

Cadmium tert-butyl benzoates: Human health tier II assessment



04 July 2014

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Benzoic acid, 4-(1,1-dimethylethyl)-, cadmium salt	4167-05-9
Benzoic acid, (1,1-dimethylethyl)-, cadmium salt	31215-94-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to

human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit: www.nicnas.gov.au

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ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are composed of cadmium *tert*-butylbenzoates. Only CAS No. 4167-05-9 refers to the cadmium salt of a specific conformation of *tert*-butylbenzoate. However, it is expected that this conformation would be a major (likely dominant) component in an isomeric mixture of these compounds (CAS No. 31215-94-8). Due to the high toxicity of both cadmium and *para*-*tert*-butylbenzoic acid (PTBBA; CAS No. 98-73-7), the isomeric mixture is expected to be well represented by the *para*- conformer.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

While no international use, import, manufacture information has been identified for the chemicals in this group, metal salts of 4-*tert*-butylbenzoate (CAS No. 98-73-7) are reported to have site-limited use as thermal stabilisers in the manufacturing process for plasticised polyvinyl chloride (PVC) (EU RAR, 2009).

In the absence of more specific information, it is assumed that the chemicals in this group have potential commercial and/or site limited use. Furthermore, these chemicals are not likely to be used in cosmetics as they are not listed in the International Cosmetic Ingredient Dictionary and Handbook. While domestic use cannot be ruled out, the absence of these chemicals from

the available international product ingredient databases [Household Products database (US) and Natural Health Products Ingredients database (Canada)] indicate that they are not likely to be widely available for domestic use.

Restrictions

Australian

No known restrictions have been identified for these chemicals or for PTBBA.

Cadmium and cadmium compounds are listed in the *Poisons Standard* (the Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP (SUSMP, 2013)) under the following Schedules:

Appendix I, The uniform paint standard

The following applies to paints containing cadmium or cadmium compounds at >0.1 % (the proportion of a substance for the purposes of this Schedule is calculated as a percentage of the element present in the non-volatile content of the paint).

'A person must not manufacture, sell, supply or use a paint containing >0.1 % of cadmium or cadmium compounds for application to:

- a roof or any surface to be used for the collection or storage of potable water; or
- furniture; or
- any fence, wall, post, gate or building (interior or exterior) other than a building which is used exclusively for industrial purposes or mining or any oil terminal; or
- any premises used for the manufacture, processing, preparation, packing or serving of products intended for human or animal consumption' (SUSMP, 2013).

Additionally, 'a person must not manufacture, sell, supply or use a paint for application to toys unless the paint complies with the specification for coating materials contained in Australian/New Zealand Standard AS/NZS ISO 8124.3:2012 entitled *Safety of toys Part 3: Migration of certain elements* (ISO 8124-03:2010, MOD)' (SUSMP, 2013).

'**Schedule 6** except when:

(a) included in Schedule 4; or

(b) in paints or tinters containing 0.1 per cent or less of cadmium calculated on the non-volatile content of the paint or tinter' (SUSMP, 2013).

Schedule 6 substances are considered to have 'moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label' (SUSMP, 2013).

Cadmium and its compounds are also listed as restricted hazardous chemicals in the Australian Work Health and Safety Regulations 2011 for 'use in abrasive blasting at a concentration of greater than 0.1 % as cadmium' (SafeWork Australia).

International

No known restrictions have been identified for these chemicals or for PTBBA.

Cadmium and cadmium compounds are listed on the following (Galleria Chemica):

- EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and

- Health Canada List of prohibited and restricted cosmetic ingredients (The "Hotlist").

Cadmium and its compounds are also restricted in the EU under Annex XVII of the European Chemicals Agency (ECHA) REACH Regulation. Cadmium compounds (as Cd) cannot be used in substances and preparations placed on the market for sale at the following concentrations in:

- plastic materials $\geq 0.01\%$ by weight of the plastic material;
- paints with a zinc content of $>10\%$ by weight of the paint $\geq 0.1\%$ by weight;
- metal plating; and
- brazing (soldering/welding) fillers $\geq 0.01\%$ by weight.

Existing Worker Health and Safety Controls

Hazard Classification

Cadmium compounds not individually listed on the HSIS are, by default, covered by a generic 'cadmium compounds' classification (Safe Work Australia) as hazardous with the following risk phrase for human health.

Xn; R20/21/22: Harmful by inhalation, in contact with skin and if swallowed.

Exposure Standards

Australian

Cadmium and cadmium compounds have an exposure standard of 0.01 mg/m^3 time weighted average (TWA) (Safe Work Australia).

