decreased SOD activity (7 and 42 days), MDA level (42 days), whereas activity of GST was increased (42 days). Further, several mineral levels were statistically significantly altered, i.e. increased Ca (7 days, transient), increased Cu (7 days, transient), whereas Fe (7 days, transient), Mg (42 days) and Zn (42 days) were decreased. Statistically significantly reduced body weights were evident only after seven days of Cd exposure.

Nai, G.A. et al. (2015) investigated the effect of water pH on the induction of cancer induced by $CdCl_2$ exposure. Fifteen male rats per group were exposed for six months to water (at pH 5, 7, and 8) only and water containing $CdCl_2$ (at pH 5, 7, and 8) at a concentration of 400 mg/L both. Rats exposed to $CdCl_2$ showed a statistically significantly increased incidence of grade one prostatic intraepithelial neoplasia (PIN I) (Cd groups: 3/14, 4/14, 3/14 vs. water control groups: 0/14, 0/13, 0/15), which is considered as pre-neoplastic lesion. Moreover, an adenocarcinoma was found in a single Cd-exposed individual (1/13). The testis and seminal vesicles as well as the kidney, liver, and pancreas showed no hyperplastic changes, precancerous lesions, and malignant or benign neoplasms. Except for two premature deaths due to acute pulmonary oedema, no information on systemic toxicity is provided.

Ohta, H. et al. (2019) investigated on metallothionein-like cadmium-binding protein (MTLCdBP) expression after Cd exposure. Five mare rats received daily gavages of 0 and 20 mg $CdCl_2$/kg bw for 5, 10, or 15 weeks. Rats exposed to $CdCl_2$ showed a time dependent Cd accumulation in the testis. Moreover, the testicular expression MTLCdBP was markedly increased in time dependent manner. Further, the testicular level of Cu was statistically significantly decreased but not altered in a time dependent manner. No statistically significant effects were observed for absolute and relative testis weight, Zn level, Fe level, GSH level, and GST activity. Further, no effects on p53, MT-I, MT-I, MT-III, iNOS, HO1 and COX2 expression

were observed. Overall, the authors suggested a protective role of MTLCdBP in testicular Cd toxicity. Systemic toxicity was not investigated.

Wang, H.-F. et al. (2017) examined on sperm function after Cd exposure. Five male mice per group were exposed to 0 and 3 mg $CdCl_2$ for five weeks. Exposure to CdCl2 resulted in a statistically significantly increased blood Cd concentration. The Cd-exposed rats showed an altered testicular histopathology accompanied by a statistically significantly decreased relative testis weight. Moreover, a statistically significantly decreased in sperm function parameters, i.e. motility, progressive motility, viability, and spontaneous acrosome reaction was reported. Further, CatSper (sperm specific Ca2+ current) was statistically significantly decreased. CatSper and Slo3 subunit mRNA and protein levels were reduced as well. Information on systemic toxicity is not provided.

2.1.3.2 Developmental effects

Medium-quality references:

No medium-quality references containing relevant information on developmental effects were obtained.

Low-quality references:

Banzato, T.P. et al. (2012) investigated on the sperm quality of male rats exposed to Cd in utero and during lactation. Ten dams per group were exposed to natrium acetate (control) and CdAc at a dose of 10 mg/L via drinking water. The treatment started at GD0 and was terminated on PND21. Ten F1 males (1 individual per litter) pre group were examined on PND90. Cadmium-exposed males from the F1 generation showed a statistically significantly compromised sperm morphology and motility, whereas sperm count and production were not markedly affected. Moreover, the apoptosis rate was increased in the seminiferous tubules (mainly spermatids). However, histopathological examination as well as absolute and relative testis weights showed no alterations after Cd exposure. Further, no effects serum levels of testosterone, LH, and FSH were observed. The epididymis showed a slightly but statistically significantly increased in the relative organ weight. However, histopathological alterations were not observed. The prostate and vas deferens showed no statistically significant changes in the absolute and relative organ weights. The body weight gain of Cd-exposed rats was not affected. No further information on maternal or signs of general toxicity in F1 is not provided.

Davis, J. et al. (2013) examined on the effects of maternal oral exposure to Cd during pregnancy on mammary cancer risk in female offspring. Rat dams were exposed to 0, 75, and 150 ppb (ca. 0, 2-5, and 5-10 µg/kg bw/week) $CdCl_2$ via feed. Each dam nursed a total of ten female pups. On PND 28 and 50, five offspring per group and cage were sacrificed and mammary glands and serum were examined. At PND 50, 25-26 rats per group were administered 10 mg of the mammary carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) by oral gavage. The monitoring of tumorigenesis started six and ended 20 weeks after DMBA administration. Females from the F1 generation showed a statistically significantly increased body weight gain, which however, was only transient and not observed in the high dose group. Body weight at birth was not statistically significantly impacted. The serum testosterone levels of Cd-exposed F1 females was statistically significantly increased in a dose related manner and persisted until PND50 in high-dose group animals. Serum E2 was statistically significantly decreased at 75 ppm $CdCl_2$ and increased at 150 ppm $CdCl_2$ at PND50. Thus, no dose related effect on E2 was apparent. Females treated at 75 ppm $CdCl_2$ showed a statistically significantly earlier vaginal opening. No such effect was observed at the high dose group. Furthermore, statistically significantly increased numbers of mammary terminal end buds were only transiently and only in the low dose group observed. Moreover, the mammary glands showed a statistically significantly increased apoptosis rate in the low dose group at PND28 and in the high dose group at PND50. The Cd-exposed F1 females showed no statistically significant difference in mammary duct length, mammary area of parenchyma, mammary gland cell proliferation (Ki67 level). The

mammary gland ER-α protein level was statistically significantly increased in the high dose group (PND50) and showed a dose related response. In contrast, the statistically significant decrease in mammary gland AR protein levels was observed at PND50 in both Cd dose groups but was apparently not dose related. Twenty weeks after DMBA exposure, low-dose group F1 females showed a statistically significantly increased number of hyperplastic alveolar nodules (HANs) in the 4th mammary glands. No effects on latency of the appearance of first tumour per animal, and tumour multiplicity were observed. Signs of general toxicity in F1 females and maternal toxicity were not investigated.

Dhir, V. and Gupta, S.K. (2011) investigated Cd-toxicity in rats after sub-chronic exposure. Parental female rats received $CdSO_4$ at doses of 0 and 50 mg/kg bw/day via gavage for 90 days and were afterwards mated with untreated males. Cadmium-exposed rats from the F1 offspring generation showed a poor growth rate, poor fur growth, and a late vaginal opening. Parental female rats exposed to Cd showed in irregular oestrus cyclicity, a reduced fertility rate (ca. -50%) and a high foetal mortality rate. Moreover, the ovaries showed statistically significantly increased AST, ALT, AP and acid phosphatase levels. Moreover, hepatic and renal cellular damage was indicated by increased biomarker levels. Maternal toxicity was not further evaluated.

Cognitive development of male offspring maternally exposed to Cd was examined by Feng, J. et al. (2019). Dams received gavages of 0, 1, and 5 mg $CdCl_2$/kg bw from GD0 until PND21. Four to ten male F1 per group were examined on PND21. The Cd level in the cerebral cortex was statistically significantly increased in F1 males of the high-dose group. The males of both Cd-dose groups showed statistically significantly impaired learning and cognitive development as evidenced by Morris water maze test. Moreover, the neurons of the hippocampus of Cd-exposed males showed a statistically significantly decreased length of the active zone and mean post synaptic density as well as an increased mean width of the synaptic cleft width. These effects indicate that filopodia growth is inhibited and that the synaptic plasticity is impaired in the Cd-exposed rats. Moreover, all components of the hippocampal CORO1A-RAC1-PAK1-GPM6A signalling pathway, mediating Cd neurotoxicity, are statistically significantly downregulated. Information on maternal toxicity and signs of general toxicity in F1 offspring is not provided.

2.1.3.3 SCOEL 2017 opinion on reproductive toxicity in animals

"While effects on reproductive organs and fertility have been noted in experimental studies at high doses of Cd compounds (oral LOAEL 1 mg/kg/d, effect on seminiferous tubules in rats, and inhalation NOAEL 0.1 mg/m³, increased length of oestrus cycle), further information is needed to better understand the possible effect of low doses of Cd 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/m3 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/m3, 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/m3 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/m3 level. Developmental toxicity was evidenced by lower fetal weights in the 0.5 and 2 mg/m3 groups and an increase in the incidence of reduced sternebral ossification in the 2 mg/m3 group. Reproductive toxicity was observed in the 1 mg/m3 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)."

2.2 Human data

2.2.1 Kidney

SCOEL concluded in its 2017 opinion that "*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. 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.*"

During the literature search 16 references have been identified addressing kidney effects in humans, which have not been by SCOEL. In a strict relevance screening 3 references were considered further and are summarised in Appendix 42.

Chaumont et al. (2011) investigated 599 workers (451 men, mean age 45.4 years) who were employed in four nickel-cadmium battery plants for 18.8 years on average (2 in France n1=251 n2=221, 1 in Sweden n=111, and USA n=16). The median CdU was for France 1: 3.40 µg/g creatinine (1.74-6.40), France 2: 1.24 µg/g creatinine (0.51-2.81), Sweden: 0.81 µg/g creatinine (0.31-1.92), USA: 0.98 µg/g creatinine (0.73-1.31). The total median over all plants was 1.82 µg/g creatinine (0.75-4.11).

After stratifying workers for covaries (Sex, Age, Smoking) in seven categories of increasing CdU (mg/g creatinine) using as referents subjects with CdU <1 µg/g the BMD5/BMDL5 of abnormal RBPU and b2-mU were estimated at 5.1/3.0 and 9.6/5.9. When excluding ever smokers from the analysis, The BMD5/BMDL5 values for abnormal RBPU and b2-mU were estimated at 12.6/6.6 and 12.2/5.5. The BMD5/BMDL5 values for abnormal RBPU and b2-mU in ever smokers were assessed at 6.3/4.9 and 4.3/3.5, respectively.

Authors estimate the BMDL5 values of CdU for LMW proteinuria induced by occupational exposure to cadmium between 5.5 and 6.6 µg/g creatinine.

Gao et al (2016) investigated 41 female former workers of a nickel–cadmium battery factory in a longitudinal study. Workers were recruited from the year 2004 to 2009. Spot urine samples were collected on three consecutive days at enrolment and in every follow-up year until 2014. The median of baseline Cd concentrations at enrolment was 6.19 µg/g creatinine. Urinary β2-m and RBP concentrations were both related to Cd concentrations over the years (βabsolute-β2-m = 9.16, P = 0.008 and βabsolute-RBP = 6.42, P < 0.001, respectively). Cd, β2-m and RBP concentrations in the follow-up years were all associated with their baseline concentrations (βabsolute-Cd = 0.61, P < 0.001; βabsolute-β2-m = 0.64, P < 0.001; and βabsolute-RBP = 0.60, P < 0.001, respectively), and showed a decreasing tendency with the number of elapsed years relative to their baseline concentrations. A 37% loss to follow-up increased the concern for selection bias and small sample size raises concern with regard to the statistical power of the study.

In a prospective cohort study, Thomas et al. (2014) assessed the association between dietary cadmium exposure and chronic kidney disease (CKD) incidence in two large population-based, prospective cohorts of men (Cohort of Swedish Men, n=40,378) and women (The Swedish Mammography Cohort, n=33,929) with no history of kidney disease. At baseline 1997, men (45–79 years) and women (48–83 years), completed a self-administered questionnaire on diet and lifestyle.

The mean dietary cadmium uptake was 19 µg/day (SD 3.7) for men and 13 µg/day (SD 3.1) in women. Dietary cadmium exposure was not associated with increased CKD incidence among men HR 0.97(95% confidence interval (CI): 0.77–1.21) or women HR 0.74 (95% CI: 0.53–1.04), comparing highest tertile with

lowest. A multivariable adjusted model with men and women categorised into quintiles of dietary cadmium exposure showed no significantly increased risk of CKD in relation to dietary cadmium exposure.

In nine additional cross-sectional studies, authors investigated the association between cadmium exposure and kidney effects (Boonprasert et al. (2018), Chung et al. (2014), Ferraro et al. (2010), Hwangbo et al. (2011), Kim et al. (2015), Satarug et al. (2018), Tangvarasittichai et al. (2015, b), Tsai et al. (2017)). The studies largely suffer from a low sample size number and show some reporting deficiencies. The quantitative data is insufficient for the purpose of effect level identification to be used in the derivation of an occupational exposure limit. The remaining 4 studies are not suitable for hazard assessment purposes, as the study design does not allow to conclude on whether effects are in causal relationship with cadmium exposure.

In a recent meta-analysis Byber et al. (2015) performed a systematic review of 81 eligible references (published between 1950 and 2013) on the association between occupational cadmium exposure and chronic kidney disease (CKD). These references comprised cohort, case–control and case-series with follow-up including individual and objective assessment of occupational or environmental exposure. CKD was defined as (clinically relevant) kidney damage or a reduced glomerular filtration rate below 60 mL/min/1.72 m^2 over 3 months. Authors highlight that the lack of information about methods, risk of bias and heterogeneity precluded conducting a meta-analysis. The review concluded that there was no evidence supporting a risk of progression to CKD in populations exposed to cadmium.

Most of the previously published risk assessments for human health effects of cadmium have used the adverse effects on kidneys as the critical effect, recognising that long-term, high-level cadmium exposures give rise to both glomerular and tubular effects on the kidneys. On the basis of the most recent studies conducted in Europe, SCOEL concluded that renal effects can be detected in the general population for urinary cadmium below 5 µg Cd/g creatinine and even from 2 µg Cd/g creatinine or below. These studies detected associations between urinary cadmium and markers of tubular effect.

Recent evidence questions the causality of the associations between urinary cadmium and biomarkers of kidney effects (urinary proteins) in populations with low levels of exposure. There are physiological mechanisms that could potentially result in an association between excretion of cadmium and LMM protein excretion, without cadmium toxicity being the cause. Nordberg et al. provides a comprehensive discussion:

After filtration through the glomeruli, LMM proteins, albumin (in small amounts), and cadmium-MT compete for reabsorption in the proximal tubules. LMM proteins and cadmium-MT seem to have similar affinity for tubular binding sites (Bernard et al. 2008, Haddam et al. 2011, Chaumont et al. 2011, Chaumont et al. 2012) and normal physiological changes in renal tubular reabsorption function can therefore cause a co-excretion of cadmium and LMM proteins. It should be noted that, compared to the LMM proteins used for screening cadmium nephrotoxicity, MT occurs in tubular fluid in much lower concentrations and its tubular reabsorption can be competitively inhibited by these LMM proteins, as well as by albumin. Variation in diuresis (urinary flow rate) is an example of such normal renal physiological variability and can result in altered tubular reabsorption of solutes and water (Jarup et al. 1983). Moreover, urine flow rate had a clear positive impact on the excretion of cadmium within individuals. Thus, it is possible that normal physiological variability in renal reabsorption of LMM proteins causes an increase in urinary cadmium by inhibiting tubular uptake of MT-bound cadmium; in other words, this is a possible case of reverse causality (Chaumont et al. 2012).

These recent findings suggest that at low environmental exposures, urinary cadmium would be more a reflection of the functional integrity of the nephron than of the cadmium exposure or of the cadmium body burden (Chaumont 2012). These reverse causality mechanisms might have important implications in the

risk assessment of cadmium for the general population, which currently largely relies on the use of urinary cadmium as exposure indicator (Chaumont et al 2012).

2.2.2 Other effects

Further studies were identified, suggesting other relevant health effects may be observed in relationship with cadmium exposure, which may however be associated with the already known effects. The quantitative data is insufficient for the purpose of effect level identification to be used in the derivation of an occupational exposure limit. Reference is given to the studies as follows:

Endocrine system: Ali et al. (2014) investigated the influence of blood and urine cadmium levels on sex hormones in 438 postmenopausal Swedish women. There was some evidence that cadmium interferes with the levels of testosterone and estradiol in postmenopausal women, however no firm conclusion can be drawn from this study due to lack of reporting detail.

Eye: Wu et al. (2014) investigated in a cross-sectional study the correlation between blood and urine cadmium levels and increased risk of age-related macular degeneration. No firm conclusion was drawn by the authors.

Liver: Baba et al. (2013) investigated the cadmium concentration in liver samples of itai-itai disease patients against those in control patients. A histopathological examination was also conducted. No firm conclusion was drawn by the authors. In a cross-sectional study by Hyder et al. (2013) the association between urinary cadmium and several liver injuries-associated mortalities, including cancer, was investigated. According to the authors, some correlation was seen between cadmium levels in urine and liver disease mortality but no correlation with cancer related mortality.

Metabolic syndrome: Noor et al. (2018) investigated in a cross-sectional study the association between urinary cadmium and metabolic syndrome. No association between metabolic syndrome and higher urine cadmium was observed, however authors were unable to draw a firm conclusion.

Muscle weakness: Two cross-sectional studies by Garcia-Esquinas et al. (2015, 2020) investigated reduced grip strength and frailty in association with cadmium exposure in NHANES III participants. Some association was observed for grip strength reduction but not for frailty. However, authors were unable to draw a firm conclusion.

Diabetes: In the SCOEL 2017 opinion, it was highlighted that "*Several studies have also suggested that diabetics may represent a population with an increased susceptibility to the renal effects of Cd (Buchet et al., 1990; Hellström et al., 2001; Hotz et al., 1999; Åkesson et al., 2005), but this hypothesis needs confirmation.*".
In addition to these studies, one cross-sectional study by Trouiller-Gerfaux et al. (2019) and two meta-analysis reports (Guo et al., 2019 and Wu et al. 2017) were identified in the literature search.
Trouiller-Gerfaux et al. included 2749 middle-aged adults from the French cross-sectional ELISABET survey. No firm conclusion was drawn by the authors.
Guo et al. performed a meta-analysis of 12 cross-sectional and 1 prospective cohort studies on cadmium-induced diabetes mellitus. Results showed a positive association between cadmium levels in the body and DM (OR = 1.27; 95% CI, 1.07–1.52). According to the authors, the study was limited by the heterogeneity across studies, most studies were cross-sectional where exposure and disease was measured simultaneously and that only 6 studies provided quantitative UCd values. In addition, the quality rating of the studies selected for metal analysis was not documented.
Wu et al. examined relationship between urinary/blood cadmium exposure and diabetes mellitus risk in 2 cohort studies (Sweden), 9 cross-sectional (Australia, Thailand, Korea, China, USA, Sweden) studies,

number of cases ranged from 28 to 1,346. Analysis of high U-Cd exposure in 7 studies was not correlated with an increased risk of diabetes mellitus (OR = 1.19; 95% CI = 0.83–1.71), the analysis of high B-Cd exposure in 5 studies was not associated with increased risk of diabetes mellitus (OR = 1.16; 95% CI = 0.84-1.62) in the general population.

Vascular system: In the SCOEL 2017 opinion, it was already highlighted that "*some studies reported an association between environmental exposure to Cd and increased risks of cardio-vascular diseases (Everett and Frithsen 2008; Schutte et al. 2008; Tellez-Plaza et al. 2008), other studies did not detect such an increased risk (Staessen et al. 1991). Studies on the cardiovascular effects of occupational exposure were not located.*"
Two case-control studies were performed in the Malmö Diet and Cancer (MDC) cohort, investigating risk of aortic aneurism (Fagerberg et al. 2017) and subarachnoid haemorrhage (Sonderholm et al. 2020). Both studies suffered from a very low number of cases and in additional one study also from a low response rate of the participants. Consequently, authors could not draw a firm conclusion.
Two cross-sectional studies (Lee et al. 2011 and Lukkhananan et al. 2015) also showed a small sample size and due to the study design is not suitable for assessing the possible causal nature of the observed relationship between cadmium and vascular effects.

Neurotoxicity – Alzheimer's disease: Peng et al. (2017) investigated the association between Alzheimer's disease mortality and urinary cadmium for both the NHANES 1999-2006 cycles and NHANES III interviews in 1988-1994. No firm conclusion was drawn by the authors, as sensitivity of the analysis was questioned by the authors.

A number of references have been identified, reporting an association between cadmium exposure (primarily via food) and non-proliferating diseases, such as endocrine effects, liver diseases, muscle weakness, diabetes, effect on the cardio-vascular system or neurologic effects. However, it is not possible to state whether the effects have a true quantifiable causal relationship with cadmium exposure. Thus, dose-response relationships cannot be established.

3 Carcinogenicity

3.1 Animal data

3.1.1 Data obtained by the literature search

None of the reviewed reference contained information which provide relevant data on the carcinogenicity of Cd in animals.

3.1.2 SCOEL 2017 opinion on carcinogenicity in animals

"Experimental studies have indicated that several cadmium compounds (CdCl2, CdSO4, 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 CdCl2 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 Cd concentrations in the rat, it should be considered that tumours were induced under an unusual exposure regimen (23 h/day, 7 days per week)."

3.2 Human data

Data are summarized in Appendix 4

3.2.1 Lung

No references investigating the causal relationship between inhalation exposure of cadmium substance and lung cancer incidences were identified.

3.2.2 Prostate

In the SCOEL opinion (2017) it is highlighted that the concern for cadmium associated prostate cancer risk was raised early "*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 Cd metal (Lemen et al., 1976) reported an association between Cd 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*."

Chen et al. (2016) conducted a meta-analysis of the association between cadmium exposure and the risk of prostate cancer in 9 case control studies (3 in the general population with 334 cases/670 controls; 6 in occupational populations, with 1,315 cases/4,477 controls) and 12 cohort studies (5 in general population with 78,263 participants/4731 events in 12.1 follow-up years; 7 in occupational population with 13,434 participants/83 events and 43.0 follow-up years).

The weighted relative risk among cohort studies in general population showed no association between cadmium exposure and prostate cancer incidence (RR = 1.05; 95%CI [0.91, 1.22]) or mortality (RR = 0.83; 95%CI [0.35, 1.98]. The weighted SMR among occupational cohort studies did not indicate any significant

association (SMR = 98; 95%CI [75, 126] case-control in general population, weighted OR = 1.27; 95%CI (0.58, 2.78); occupational case-control studies, weighted OR = 1.17; 95%CI (0.85, 1.62). Based on the findings of the meta-analysis, there is no evidence supporting an association between cadmium exposure and the risk of prostate cancer in general or occupational populations.

Julin et al. (2012) conducted a prospective study in cohort of Swedish men (1997-1998, n=41,089), aged 45–79 years. The dietary cadmium intake was assessed by food frequency questionnaire. During the follow-up of 10 years, 3,085 incident cases of prostate cancer were identified, The mean energy-adjusted cadmium exposure was estimated as 19 µg Cd/day, SD= 3.7 µg Cd/day. Authors conclude that dietary cadmium exposure was associated with significant RR = 1.13 (95% CI: 1.03–1.24) of overall prostate cancer, after multivariable-adjustment. However, no firm conclusion could be drawn by the authors. This study was included in the meta-analysis by Chen et al. (2016).

Eriksen et al. (2015) conducted a prospective Diet, Cancer and Health cohort study in 26,778 men aged 50–65 years (recruited 1993-1997, identical with Eriksen 2014) with no previous cancer diagnosis. A total of 1,567 cases were diagnosed with prostate cancer during 13 years follow-up. The mean dietary intake was 16 µg Cd/day (5-95% percentiles = 9–25 µg). Authors did not observe an association between dietary cadmium intake and prostate cancer risk (adjusted incidence rate ratio per 10 µg/day= 0.98 (95% CI = 0.88-1.10)). Educational level, smoking status, BMI, zinc or iron intake did not modify the association. However, no firm conclusion could be drawn by the authors. This study was included in the meta-analysis by Chen et al. (2016).

Zhang et al. (2016) conducted a meta-analysis of 11 publications representing 14 separated studies in humans with prostate carcinoma. The criteria for the study selection were (i) exposed and control group needed to be present and (ii) cadmium levels in tissues were determined. The studies used in the meta-analysis were of variable age (published between 1976 and 2015) and had small sample sizes (case: 7-115, control: 3-227). The studies were insufficiently characterised, e.g. type of study not reported, thus robustness of the underlying data cannot be judged. Authors did not draw a firm conclusion and highlighted the need for studies with larger sample size.

3.2.3 Breast/Endometrium/Ovaries

Adams et al. (2014) conducted a prospective study comprising observational study and randomized clinical trial on the association between dietary cadmium intake and risk of breast, endometrial, and ovarian cancer. The study population was enrolled in the WHI study in 1993–1998, comprising 150,889 postmenopausal women aged 50–79 years. Dietary intake was assessed via food frequency questionnaire (FFQ). Urinary cadmium concentration was measured in a subset of the participants (n = 1050). Over an average of 10.5 years, 6,658 invasive breast cancers, 1,198 endometrial cancers, and 735 ovarian cancers were reported. Estimated dietary cadmium ranged from 0.02 to 59.4 µg/day (mean, 10.9 µg/day; median, 10.3 µg/day). Authors were unable to observe a statistically significant associations between dietary cadmium and risk of breast, endometrial, and ovarian cancer after adjustment for potential confounders including. This study was included in the meta-analysis by Van Maele-Fabry et al. (2016).

Adams et al. (2016) conducted a prospective case-control study in 12,701 postmenopausal women aged ≥ 50 years enrolled in a WHI study of bone mineral density. After a median of 13.2 years of follow-up (1993–2010), 508 cases of invasive breast cancer and 1,050 comparison women were identified for a case-cohort analysis. Urinary cadmium in the comparison cohort women: mean = 0.63 µg/g-Cr (SD=0.50), median, 0.51 µg/g-Cr (interquartile range, 0.33–0.77)). The U-Cd concentration in cases: mean = 0.58 µg/g-Cr (SD=

0.36), median, 0.50 µg/g-Cr (interquartile range, 0.32–0.71)). Authors did not observe an association of breast cancer risk with U-Cd parameterized in quartiles (comparing highest quartile with lowest quartile, hazard ratio (HR) = 0.80, 95% confidence interval (CI): 0.56, 1.14; P for trend = 0.20).

Eriksen et al. (2014) conducted prospective cohort study in the Danish Diet, Cancer and Health cohort with 23,815 postmenopausal women aged 50–65 years (recruited 1993-1997, identical with Eriksen 2015), who had no previous cancer diagnosis. From enrolment, 1390 breast, 192 endometrial and 146 ovarian cancer cases were diagnosed during the 13-17 years follow-up. The mean dietary intake was 14 µg Cd/day (5–95% percentiles =8–22 µg Cd/day), no difference in the cadmium uptake was seen between cases and cohort. Authors did not observe a significant association between dietary cadmium intake and cancer risk for any of the three hormone-related cancers; breast cancer incidence rate ratio (IRR) = 0.99, 95% CI: 0.87–1.13 per 10 mg higher dietary Cd intake/day; endometrial cancer, IRR = 1.08, 95% CI: 0.76–1.53; ovarian cancer, IRR = 1.15, 95% CI: 0.78–1.70. In general, authors did not observe a significant associations between dietary cadmium intake and cancer risk for any of the three investigated hormone-related cancers. This study was included in the meta-analysis by Van Maele-Fabry et al. (2016).

Grioni et al. (2019) conducted a prospective cohort study in 8,924 Italian women (start 1987- 1992) with a median follow-up of 22 years. Dietary cadmium intake was estimated by food frequency questionnaire, showing a mean dietary cadmium intake of 7.8 µg Cd/day (SD =1.4 µg Cd/day). Authors report a significant increased breast cancer risk with the fully adjusted model (HR = 1.54, 95% CI, 1.06–2.22) also showing an exposure-dependant trend (p = 0.028). Data on non-smokers were not shown (however, authors report risk remains significant).

The recent meta-analysis by Van Maele-Fabry et al. (2016) reviewed studies with (i) dietary cadmium exposure, (ii) breast cancer in postmenopausal women was included as outcome and (iii) the study followed a cohort or case-control design. A total of 6 studies were considered, 5 prospective cohort and 1 case control study. Dietary intakes were assessed in all studies by using a food frequency questionnaire (FFQ). Authors did not detect a statistically significant increased risk of breast cancer among postmenopausal women related to dietary Cd intake. However, a high heterogeneity and degree of inconsistency among the 6 relative risk estimates was seen. Subgroup analyses allowed identifying several sources of inconsistency between studies including geographical location, tumour ER, PGR and smoker status, HRT use, BMI, zinc and iron absorption. No firm conclusion was reached by the authors, highlighting the need to focus on improved accuracy of individual dietary Cd intakes and differentiation of breast cancers by pathologic features.

Wu et al. (2015) published a meta-analysis of a case-control (n=1) and cohort studies (n=5) on dietary cadmium exposure identifying a breast cancer incidence. A total of 11,978 cases in 32,1315 participants were analysed. No statistically significant positive association was seen between dietary cadmium exposure and breast cancer risk, the combined RR and corresponding 95% CI was 1.01 [0.88, 1.14]. No firm conclusion was reached by the authors, highlighting the need for further cohort studies based on diverse populations.

Gallagher et al. (2010) conducted a case-control study investigating the association between breast cancer with urinary cadmium in two groups (i) sample Long Island, NY (100 cases, 98 controls), (ii) sample of NHANES 1999-2008 (92 cases 2,884 controls). Women in the highest cadmium quartile showed a greater risk for breast cancer relative to those in the lowest cadmium quartile for both Long Island (OR=3.54; 95% CI=1.49, 8.42; p 0.004) and NHANES (OR=3.39; 95% CI=1.64, 7.05; p=0.001), however authors were

unable to draw a firm conclusion. The study suffered of small numbers of cases, especially among sub-groups, impairing statistical robustness, only smoking as non-dietary Cd exposure was taken into account, other confounders (such as occupational exposure) was not considered.

McElroy et al. (2017) conducted on case-control study with 631 incident cases of endometrial cancer (diagnosed from January 2010 to October 2012) and 879 age-matched population-based controls (ages 18-81 years, mean age 65 years). Urinary cadmium was determined in self-collected samples from the participants, suspected endometrial risk factors collected via telephone interview. Urinary cadmium values were 0.005 - 0.417 (mean 0.037) µg/g in cases, 0.006 to 0.649 (mean 0.041) µg/g in control subjects. Higher creatinine-adjusted cadmium exposure was associated with a statistically significant increase of endometrial cancer risk (OR: 1.22; 95% CI: 1.03-1.44). Authors were unable to draw a firm conclusion, highlighting that further studies that employ urinary cadmium as the biomarker are necessary given the weak association with estimated cadmium from dietary sources. The low participation proportion of women diagnosed with endometrial cancer and the self-reported data is subject to recall bias.

Nagata et al. (2013) published a case-control study on association between urinary cadmium level and the risk of breast cancer in 153 Japanese women newly diagnosed with breast cancer and 431 controls individually matched to cases by age and menopausal status. Spot urinary cadmium was collected. Women in the highest tertile of urinary cadmium (2.620 µg/g) had significantly elevated OR breast cancer relative to those in the lowest tertile (<1.674 µg/g) after controlling for covariates OR = 6.05, (95 % CI 2.90, 12.62). However, no firm conclusion was drawn as small numbers of cases, especially among sub-groups, impairing statistical robustness.

Larsson et al. (2015) report on a meta-analysis of case-control (n=5), prospective cohort (n=2) and cross-sectional (n=1) studies with cadmium exposure (determined in urine) identifying a breast cancer incidence. all case-control studies found a positive relation between urinary cadmium concentration and breast cancer, results from the 2 prospective cohort studies were inconsistent. Authors highlight the need for a large prospective cohort study in order to draw a firm conclusion.

Rahim et al. (2013) conducted a meta-analysis of epidemiological studies associating cadmium exposure with increased breast cancer risk. In total 13 studies were analysed with a total of 978 exposed cases and 1279 controls. No statistically significant difference in the frequencies of breast cancer between cadmium-exposed and control groups, mean difference 0.71 (95%CI: 0.33-1.08), some evidence was seen for differences in the frequencies of breast cancer between cadmium-exposed and control groups among Asian compared with Caucasian population. However, authors were unable to draw a firm conclusion.

El Morsi et al. (2017) conducted a case-control study in 100 female patients (age 37-74 years). Breast tissue samples were measured for cadmium content in 50 cases of adenoma as control and 50 breast cancer cases. The reference exhibits some reporting deficiencies which renders it unsuitable for a further assessment.

3.2.4 Gastro-intestinal tract

Kim et al. (2019) conducted a case–control study in the Korean population with 1,245 subjects (415 cases, 830 controls). Dietary cadmium intake was assessed by food frequency questionnaire. The average total daily intake was 22.0 ± 5.8 µg Cd/day for the cases and 20.8 ± 4.4 µg Cd/day for the controls. After adjustment for covariates gastric cancer risk was non-significantly increased in the highest tertile of

cadmium intake [OR 1.33, 95% CIs 0.94–1.88]. Authors highlighted a high prevalence of H. pylori positive participants, which may have modified the association between cadmium intake and gastric cancer risk. Consequently, no firm conclusion was drawn.

Lin et al. (2018) conducted a case-control study 279 Chinese patients, with 167 gastro-intestinal cancer cases (70 oesophageal cancer, 51 gastric cancer, 46 colorectal cancer), 112 control patients recruited from two hospitals, Median levels of blood cadmium was 2.12 µg/L in cases and 1.47 µg/L in controls. Authors concluded that cadmium appears to be a risk factor for gastrointestinal cancers. The study shows a number of limitation, such as subjects were not randomly selected, number of cases and controls was low, is was unclear whether controls were representative for the general population, confounders, such as lifestyle factors, occupational exposure, family history was not considered.

Rogala et al. (2019) was investigating the association between incidence of colorectal cancer and concentration of cadmium in particulate matter (PM10) in a cross-sectional study. According to the authors significant relationship between colorectal cancer morbidity and the average annual concentration of cadmium in particulate matter PM10 in the years 1989-2008. However, these is insufficient data reported for a full assessment.

3.2.5 Kidney

Song et al. (2015) investigated the correlation between cadmium exposure and kidney cancer in 8 epidemiological studies with occupational exposure and one study with environmental exposure by means of a meta-analysis. The high cadmium exposure category showed significantly increases renal cancer risk OR = 1.47; 95% CI = 1.27-1.71. The association between cadmium exposure and renal cancer risk was not altered by geographic region and gender; mixed results were observed when stratified by sample size, study design, NOS score, adjustment for covariates, effect size, and exposure type. Authors concluded that high exposure towards cadmium in an occupational setting is associated with an increased risk of kidney cancer, however highlighted the need for further studies.

3.2.6 Liver

Hyder et al. (2013) evaluated the association of urinary cadmium with liver disease and liver-related mortality in a cross-sectional study. Individuals participating in the NHANSE III survey (1988-1994) were selected, mean age 42.2 years. The highest quartile of urinary cadmium was 0.65 µg Cd/g-Cr in men and 0.83 µg Cd/g-Cr in women. Individuals in the top quartile of urinary cadmium had no increased risk of liver cancer related mortality (HR=1.25, 95 % CI 0.37–4.27; P=0.52). However, an association between high urinary cadmium levels and enzyme markers of liver disease was observed. Authors were unable to draw a firm conclusion highlighting the need for further studies. The study was limited by the small numbers of cancer cases, especially among sub-groups, impairing statistical robustness

3.2.7 Pancreas

Djordjevic et al. (2019) included 31 patients with a histologically based diagnosis of exocrine pancreatic cancer and 29 accidental fatalities or subjects who died of a non-malignant illness as controls in a case-control study. The study merely analyses correlation between cadmium content of pancreas tissue of a low number of cancer patients and non-pancreas cancer patients. No further information was provided on the pancreatic cancer cases, consequently confounders were not considered in the analysis. The study design is not suitable for assessing the possible causal nature of the relationship between cadmium content and pancreatic cancer

3.2.8 Thyroid

Zhang et al. (2019) report on a case-control study, investigating the associations of urine Cd, CLOCK gene polymorphisms and thyroid cancer risk. Spot samples of urinary cadmium was collected from 218 thyroid cancer cases and 218 controls. The mean urinary cadmium was 0.22 µg/g (females: 0.29 µg/g, males: 0.12 µg/g). The frequency of family history of cancer was higher in cases compared with controls. There was an association between high urinary cadmium and thyroid cancer risk, OR = 1.72, 95%CI 1.04–2.85). No firm conclusion was drawn by the authors. The study was limited by the low number of cases/controls, especially in sub-groups; confounders, omission to consider lifestyle factors, occupational exposure as confounder.

Stojsavljevic et al. (2019) investigated in a comparative analysis 66 cases with papillary thyroid carcinoma (mean age: 54 ± 14 years) the Cd content in healthy an malignant tissue (further metals were analysed, such as Co, As, Ni, Pb, Th, U), Cd, U and Se were significantly higher in content of malignant thyroid tissue compared with healthy thyroid tissue. The study merely analyses correlation between cadmium content of malignant and healthy thyroid tissue in the same cancer patients. No control group was included. No further information was provided on the thyroid cancer cases, consequently confounders were not considered in the analysis. The study design is not suitable for assessing the possible causal nature of the relationship between cadmium content and thyroid cancer

3.2.9 Conclusions

In summary, the literature search did not identify any new data related to the carcinogenicity of cadmium in humans after inhalation. It cannot be excluded that some references were not identified during the literature search. Thus, the evidence for lung cancer in humans discussed in the most recent risk assessment documents (AGS, 2019 and Nordberg et al., 2018) is presented below in relation with the SCOEL, 2017 opinion.

The SCOEL concluded in the 2017 opinion that *"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. However, insufficient epidemiological evidence exists in humans to perform a working-life risk assessment for the cancer risk for exposure to Cd alone. When an increased risk was observed in Cd exposed populations, co-exposures to e.g. arsenic did appear to play a central role."*

In the mode of action consideration, SCOEL assumed that *"the mechanism of the carcinogenic activity of cadmium, at least in part, involves 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)*."*
This is line with the recent review on the mechanisms of action for the genotoxic activity of cadmium and cadmium compounds (see paper submitted in this call for evidence), which concludes on available lines of evidence that cadmium compounds should be considered as indirectly genotoxic with a mechanism of action-based threshold.

"There is also some epidemiological evidence that Cd does not seem to induce an excess of lung cancers at exposure levels sufficient to cause renal and respiratory toxicity (Sorahan and Esmen, 2004). On the basis of non-cancer respiratory effects (lung function impairment), a TWA of 4µg/m³ (alveolar fraction) has been derived."

Nordberg et al. confirms the position by SCOEL, on the presence of non-neoplastic respiratory effects, but considers the systemic effects in kidneys as the most critical effect. It is highlighted that respiratory effects

have been observed even after lower-level exposures to workroom air (approximately 20 µg/m³ of respirable cadmium 8 hours per day, 5 days per week, Elinder et al. 1986) , but these respiratory effects have previously not been considered to occur at low occupational exposures (below 20 µg/m³). However, such exposures can still cause dysfunction of the kidneys, justifying the recognition of this as the critical effect.

The recent evaluation by the German AGS concluded that a sub-linear exposure-risk relationship could be assumed with reference to the mode of action, amplifying the effect through inflammatory processes, which appear to play an important role in the respiratory tract.

The literature search revealed a number of references, reporting an association (or lack thereof) between cadmium exposure and cancer incidence in prostate, breast/endometrium/ovaries, gastro-intestinal tract, kidney, liver and thyroid. No clear conclusion can be drawn from the above discussed references, as positive results as well as negative were reported, or the study design did not allow a conclusion on the causal relationship between exposure and increase in cancer incidence.

SCOEL highlighted that cadmium exposure and tumours at other locations including kidney, breast, and prostate may be relevant as well, however none of these effects were discussed further. The AGS discussed in its previous documentation (AGS, 2014) references reporting an association between cadmium exposure and prostate, breast, endometrium, kidney and pancreas. After quantitative analysis of the data, no exposure-risk relationship could be established for any of the cancers.

Nordberg et al. was unable to assess the risk of cancer in numerical terms because of the lack of consistent relationships in epidemiological studies and the complex interactions with smoking and other competing or co-carcinogenic factors. For prostate cancer it was highlighted that positive as well as negative findings have been reported. Thus, the authors were unable to derive a dose-frequency relationship from the data available and to set this against the dose frequency deemed sufficiently low to be considered tolerable.

5. Conclusions

As outlined in chapter 0 above, the aim of the updating literature search and evaluation was to provide further evidence to the questions:

A. Is the kidney still the critical organ (systemic) after repeated exposure? And what is the effect level?

On the basis of the evidence collected in human and animal studies reviewed following the literature search and with reference to the most recent risk assessment reports (Nordberg et al. 2018, AGS 2019), it is concluded, that the kidney is the critical organ for systemic effects after repeated exposure.

Consequently, the conclusion as reported in SCOEL (2017) as well as in AGS (2019) and Nordberg et al. (2018) is maintained: "*there is evidence showing dose-effect and dose-response relationships between cadmium exposure and kidney effects in terms of LMM proteinuria. Long term cadmium exposures with urine cadmium of 2 µg/g creatinine cause such effects in a susceptible subsection of the population.*"

Therefore, the following conclusions of SCOEL 2017 should still be considered as protective:

"Biological markers such as Cd-U (cadmium excretion in urine) allow the assessment of body burden, and to integrate all sources of Cd 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 Cd, mainly renal and bone effects."

*"Therefore, a **BLV of 2 µg Cd/g creatinine** is proposed."*

B. Are other systemic endpoints (bone, ED) covered by this effect level?

A discussed above, several references have been identified, indicating an association between cadmium exposure and other (systemic) effects. However, no direct causal relationship was identified and no dose-response relationship could be established.

SCOEL identified the bone tissue as another target organ for populations exposed occupationally and/or environmentally to cadmium compounds. 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.

Nordberg et al. Also highlight the lack of quantitative information: "*When interpreting epidemiological findings on bone effects, additional information is required. This includes information about nutritional factors, as well as the toxicodynamics associated with tissue levels of cadmium that cause decalcification of bone. It is also important to have a better understanding of the toxicokinetics of cadmium in bone and the relationship between bone effects and biomarkers of exposure. Without this information, while it is possible to conclude these effects are adverse, it is not possible to be certain that there is a causal relationship between urine cadmium in the range 0.5–5 µg g−1 creatinine (0.5–5 nmol mmol−1 creatinine) and decreased BoneMD. Consequently, it is not possible to establish a satisfactory LOAEL/BMD for this effect.*".

The AGS also concluded that the current data base is insufficient to establish a dose descriptor for bone effects unassociated with nephrotoxicity. It was concluded that the LOAEL for kidney effects is also protective for bone effects.

Therefore, the following conclusions of SCOEL 2017 should still be considered as protective:

"Biological markers such as Cd-U (cadmium excretion in urine) allow the assessment of body burden, and to integrate all sources of Cd 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 Cd, mainly renal and bone effects."

*"Therefore, a **BLV of 2 µg Cd/g creatinine** is proposed."*

C. Is lung function impairment still the critical effect after inhalation exposure and what is the effect level? (Consequently can 4 µg/m³ respirable fraction still be retained as protective for this end point)?

Due to the lack of new animal or human data identified during the literature search, it is assumed that lung function impairment is still the critical effect after inhalation and no correction should be made to the SCOEL 2017 conclusion.

"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 Cd exposure."

D. Is an OEL-only based approach protective against renal effects?

SCOEL argues in the 2017 opinion that an isolated 8h TWA OEL of 4 µg/m³ (respirable fraction) does not appear equally protective against nephrotoxicity of cadmium. With reference to the evaluation of the German AGS (BAuA, 2014), it is hypothesised that nephrotoxic effects could arise in about 1% of the workforce after 40 years of airborne exposure to 4 µg Cd/m³. In the evaluation of the German AGS, it is made reference to the ATSDR (2012) for the extrapolation from a cortex cadmium concentration to an inhalation exposure of cadmium particles. The ATSDR itself uses the pharmacokinetic model developed by Kjellström and Nordberg (1978) and the ICRP Human Respiratory Tract Model (1994) to predict cadmium air concentrations. Such an extrapolation is built on a number of assumptions, which require verification in order to reliably predict safe exposure levels. The ATSDR concludes that "*Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (AMAD=1 µm) and oral intakes that yield the same urinary cadmium level, exposure to an airborne cadmium concentration of 0.1 µg/m³ and a dietary intake of 0.3 µg/kg/day would result in a urinary cadmium level of 0.5 µg/g creatinine*"
Based on this, the German AGS concludes that a urinary cadmium of 1.4 µg/g creatinine corresponds an inhalation exposure of 2.7-5.1 µg Cd/m³, which was "pragmatically" defined as 4 µg/m³. This value is associated with a relatively high degree of uncertainty, since:

- the methodology treats ingestion as a fixed value, whereas workplace conditions show that actual ingestion can vary widely across individuals, depending on their specific workplace and personal hygiene. Therefore, it seems the control measure should be based on an indicator controlling exposure from all possible modes of uptake.
- inhalation exposure was assumed to be towards an aerosol with an MMAD of 1µm which appears to be a simplified approximation of the workplace exposure conditions
- a point estimate for baseline non-occupational cadmium dietary intake of 0.3 µg/kg/d was assumed, which may constitute an underestimation of the true exposure
- absorption factors for oral and inhalation were not reported in the ATSDR or the German AGS paper
- the pharmacokinetic model uses a point estimate for the correlation of cortex cadmium concentration and urinary cadmium concentration (84 mg/kg corresponding to a mean 1,4 µg Cd/g), although lower and higher values are also within the confidence interval

This approach is based on the total cortex cadmium concentration as dose descriptor for kidney adversity. However, this approach does neither consider any pre-occupational cadmium exposure nor does it foresee any modification to the above described uncertainties. In order to safely protect workers against cadmium related kidney toxicity, urinary cadmium determination appears the best possible way forward, also knowing that its monitoring is already widely in use in the cadmium industry.

It is also highlighted that the authors of the Jarüp study (1988), which is key in developing the OEL proposal of 1 µg Cd/m³ (inhalable fraction), state (p228) that data "*(…) indeed suggests that the cumulative blood cadmium dose is a more sensitive predictor of renal damage than cadmium in air, particularly at low levels of air cadmium concentrations*", hence giving clear preference of the use of an exposure biomarker over an OEL for the prevention of systemic adverse effects.

The SCOEL 2017 health-based advisory value of 1µg cadmium/m³ (inhalable fraction) for cadmium and inorganic cadmium compounds has also been evaluated by the Health Council of the Netherlands.

The Dutch Expert Committee on Occupational Safety (DECOS) concludes that *"this value is scientifically insufficiently substantiated. The studies used by the SCOEL for derivation are poorly mutually comparable and have methodological limitations. For instance, damage to the kidneys is defined in different ways, in several studies it is not clear which fraction of cadmium in air was measured, and the number of individuals examined is very limited. The Committee emphasizes that the previous recommendation (a biological limit value in combination with an advisory value in air) takes into account that people can also be exposed non-occupationally to cadmium. This is important as cadmium accumulates in the body. The Committee recommends to maintain the previous recommendation of the Health Council of the Netherlands, which consists of a biological limit value in the urine of 2 µg cadmium/g creatinine combined with a health-based advisory value in air of 4 µg cadmium/m3 (respirable fraction)." (Health Council of the Netherlands, 2019).*

In the SCOEL opinion (2017) reference is made also to human epidemiological data for the carcinogenic risk assessment: *"Based on epidemiological data [Park et al. (2012) update of the Thun et al. (1985) cohort], Haney (2016) estimated an excess risk level of 1:100,000 for a lifetime air concentration of 0.02 µg Cd/m³ (continuous environmental exposure, corresponding to 1:1000 at 2 µg Cd/m³) for the general population in the State of Texas."* After some back calculations from the general exposure to occupational exposure, there seems to be some discrepancies when comparing animal data (German AGS) with human data in terms of lung cancer incidence.

Appendices: Tables and References

Appendix 1 Repeated dose toxicity – animal data

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
Impact of acute and chronic inhalation exposure to CdO nanoparticles on mice	Lebedova, J.; Blahova, L.; Vecera, Z.; Mikuska, P.; Docekal, B.; Buchtova, M.; Misek, I.; Dumkova, J.; Hampl, A.; Hilscherova, K.	Environmental Science and Pollution Research, (2016) Vol. 23, No. 23, pp. 24047-24060. CODEN: ESPLEC. ISSN: 0944-1344.	RDT inhalation (NANO) - Lung effects	Mice	Unknown number of female mice per group: 0, 12.7, and 31.7 µg CdO/m³ (0, 1.18, and 2.95x10^6 particles/cm³, respectively); 24 h/day, 7 days/week; for 1-13 weeks; via whole body inhalation	CdO (NANO)	Cd impacts lung and liver morphology and oxidative stress parameters: Lung: presence of NPs; aggregates in the cytoplasm of different types of cells underlying the alveoli and capillaries (TEM) Cd accumulation and distribution depended on the dose and duration sig. increased abs. organ weight (dependent on the dose and duration) histopathology (low dose): only minute pathological changes in bronchioli (12.7 µg/m³) histopathology (high dose): the lumen of bronchioli was filled by mucous secretion, desquamated epithelial cells, and inflammatory cells as well as increased number of macrophages inside the alveolar spaces and occasionally foamy lipid-laden macrophages (31.7 µg/m³). After 5 and 7 weeks of exposure (increased with time and concentration), the lungs of animals exhibited light hyperaemia, focal haemorrhage, and alveolar emphysema, small areas od atelectasis, focal acute catarrhal bronchiolitis, and alveolitis in some animals. Long-term exposure (11 and 13 weeks) increased the presence of necrotic debris in the pulmonary alveoli. The necrosis of alveolar macrophages, large necrosis of the alveolar parenchyma of lungs, and destroyed alveolar septae. Areas of alveolar emphysema were observed in most exposed animals, and focal haemorrhage occurred in several parts of the lungs. Enhancement of bronchus-associated lymphoid tissue in exposed mice and numerous foamy lipid laden macrophages in alveolar spaces sig. increased GSH in 9 and 11 weeks (12.7 µg/m³) and GSH/GSSG ratio after 1, 5, 7, 9, 11, and 13 weeks sig. increased lipid peroxidation after 5 and 13 weeks (31.7 µg/m³) Liver: presence of NPs (TEM)	Lung Liver Kidney Spleen Brain	Low / medium	only two dose groups; number of animals per group not specified; sacrifices at week 1-13 (high resolution); histopathology description lacks details; MMAD not determined

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
							Cd accumulation and distribution depended on the dose and duration histopathology: fatty vacuolation of periacinal hepatocytes and pleomorphic cell inflammation together with large areas of hepatocytic necrosis sig. increase GST activity after 13 weeks (31.7 µg/m³); sig. decreased GSH content after 1, 3, 11, and 13 weeks (31.7 µg/m³) sig. decrease GSSG after 1 (12.7 µg/m³) and 5 weeks (31.7 µg/m³) and an increase after 13 weeks (31.7 µg/m³) and GSH/GSSG ratio after 12 h and after 13 weeks (31.7 µg/m³) sig. increased TBARS after 1 (12.7 µg/m³), 2, 3, and 7 weeks (31.7 µg/m³) and after 5 weeks (12.7 and 31.7 µg/m³) Kidney: presence of NPs (TEM); Cd accumulation and distribution depended on the dose and duration no effect on abs. organ weight, histopathology Spleen: presence of NPs (TEM); Cd accumulation and distribution depended on the dose and duration no effect on abs. organ weight, histopathology Brain: presence of NPs (TEM); Cd accumulation and distribution depended on the dose and duration no effect on abs. organ weight, histopathology sig. decreased GST activity after 7 and 9 weeks (both doses), and sig. decreased GSSG level after 2 weeks (31.7 µg/m³) sig. increased lipid peroxidation after 1, 3, and 7 weeks (31.7 µg/m³)			
Effects of sub-chronic, low-dose cadmium	Liu, Qiling; Wang, Xiang	Annals of Translational Medicine, (1 Apr 2019)	RDT oral - kidney effects	Rats	10 male rats per group: 0, 1, 2.5, and 5.0 mg/kg; 60 days; daily; via gavage	$CdCl_2$	Cd exposure induced renal damage and antioxidant system imbalance: Kidney:	Kidney	medium	three dose groups; animal N; not all responses appear dose-related; several RDT parameters not examined

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
exposure on kidney damage and potential mechanisms.	Liu, Qiling; Zhang, Rongqiang; Shen, Xiangli; Wang, Peili; Sun, Na; Li, Xiangwen; Li, Xinhui Hai, Chunxu (correspondence) Hai, Chunxu (correspondence)	Vol. 7, No. 8. arn. 177. Refs: 37 ISSN: 2305-5839; E-ISSN: 2305-5847					sig. decreased 24-h urine vol. (2.5 + 5 mg/kg, dose related) serum BUN, SCr and β2-MG (already at 1 mg/kg) increased sig. (2.5+ 5 mg/kg, dose related) histopathology: renal injury, deteriorated in a dose related manner (the renal tubules had slightly swelling and the interstitium showed hyperaemia (1 mg/kg); glomerular and renal tubules displayed significantly swelling, the structure was damaged severely, the number of cells increased, the cells were arranged irregularly, the lumens were narrow, the epithelial cells were necrotic, the interstitium had hyperaemia and infiltration of inflammatory cells (2.5 mg/kg); glomeruli were swelling, the capillary network was cracked, renal tubules were extensively lesioned, the epithelial cells became necrotic, a large number of cells accumulated in the lumen and were positive for eosin, renal interstitial congestion was more serious, and more inflammatory cells infiltrated into the interstitium (5 mg/kg)) dose related mitochondrial swelling, deformation, vacuolar degeneration, and mitochondrial ridge abnormality sig. increased ROS levels in renal cortex and mitochondria (DHE stain; apparently not dose related) altered antioxidant enzyme expression (sig. and dose related decrease of SOD2 and CAT at 2.5 and 5 mg/kg; sig. increase of SOD1 expression) sig. increased apoptosis protein expression (Bax/Bcl-2M; sig. and dose related increase at al doses) Systemic: loss of appetite, rough fur and irritable mood (more evident with increasing dose) body weight decreased sig. (2.5 + 5 mg/kg) sig, decreased 24-h water intake (2.5 + 5 mg/kg) serum Cd concentration increased sig. but the Fe2+ concentration decreased markedly in a Cd-dose dependent manner			

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
							serum MDA level and SOD1 activity increased sig., but SOD2 (already at 1 mg/kg) and CAT activity decreased markedly and sig. (2.5 + 5 mg/kg)			
Metabolomic analysis of the toxic effect of chronic exposure of cadmium on rat urine	Chen Shuai; Zhang Meiyan; Bo Lu; Li Siqi; Hu Liyan; Zhao Xiujuan; Sun Changhao	Environmental science and pollution research international, (2018 Feb) Vol. 25, No. 4, pp. 3765-3774. Electronic Publication Date: 22 Nov 2017. Journal code: 9441769. E-ISSN: 1614-7499. L-ISSN: 0944-1344.	RDT oral – kidney effects	Rats	10 male rats per group: 0, 0.13, 0.8, and 4.9 mg/kg bw; 24 weeks; via drinking water	$CdCl_2$	Cd exposure induced kidney damage and affected energy and lipid metabolism: Kidney: serum creatinine, uric acid, and blood urea nitrogen sig. increased in high dose animals (apparently dose related) renal enzymatic antioxidant activities (SOD, CAT) and GSH levels sig. decreased, whereas malondialdehyde level sig. increased in high dose group (apparently dose related) the treatment groups exhibited sig. changes for some metabolites (PAH, GSA, GBA levels sig. increased in high dose group) Liver: affected lipid metabolism and liver injury is indicated by sig. increased urine metabolite levels (PAG and LysoPC) in the high dose group Nervous system: increased GBA and GSA levels in high dose group rat urine implied that the exposure to Cd can affect the nervous system Systemic: no change in body weight	Kidney	medium	several RDT parameters not examined (only body weight, urinary metabolites, kidney retention markers, and renal antioxidant markers determined); effects dose related; drinking water consumption determined; actual test material intake estimated; three dose groups; animal N not too low
Impact of chronic and low cadmium exposure of rats: sex specific disruption of glucose metabolism	Demeilliers, Christine (Reprint) Jacquet, Adeline; Arnaud, Josiane; Hininger-Favier, Isabelle; Couturier, Karine; Lenon, Marine; Lamarche, Frederic; Ounnas, Faycal; Fontaine, Eric; Moulis, Jean-	CHEMOSPHERE, (SEP 2018) Vol. 207, pp. 764-773. ISSN: 0045-6535.	RDT oral - glucose homeostasis	Rats	9 rats per sex and groups: 0, 5, 50, and 500 µg/kg bw/day; three months; via drinking water	$CdCl_2$	Glucose homeostasis is sensitive to chronic Cd exposure in a gender specific way: Plasma: Cd accumulation (50 and 500 µg/kg bw/day) sig. increased TBARS level (slightly, only in males, 50 and 500 µg/kg bw/day) sig. increased insulin concentration in fasted and stimulated state (only females, 50 and 500 µg/kg bw/day, apparently dose related)	Glucose homeostasis	medium	three dose groups; animal N; not all responses appear dose-related; several RDT parameters not examined

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
	Marc; Demeilliers, Christine (Reprint) Arnaud, Josiane; Hazane-Puch, Florence; Fontaine, Eric Moulis, Jean-Marc						sig. decreased Quantitative Insulin Sensitivity Check Index (only females, 50 and 500 µg/kg bw/day) no effect on GPx level, triglyceride level, <total cholesterol level, HDL level, FFA level, glucose level, fasting C peptide levels (suggesting impaired hepatic insulin extraction), IpGTT (intra-peritoneal glucose tolerance test) Kidney: in general, no kidney toxicity: Cd accumulation (50 and 500 µg/kg bw/day) no effect on rel. organ weight, Kim-1 excretion, Liver: in general, no hepatoxicity: Cd accumulation (50 and 500 µg/kg bw/day) no effect on rel. organ weight, ASAT activity, ALAT activity Pancreas: no effect on rel. organ weight Heart: no effect on rel. organ weight Gastrocnemius muscle: no effect on rel. organ weight no effect on mortality, body weight, sex specific Cd accumulation			
Hepatic oxidative stress and inflammatory responses with cadmium exposure in male mice	Liu, Ling; Tao, Runhua; Huang, Jie; He, Xingzhi; Qu, Lanya; Jin, Yuanxiang; Zhang, Songbin; Fu, Zhengwei	Environmental Toxicology and Pharmacology, (2015) Vol. 39, No. 1, pp. 229-236.	RDT oral - liver effects	Mice	7 male mice per group: 0, 3, 10, and 30 mg/L (about 0, 0.43, 1.29, and 4.3 mg/kg bw); for 7 and 21 days; via drinking water	$CdCl_2$	Cd induced inflammatory response and hepatic oxidative stress: Liver: sig. decreased rel. organ weights (30 mg/L, after 21-day exposure) large interstitial spaces between hepatocytes (histopathology; 10 and 30 mg/L, after 21-day exposure) and some binucleate cells (30 mg/L, after 21-day exposure)	Liver Immune response	medium	three dose groups; two different exposure durations; several RDT parameters not examined

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
		CODEN: ETOPFR. ISSN: 1382-6689.					sig. increased nucleoplasmic ratio (30 mg/L, after 21-day exposure) sig. increased MDA level (30 mg/L, after 21-day exposure), GSH level (3 mg/L, after 21-day exposure; 10 and 30 mg/L, after 7- and 21-day exposure); SOD activity (30 mg/L, after 21-day exposure), CAT activity (10 and 30 mg/L, after 21-day exposure), GPx activity (3, 10, and 30 mg/L, after 21-day exposure), and GST activity (10 and 30 mg/L, after 21-day exposure) sig. increased mRNA levels of SOD1 (30 mg/L, after 7- and 21-day exposure), SOD2 (10 mg/L, after 21-day exposure; 30 mg/L, after 7- and 21-day exposure), CAT (10 mg/L, after 7-day exposure; 30 mg/L, after 7- and 21-day exposure), GPx2 (30 mg/L, after 7- and 21-day exposure), Gsta1 (10 and 30 mg/L, after 21-day exposure), Gss (10 mg/L, after 7-day exposure; 30 mg/L, after 7- and 21-day exposure), Gr (3, 10, and 30 mg/L, after 7-day exposure; 10 mg/L, after 21-day exposure), Hol (30 mg/L, after 7- and 21-day exposure) sig. increased mRNA expression of TNFα (3 and 30 mg/L, after 21-day exposure), IL6 (10 mg/L, after 21-day exposure; 30 mg/L, after 7- and 21-day exposure), IL1α (30 mg/L, after 7-day exposure), INOS (30 mg/L, after 7- and 21-day exposure), INFγ (30 mg/L, after 7- and 21-day exposure) General: sig. increased serum TNFα level (10 mg/L, after 7-day exposure; 30 mg/L, after 21-day exposure), IL6 level (30 mg/L, after 7- and 21-day exposure), IL1β level (10 mg/L, after 7-day exposure; 30 mg/L, after 21-day exposure) no effect on body weight			
Bone mineral health is sensitively related to environmental cadmium exposure-experimental and human data	Buha, Aleksandra (Reprint) Buha, Aleksandra (Reprint); Matovic, Vesna; Bulat, Zorica; Antonijevic, Biljana	ENVIRONMENTAL RESEARCH, (SEP 2019) Vol. 176. ISSN: 0013-9351.	RDT oral - bone effects	Rats	7 male rats per group: 0, 0.3, 0.6, 1.25, 2.5, 5, and 10 mg/kg bw/day; daily; for 28 days; via gavage	$CdCl_2$	Cd exposure impacted bone mineral health Bone: sig. increased Cd burden in femur (all doses, dose dependent) sig. decreased Ca level, P level, Mg level (all doses, equally decreased in all groups; suggested to be already a plateau and dose dependent effects are suggested to occur at lower doses), Zn level (all doses, dose dependent), B level (all doses) and Mn level (all doses)whereas sig. increases were	Bone	medium	6 dose groups; low animal N; several RDT parameters not examined (focus on bone minerals + biomarkers)

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
	Jugdaohsingh, Ravin; Powell, Jonathan J. Kerns, Jemma G. Goodship, Allen; Hart, Alister						observed for Cu level (2.5 and 5 mg/kg bw), Si level (1.25 and 5 mg/kg bw/day) Kidney: sig. increased serum creatinine level (10 mg/kg bw/day), urea level (5 and 10 mg/kg bw/day), whereas a sig. decrease was observed in the serum albumin level (all doses, dose dependent) General: sig. decreased body weight gain (≥1.25 mg/kg bw/day) increased Cd blood level (dose dependent) sig. decreased Ca blood levels (≥1.25 mg/kg bw/day) no effect on clinical signs			
Effects of low, moderate and relatively high chronic exposure to cadmium on long bones susceptibility to fractures in male rats.	Brzoska, Malgorzata M. (correspondence); Kupraszewicz, Elzbieta Majewska, Katarzyna	Environmental Toxicology and Pharmacology, (May 2010) Vol. 29, No. 3, pp. 235-245. Refs: 49 ISSN: 1382-6689 CODEN: ETOPFR	RDT oral - bone effects	Rats	10 male rats per group: 0, 1, 5, and 50 mg/L (actual test material intake for dose groups: 0.049-0.223, 0.238-0.977, and 2.073-10.445 mg/kg bw); 12 months (since weaning up to skeletal maturity); via drinking water	$CdCl_2$	Chronic Cd exposure affected bone structure: Bone: increased risk of fractures of long bones at mid and high doses: 1 mg/L caused only very subtle changes in biomechanical properties at the femoral neck and distal femur 5 mg/L caused decrease in the distal femur BMD (by 5.5%) and enhanced vulnerability to fracture at the femoral neck, distal femur, and tibia diaphysis 50 mg/L caused BMD decreased (by 6.5–11%),biomechanical properties weakened at all regions of femur and tibia; decrease in the femur and tibia content of mineral components (by 11.5% and 10%, respectively) and the tibia content of organic components (by 7%) sig. weight reduction of femur and tibia (50 mg/L) sig. reduction in femur M-L width (50 mg/L) sig. Cd accumulation in femur and tibia (all doses, dose related)	Bone	medium	three dose groups; 10 animals per group; actual test material intake; no information on body weight and clinical signs; effects dose related; high top dose; several RDT parameters not examined (focussed on bone mineral density and mechanical stability)
Subchronic Exposure to Cadmium Causes	Nasiadek, Marzenna [Reprint Author]; Danilewicz,	Oxidative Medicine and Cellular Longevity,	Reproductive toxicity oral – fertility,	Rats	8 female rats per group: 0 (oil and distilled water control), 0.09, 0.9, 1.8, and 4.5 mg/kg bw; 0.03	Cd-category	Sub-chronic oral Cd exposure of female rats may result in impaired fertility processes: Uterus/ovary/fertility:	Fertility	medium	three dose groups; one positive and two negative control groups; several RDT parameters not examined (focus on

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
Persistent Changes in the Reproductive System in Female Wistar Rats	Marian; Klimczak, Michal; Stragierowicz, Joanna; Kilanowicz, Anna	(DEC 18 2019) Vol. 2019, pp. Article No.: 6490820. http://www.hindawi.com/journals/oximed/. ISSN: 1942-0900. E-ISSN: 1942-0994.	endocrine effects		mg/kg bw 17β-E2; daily; for 90 days (0, 90, and 180 days post-exposure period); via gavage		sig. increase in Cd level (dose dependent) which decreased not markedly within the exposure periods no effect on rel. and abs. organ weight sig. increase in uterine E2 (estradiol)(0.009 mg/kg bw, transient: only 0 days PE) and decrease in E2 (0.9, 1.8, and 4.5 mg/kg bw bimodal response speculated, persistent decrease) sig. increase in uterine P (progesterone) (0.009 mg/kg bw, transient: only 0 days PE) sig. increased uterine P/E2 ratio (0.9, 1.8, and 4.5 mg/kg bw, persistent) disruption of length of oestrus phases (0.09 and 0.9 mg/kg bw, persistent; 1.8 and 4.5 mg/kg bw, transient) sig. increase of endometrial thickness (only 0.09 mg/kg bw at day 90), whereas sig. decreases were observed at high doses at postexposure day 180 (1.8 and 4.5 mg/kg bw) degeneration of the corpus luteum and damaged and less numerous oocytes (ovary histopathology; 4.5 mg/kg bw) sig. increased uterine MDA level (1.8 and 4.5 mg/kg bw, persistent at the highest dose), whereas activity of CAT was sig. decreased (4.5 mg/kg bw) Blood: sig. increase in blood Cd level (dose dependent) which decreased time dependently within the exposure periods sig. decrease in E2 (estradiol) (0.9, 1.8, and 4.5 mg/kg bw, apparently not dose dependent, bimodal response speculated, transient: only 0 days PE) sig. increased P/E2 ratio (0.9, 1.8, and 4.5 mg/kg bw, apparently not dose dependent, bimodal response speculated, transient: only 0 days PE) no effect on P (progesterone) Liver: no effect on rel. and abs. organ weight Kidney:			histopathology + hormone level + organ weights + oestrus cyclicity + Cd burden)

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
							no effect on rel. and abs. organ weight General: no effect on behaviour, animal appearance, mortality, feed intake, water intake, body weight			
The effect of repeated cadmium oral exposure on the level of sex hormones, estrous cyclicity, and endometrium morphometry in female rats	Nasiadek Marzenna; Darago Adam; Stragierowicz Joanna; Kilanowicz Anna; Danilewicz Marian; Sitarek Krystyna; SwiAtkowska Ewa	Environmental science and pollution research international, (2018 Oct) Vol. 25, No. 28, pp. 28025-28038. Electronic Publication Date: 31 Jul 2018. Journal code: 9441769. E-ISSN: 1614-7499. L-ISSN: 0944-1344. Report No.: PMC-PMC6153670.	Reproductive toxicity - fertility, endocrine effects	Rats	10 female rats per group: 0 (pure and oil control), 0.09, 1.8, and 4.5 mg/kg bw as well as positive control (0.03 mg/kg bw 17β-estradiol); daily; for 30 days (0 and 90 days postexposure groups); via gavage	$CdCl_2$	Cd altered plasma hormone levels, irregular oestrus cyclicity, endometrial oedema, and damage of the ovaries: Fertility/uterus/ovaries: no effect on abs. and rel. uterus weight sig. reduced plasma estradiol level (4.5 mg/kg bw, post exposure group only), whereas a sig. decrease was observed in plasma progesterone (all doses; post exposure group only), and P/E2 ratio (4.5 mg/kg bw, persistent; 0.09 and 1.8 mg/kg bw, post exposure group only) no sig. effect on uterine hormone levels sig. disturbed oestrus cyclicity, incl. prolonged dioestrus phase (4.5 mg/kg bw, persistent) and total cycle length (transient) morphometric analysis during the estrous stage exhibited a sig. increased endometrium thickness (all doses, not dose related and transient) (suggested to be due to endometrial oedema) no marked effect on uterus histopathology, restricted to altered endometrial thickness ovary damage, incl. areas of degeneration of corpora luteum and the oocytes were damaged and less numerous, some moderate signs of degeneration of granulosa cells were present (4.5 mg/kg bw; histopathology) sig. increased uterine Cd level (1.8 and 4.5 mg/kg bw, persistent) Brain: no effect on abs. and rel. organ weight sig. increased Cd level (1.8 and 4.5 mg/kg bw, persistent) General:	Fertility / uterus / ovary	medium	three dose groups; one positive and two negative control groups; several RDT parameters not examined (focus on histopathology + hormone level + organ weights + oestrus cyclicity + Cd burden)

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
							sig. increased blood Cd level (1.8 and 4.5 mg/kg bw, persistent; 0.09 mg/kg bw, persistent) no effects on body weight, water intake, food consumption, plasma total cholesterol			
Involvement of oxidative stress in the mechanism of cadmium-induced toxicity on rat uterus	Nasiadek Marzenna; Skrzypinska-Gawrysiak Malgorzata; Darago Adam; Zwierzynska Ewa; Kilanowicz Anna	Environmental toxicology and pharmacology, (2014 Sep) Vol. 38, No. 2, pp. 364-73. Electronic Publication Date: 19 Jul 2014. Journal code: 9612020. E-ISSN: 1872-7077. L-ISSN: 1382-6689.	Reproductive toxicity oral - fertility	Rats	8 female rats per group: 0, 0.09, 0.9, 1.8, and 4.5 mg/kg bw; daily; for 28 days (0 and 90 days postexposure period); via gavage	$CdCl_2$	Cd bioaccumulation can induce oxidative stress in the uterus of rats: Fertility/uterus: Cd accumulates in a dose dependent manner in blood and uterus and did not markedly decrease in the regeneration group (0.9, 1.8, and 4.5 mg/kg bw, persistent) sig. decreased uterine CAT activity (1.8 and 4.5 mg/kg bw, persistent) and sig. increased uterine MDA levels (1.8 and 4.5 mg/kg bw, persistent) no effect on abs. and rel. uterus weight Blood: no effect on plasma TAS level and CAT activity in erythrocytes General: no effect on water consumption, feed consumption, final body weights, liver weight, kidney weight	Fertility	medium	four dose group; animal N; several RDT parameters not examined (focus on specific organ weight + biochemical markers + accumulation)
Mechanism of cadmium poisoning on testicular injury in mice	Ren, Yaping; Shao, Wenhua; Zuo, Lijun; Zhao, Wei; Qin, Haizhang; Hua, Yingjie; Lu, Dejie; Mi, Chao; Zeng, Sien; Zu, Liao	Oncology Letters, (2019) Vol. 18, No. 2, pp. 1035-1042. CODEN: OLNEB5. ISSN: 1792-1082.	Reproductive toxicity oral - fertility	Mice	6 male mice per group: 0, 2, 4, and 8 mg/kg bw; daily; for 8 weeks; via gavage	$CdCl_2$	Cd induced testicular injury and altered LHR, 17α-hydroxylase, and eNOS levels in testicular stromal cells (a non-monotonic dose response is postulated for hormone effects): Fertility/testis: sig. decreased serum androgen level (2 and 4 mg/kg bw, not sig. in the highest dose group, apparently not dose related) histopathology: decreased thickness of the testicular seminiferous tubule walls, and less apparent swirling contours of spermatogenic cells (2 mg/kg bw); thin germinal epithelium, sporadic bleeding in the testicular stroma, cells with aberrant swirling contours, and decreased spermatogenesis (4 mg/kg bw); very thin germinal epithelium, seminiferous tubules with aberrant morphology, markedly low level of normal spermatogenesis, no swirling	Fertility/testis	medium	three dose groups; low animal N; several RDT parameters not examined (focus on histopathology + hormone level + apoptosis); no recovery group

Title	Author	Source	Endpoint	Species	Study design (number of animals, dose groups, treatment duration and frequency, ...)	Test substance	Toxicological findings	Target organ	Quality (low, medium, high)	Rationale for quality rating
							contours, apparent abnormalities of the testicular stroma (stromal vacancy), and spots of bleeding (8 mg/kg bw) sig. increased expression level of testicular 17α-hydroxylase (2 mg/kg bw, not sig. in high dose groups, apparently not dose related) and luteinizing hormone receptor (LHR) (2 and 4 mg/kg bw, not sig. in high dose group, apparently not dose related); eNOS not sig. altered sig. increased apoptosis in testicular tissue (TUNEL staining; all doses, dose related) sig. increased protein expression (Western blot) level in Leydig cells of 17α-hydroxylase (all doses, apparently not dose related), LHR (all doses, apparently not dose related), and eNOS (4 and 8 mg/kg bw) General: no effect on body weight			

Appendix 2 Repeated dose toxicity – human data

Title	Author	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
A longitudinal study on urinary cadmium and renal tubular protein excretion of nickel-cadmium battery workers after cessation of cadmium exposure	Gao Yanhua; Zhang Yanfang; Yi Juan; Zhou Jinpeng; Huang Xianqing; Shi Xinshan; Xiao Shunhua; Lin Dafeng	International archives of occupational and environmental health, (2016 Oct) Vol. 89, No. 7, pp. 1137-45. Electronic Publication Date: 4 Jul 2016. Journal code: 7512134. E-ISSN: 1432-1246. L-ISSN: 0340-0131.	RDT - kidney effects	Forty-one female, non-smoking workers were recruited from the year 2004 to 2009 when being removed from a nickel–cadmium battery factory, and they were asked to provide morning urine samples on three consecutive days at enrolment and in every follow-up year until 2014. Urinary Cd and renal tubular function biomarkers including urinary β2-microglobulin (β2-m) and retinol-binding protein (RBP) concentrations were determined	Cd-category	The medians of baseline Cd, β2-m and RBP concentrations at enrolment were 6.19, 105.38 and 71.84 μg/g creatinine, respectively. Urinary β2-m and RBP concentrations were both related to Cd concentrations over the years (βabsolute-β2-m = 9.16, P = 0.008 and βabsolute-RBP = 6.42, P < 0.001, respectively). Cd, β2-m and RBP concentrations in the follow-up years were all associated with their baseline concentrations (βabsolute-Cd = 0.61, P < 0.001; βabsolute-β2-m = 0.64, P < 0.001; and βabsolute-RBP = 0.60, P < 0.001, respectively), and showed a decreasing tendency with the number of elapsed years relative to their baseline concentrations (βrelative-Cd = −0.20, P = 0.010; βrelative-β2-m = −17.19, P = 0.002; and βrelative-RBP = −10.66, P < 0.001, respectively).	Kidney	medium	longitudinal study 37 % of the participations were lost to follow-up inevitably leads to the concern for selection bias small sample size raises concern for the statistical power of the study
Dietary cadmium exposure and chronic kidney disease: A population-based prospective cohort study of men and women	Thomas, Laura D. K.; Elinder, Carl-Gustaf; Wolk, Alicja; Aakesson, Agneta	International Journal of Hygiene and Environmental Health, (2014) Vol. 217, No. 7, pp. 720-725. CODEN: IJEHFT. ISSN: 1438-4639.	RDT - kidney effects	assess the association between dietary cadmium expo-sure and chronic kidney disease (CKD) incidence in two large population-based, prospective cohorts of men (Cohort of Swedish Men, n=40378) and women (The Swedish Mammography Cohort, n=33929) with no history of kidney disease. At baseline 1997, men (45–79 years) and women (48–83 years), completed a self-administered questionnaire on diet and lifestyle.	Cd-category	Estimated dietary cadmium exposure was not associated with increased CKD incidence among men HR 0.97(95% confidence interval (CI): 0.77–1.21) or women HR 0.74 (95% CI: 0.53–1.04), comparing highest tertile with lowest. No positive association between CKD incidence and dietary cadmium exposure either before or after stratification for smoking status. Adjustment for dietary protein, and intake of vegetable and whole-grain did not change the results. A multivariable adjusted model with men and women categorised into quintiles of dietary cadmium exposure showed no significantly increased risk of CKD in relation to dietary cadmium exposure.	Kidney	medium	prospective cohort study dietary cadmium exposure estimates based on self-report narrow Cd exposure over all participants (no occupational exposure) - exposure concentration may be too low to show an effect
The threshold level of urinary cadmium associated with increased urinary excretion of retinol-binding protein and beta 2-microglobulin: a re-	Chaumont Agnes; De Winter Frederic; Dumont Xavier; Haufroid Vincent; Bernard Alfred	Occupational and environmental medicine, (2011 Apr) Vol. 68, No. 4, pp. 257-64. Electronic Publication Date: 8 Oct 2010. Journal code:	RDT - kidney effects	Study investigated 599 workers (451 men, mean age 45.4 years) who were employed in four nickel-cadmium battery plants for 18.8 years on average (2France, Sweden, USA).	Cd-category	The median CdU was for France 1: 3.40 μg/g creatinine (1.74-6.40), France 2: 1.24 μg/g creatinine (0.51-2.81), Sweden: 0.81 μg/g creatinine (0.31-1.92), USA: 0.98 μg/g creatinine (0.73-1.31). The total median over all plants was 1.82 μg/g creatinine (0.75-4.11). Threshold values of CdU were then estimated by calculating the benchmark dose (BMD5) and the benchmark dose lower CI limit (BMDL5) for a 5% excess in the background prevalence of abnormal RBPU and b2-mU. Dose effect/response relationships were then	Kidney	medium/high	retrospective cohort study some information on disease likely to affect renal function or to modify the renal response to Cd could not be retrieved (eg, hypertension, diabetes, urinary tract infection, etc) data on alcohol consumption, physical activity and possible exposure to other nephrotoxicants was not

Title	Author	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
assessment in a large cohort of nickel-cadmium battery workers		9422759. E-ISSN: 1470-7926. L-ISSN: 1351-0711. Report No.: PMC-PMC3060309.				assessed by stratifying workers in seven categories of increasing CdU (mg/g creatinine) using as referents subjects with CdU<1. When considering all workers, RBPU adjusted for covariates including pack-years increased significantly from CdU>6e10. benchmark dose (BMD5) and the benchmark dose lower limit (BMDL5) for a 5% excess in the background prevalence of abnormal RBPU and b2-mU were estimated at 5.1/3.0 and 9.6/5.9. When excluding ever smokers from the analysis, the odds for abnormal RBPU and b2-mU were significantly increased only among workers with CdU>10 (RBPU: OR 21.8, 95% CI 6.4 to 74.4; b2-mU: OR 15.1, 95% CI 3.6 to 63.1). The BMD5/BMDL5 values for abnormal RBPU and b2-mU in never smokers were estimated at 12.6/6.6 and 12.2/5.5. The BMD5/BMDL5 values for abnormal RBPU and b2-mU in ever smokers were assessed at 6.3/4.9 and 4.3/3.5, respectively.			collected despite that the total cohort was adequate (n=599), some groups used in the analysis were small (ex-smokers n=86)

Appendix 3 Carcinogenicity – animal data

No data available.

Appendix 4 Carcinogenicity – human data

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Dietary cadmium exposure and risk of breast, endometrial, and ovarian cancer in the women's health initiative	Adams, Scott V.; Quraishi, Sabah M.; Shafer, Martin M.; Passarelli, Michael N.; Freney, Emily P.; Chlebowski, Rowan T.; Luo, Juhua; Meliker, Jaymie R.; Mu, Lina; et al.	Environmental Health Perspectives, (2014) Vol. 122, No. 6, pp. 594-600, 7 pp.. CODEN: EVHPAZ. ISSN: 1552-9924.	Carcinogenicity	Prospective study comprising observational study and randomized clinical trial postmenopausal women aged 50–79 years from the WHI study in 1993–1998; 150,889 women included in the breast cancer analyses Assessment of dietary intake via food frequency questionnaire (FFQ), cadmium concentration was measured in a subset (n = 1050) of urine samples	Cd-category	Estimated dietary cadmium ranged from 0.02 to 59.4 µg/day (mean, 10.9 µg/day; median, 10.3 µg/day), Mean creatinine corrected urinary cadmium was 0.49 µg Cd/g creatinine no statistically significant associations between dietary cadmium and risk of any of these cancers after adjustment for potential confounders including total dietary energy intake	Breast, Endometrium, Ovaries	medium	cadmium intake was estimated following food frequency questionnaire, urinary Cd measured in a small sub-cohort prospective design of a large size of the cohort, loss of follow-up was minimised, only postmenopausal women considered occupational exposure towards Cd not assessed

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Urinary Cadmium and Risk of Invasive Breast Cancer in the Women's Health Initiative	Adams, Scott V.; Shafer, Martin M.; Bonner, Matthew R.; LaCroix, Andrea Z.; Manson, Joann E.; Meliker, Jaymie R.; Neuhouser, Marian L.; Newcomb, Polly A. [Reprint Author]	American Journal of Epidemiology, (MAY 1 2016) Vol. 183, No. 9, pp. 815-823. http://aje.oxfordjournals.org/. CODEN: AJEPAS. ISSN: 0002-9262. E-ISSN: 1476-6256.	Carcinogenicity - breast cancer	Prospective case-control study, observational study and randomized clinical trial 12,701 postmenopausal women aged ≥50 years in a WHI study of bone mineral density. After a median of 13.2 years of follow-up (1993–2010), 508 cases of invasive breast cancer and 1,050 comparison women were identified for a case-cohort analysis	Cd-category	U-Cd in control women (mean = 0.63 µg/g-Cr (SD 0.50), median 0.51 µg/g-Cr (interquartile range, 0.33–0.77) no association between urinary cadmium and breast cancer risk (comparing highest quartile with lowest quartile, hazard ratio (HR) = 0.80, 95% (CI): 0.56, 1.14; P for trend 0.20), no association between quartiles of U-Cd and increased risk of breast cancer in any subgroup of women examined	Breast	medium	adequate number of cases/controls, some sub-groups with low case numbers, only postmenopausal women considered unclear whether occupational exposure towards Cd was assessed

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Cadmium exposure and risk of prostate cancer: a meta-analysis of cohort and case-control studies among the general and occupational populations	Chen, Cheng; Xun, Pengcheng; Nishijo, Muneko; Carter, Sue; He, Ka	Scientific Reports, (2016) Vol. 6, pp. 25814. CODEN: SRCEC3. ISSN: 2045-2322.	Carcinogenicity - prostate cancer	meta-analysis of the association between cadmium exposure and the risk of prostate cancer in 9 case control studies (3 in general population with 334 cases/670 controls; 6 in occupational populations, with 1,315 cases/4,477 controls) and 12 cohort studies, 5 in general population with 78263 participants/4731 events and 12.1 follow-up years; 7 in occupational population with 13434 participants/83 events and 43.0 follow-up years.	Cd-category	weighted RR among cohort studies in general population showed no association between cadmium exposure and prostate cancer incidence (RR = 1.05; 95%CI [0.91, 1.22]) or mortality (RR = 0.83; 95%CI [0.35, 1.98]; weighted SMR among occupational cohort studies did not indicate any significant association (SMR = 98; 95%CI [75, 126] case-control in general population, weighted OR = 1.27; 95%CI (0.58, 2.78),; occupational case-control studies, weighted OR = 1.17; 95%CI (0.85, 1.62); meta-analysis did not provide evidence supporting an association between cadmium exposure and the risk of prostate cancer in general or occupational populations	Prostate	medium	pooled cohort of acceptable size heterogeneity though hospital and population based cohorts general population studies showed a similar exposure range

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Dietary cadmium intake and risk of breast, endometrial and ovarian cancer in Danish postmenopausal women: a prospective cohort study	Eriksen Kirsten T; Halkjaer Jytte; Sorensen Mette; Meliker Jaymie R; McElroy Jane A; Tjonneland Anne; Raaschou-Nielsen Ole;	PloS one, (2014) Vol. 9, No. 6, pp. e100815. Electronic Publication Date: 25 Jun 2014. Journal code: 101285081. E-ISSN: 1932-6203. L-ISSN: 1932-6203. Report No.: PMC-PMC4071014.	Carcinogenicity	prospective Diet, Cancer and Health cohort study 23,815 postmenopausal women (recruited 1993-1997, identical with Eriksen 2015), no previous cancer diagnosis, from enrolment 1390 breast cancer cases, 192 endometrial cancer cases and 146 ovarian cancer cases were diagnosed during 13-17 years follow-up, aged 50–65 years	Cd-category	Mean dietary intake 14 µg Cd/day (5–95% percentiles =8–22 µg Cd/day), no difference in Cd uptake between cases and cohort, no significant association between dietary cadmium intake and cancer risk for any of the three hormone-related cancers incidence rate ratio (IRR) = 0.99, 95% CI: 0.87–1.13 per 10 mg higher dietary Cd intake/day; endometrial cancer, IRR = 1.08, 95% CI: 0.76–1.53; ovarian cancer, IRR = 1.15, 95% CI: 0.78–1.70. Positive association between cadmium and endometrial cancer for women with BMI<25 (IRR = 1.50, 95% CI: 0.94–2.39), inverse association for women with BMI>=25 (IRR = 0.69, 95% CI: 0.42–1.12)	Breast, Endometrium, Ovaries	low/medium	cadmium intake was estimated following food frequency questionnaire adequate number of participants in a prospective study design confounders through co-exposure to other pollutants not considered only smoking as non-dietary Cd exposure was taken into account, unclear whether occupational exposure was considered

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Dietary cadmium intake and risk of prostate cancer: a Danish prospective cohort study	Eriksen Kirsten T; Halkjaer Jytte; Sorensen Mette; Tjonneland Anne; Raaschou-Nielsen Ole; Meliker Jaymie R; McElroy Jane A	BMC cancer, (2015 Mar 26) Vol. 15, pp. 177. Electronic Publication Date: 26 Mar 2015. Journal code: 100967800. E-ISSN: 1471-2407. L-ISSN: 1471-2407. Report No.: PMC-PMC4397739.	Carcinogenicity - prostate cancer	prospective Diet, Cancer and Health cohort study 26,778 men (recruited 1993-1997, identical with Eriksen 2014), no previous cancer diagnosis, from enrolment 1,567 cases were diagnosed with prostate cancer during 13 years follow-up, aged 50–65 years,	Cd-category	Mean dietary intake 16 µg Cd/day (5-95% percentiles = 9–25 µg) No association between dietary cadmium intake and prostate cancer risk (adjusted incidence rate ratio per 10 µg/day= 0.98 (95% CI = 0.88-1.10)). Educational level, smoking status, BMI, zinc or iron intake did not modify the association.	Prostate	low/medium	cadmium intake was estimated following food frequency questionnaire adequate number of participants in a prospective study design confounders through co-exposure to other pollutants not considered only smoking as non-dietary Cd exposure was taken into account, unclear whether occupational exposure was considered

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Dietary cadmium and risk of breast cancer subtypes defined by hormone receptor status: A prospective cohort study	Grioni, Sara; Agnoli, Claudia; Krogh, Vittorio; Pala, Valeria; Rinaldi, Sabina [Reprint Author]; Vinceti, Marco; Contiero, Paolo; Vescovi, Luciano; Malavolti, Marcella; Sieri, Sabina	International Journal of Cancer, (MAY 1 2019) Vol. 144, No. 9, pp. 2153-2160. http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1097-0215. CODEN: IJCNAW. ISSN: 0020-7136. E-ISSN: 1097-0215.	Carcinogenicity - breast cancer	prospectiove cohort study with 8924 women (start 1987- 1992, Italy) with median 22 years follow-up, dietary Cd intake estimated by food frequency questionnaire,	Cd-category	mean dietary cadmium intake 7.8 µg Cd/day (SD =1.4 µg Cd/day) fully adjusted model HR = 1.54, 95% CI, 1.06–2.22 with a exposure-dependant trend (p = 0.028). Data on non-smokers not shown (however, authors report risk remains significant)	Breast	low/medium	cadmium intake was estimated following food frequency questionnaire adequate number of participants in a prospective study design (smaller compared with other prospective cohort studies, such as Sawada 2012, Eriksen 2014) confounders through co-exposure to other pollutants not considered only smoking as non-dietary Cd exposure was taken into account, unclear whether occupational exposure was considered

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Dietary cadmium exposure and prostate cancer incidence: a population-based prospective cohort study	Julin, B. [Reprint Author]; Wolk, A.; Johansson, J-E; Andersson, S-O; Andren, O.; Akesson, A.	British Journal of Cancer, (AUG 21 2012) Vol. 107, No. 5, pp. 895-900. http://www.nature.com/bjc/index.html. CODEN: BJCAAI. ISSN: 0007-0920. E-ISSN: 1532-1827.	Carcinogenicity - prostate cancer	prospective study in cohort of Swdish men (1997-1998, n=41089), aged 45–79 years, dietary Cd intake assessed by food frequency questionnaire, during follow-up of 10 years 3085 incident cases of prostate cancer were identified	Cd-category	The mean energy-adjusted cadmium exposure 19 µg Cd/day, SD= 3.7 µg Cd/day, Dietary cadmium exposure associated with significant RR = 1.13 (95% CI: 1.03–1.24) of overall prostate cancer, after multivariable-adjustment	Prostate	low/medium	cadmium intake was estimated following food frequency questionnaire adequate number of participants in a prospective study design only smoking as non-dietary Cd exposure was taken into account, unclear whether occupational exposure was considered
Long-term dietary cadmium intake and cancer incidence	Sawada Norie; Iwasaki Motoki; Inoue Manami; Takachi Ribeka; Sasazuki Shizuka; Yamaji Taiki; Shimazu Taichi; Endo Yoko; Tsugane Shoichiro	Epidemiology (Cambridge, Mass.), (2012 May) Vol. 23, No. 3, pp. 368-76. Journal code: 9009644. E-ISSN: 1531-5487. L-ISSN: 1044-3983.	Carcinogenicity	population-based prospective study, 90,383 Japanese men and women (age 45–74) dietary cadmium intake was estimated based on questionnaire Cd intake was validated via 24-hr urine sample measurements in a subset of participants (31 men, 57 women)	Cd-category	Cadmium intake (µg/day): median Q1=18.4, Q2=24.3, Q3=29.3, Q4=37.5 no association of dietary Cd uptake and total cancer, HRs for the highest versus lowest quartile of 0.94 (95% CI = 0.82 to 1.08) for men and 0.96 (0.81 to 1.15) for women	total cancer	low/medium	cadmium intake was estimated following food frequency questionnaire adequate number of participants in a prospective study design non-dietary Cd exposure was not taken into account, such as smoking

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Relationship between cancer mortality and environmental cadmium exposure in the general Japanese population in cadmium non-polluted areas	Watanabe, Yuuka; Nogawa, Kazuhiro; Nishijo, Muneko; Sakurai, Masaru; Ishizaki, Masao; Morikawa, Yuko; Kido, Teruhiko; Nakagawa, Hideaki; Suwazono, Yasushi	International Journal of Hygiene and Environmental Health, (2020) Vol. 223, No. 1, pp. 65-70. CODEN: IJEHFT. ISSN: 1438-4639.	Carcinogenicity	19-year cohort study in 1107 men and 1697 women in Japan; Cd exposure via diet, no occupational exposure towards Cd; participants were followed up for 19 years	Cd-category	UCd women=2.4 µg/g creatinine, UCd men=1.8 µg/g creatinine, U–Cd (+1 µg/g cre) was significantly related to all malignant neoplasms (RR=1.06, 95%CI: 1.02–1.11) and pancreas (RR=1.13, 95%CI: 1.03–1.24) in women	total cancer	low/medium	UCd determined in spot samples only confounders through co-exposure to other pollutants not considered

Title	Author/	Source	Endpoint	Study design	Test substance	Toxicological findings	Target organ	Relevance for assessment	Comments
Association between dietary cadmium exposure and breast cancer risk: an updated meta-analysis of observational studies	Wu Xiujuan; Zhu Xiaofeng; Xie Mingjun	Medical science monitor : international medical journal of experimental and clinical research, (2015 Mar 15) Vol. 21, pp. 769-75. Electronic Publication Date: 15 Mar 2015. Journal code: 9609063. E-ISSN: 1643-3750. L-ISSN: 1234-1010. Report No.: PMC-PMC4371715.	Carcinogenicity - breast cancer	Meta-analysis of case-control (n=1) or cohort studies (n=5) studies with dietary Cd exposure identifying a breast cancer incidence. A total of 11978 cases in 321315 participants were analysed.	Cd-category	No statistically significant positive association between dietary Cd exposure and BC risk, the combined RR and corresponding 95% CI was 1.01 [0.88, 1.14]	Breast	low/medium	meta-analysis of cohort or case-control studies None of the 3 meta-analysis reports on Cd-associated breast cancer shows an overlap in studies sample size in the individual studies was adequate cadmium exposure estimated based on questionnaire not all studies took into account other risk factors inclusion criteria for study selection may constitute a selection bias exposure data was not transparently reported in the meta-analysis

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