No specific exposure standards are available for PTBBA.

International

For cadmium and cadmium compounds the following exposure limits were identified (Galleria Chemica).

An exposure limit (TWA) of $0.01\text{--}0.2 \text{ mg/m}^3$ in various countries such as Canada, USA, Latvia and Switzerland.

The following exposure standards are identified for PTBBA (Galleria Chemica):

An occupational exposure limit (OEL) of 2 mg/m^3 (inhalable dust) in different countries such as Netherlands, Germany and Switzerland.

The short term exposure levels (STEL) of 4 mg/m^3 (inhalable dust) in Germany and Switzerland.

Health Hazard Information

The majority of the concerns regarding human health is expected to be mostly driven by the cadmium component of the chemicals in this group. The adverse health effects of 4-*tert*-butylbenzoate, which have been assessed by NICNAS as *p-tert*-butylbenzoic acid (PTTBA) (CAS No. 98-73-7), are also taken into account in this assessment and presented as read across in the relevant sections of this report (NICNASb).

The solubility of these cadmium compounds in this group in aqueous or acidic solutions is not known. Thus, a 'worst-case' scenario is considered where the chemicals dissociate into cadmium ions and their respective anion, *tert*-butyl benzoate, under physiological conditions.

While there are no data available on these specific chemicals, data sources for determining the hazard of the cadmium cation include animal studies on other well-characterised cadmium compounds, particularly soluble cadmium salts (cadmium chloride and cadmium sulfate) and a large amount of literature on observations of cadmium exposure in humans. The toxicity data from cadmium chloride and cadmium sulfate exposure (NICNASa) are considered relevant to the cadmium compounds in this group, as the bioavailability is expected to be similar following ingestion.

Toxicokinetics

There is a large amount of information on the toxicokinetics of the cadmium ion in humans. This information is mostly related to general cadmium exposure in workers, and is not specific to particular cadmium compounds.

Human data available on cadmium indicate that gastro-intestinal absorption is low (5–10 %), and varies depending on the source of the cadmium, presence of zinc in the diet, the body's iron stores (deficiencies are linked with increased cadmium absorption) and the person's age and physiological condition (young or pregnant or lactating animals have been shown to absorb more cadmium than non-pregnant adult animals) (OECD, 2004; EU RAR, 2007).

Dermal absorption of cadmium in rabbits following exposure to cadmium chloride solution was considered to be substantial, resulting in accumulation of up to 0.8 % of the administered dose in the kidney and liver (EU RAR, 2007).

Animal studies have demonstrated that absorption of cadmium oxide following inhalation exposure ranges from 30 % (dusts—size-dependent) to 50 % (fumes). In humans, inhalation absorption of 10–30 % (dusts, size-dependent) was reported (OECD, 2004).

In rodent dietary exposure studies using cadmium oxide, significant accumulation of cadmium was detected in the liver, kidneys, lungs and spleen. Levels in the liver and kidneys were reported to be dose-dependent. However, no significant increases in blood or urine levels of cadmium were detected. Absorption fractions following oral exposure to low doses of cadmium oxide were reported to be much greater than those determined for exposure to higher doses (EU RAR, 2007).

Following long-term low-level exposure, cadmium is reported to be widely distributed in the body and has a biological half-life of 10–20 years. The greatest accumulation occurs in the kidneys and liver, with only 0.005–0.02 % reported to be excreted in urine and faeces each day. Cadmium is also detectable in the placenta, and can cross the placental barrier, although foetal concentrations are lower than placental concentrations. Concentrations of cadmium in newborn blood were 40–50 % lower than the levels in maternal blood (EU RAR, 2007). Cadmium is reported to be found in human breast milk at <1 µg/L (OECD, 2004). In tissue, cadmium is bound to metallothionein, a low molecular weight metal-binding protein thought to play a key role in metabolising and detoxifying cadmium (EU RAR, 2007).

It should be noted that higher levels of cadmium (particularly in the kidney) are detected in smokers compared with non-smokers, as cadmium has been shown to accumulate in tobacco plant leaves (WHO, 2010).

Based on the physical and chemical properties of PTBBA (molecular weight <200 g/mol and log Kow of 3.4) and adverse effects observed in experimental animals, extensive absorption and distribution can be assumed (NICNASb).

Acute Toxicity

Oral

The chemicals in this group are not individually listed in HSIS and by default, they are covered by the generic 'cadmium compounds' hazard classification with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). While there are no experimental data available for the chemicals in this group, data from soluble cadmium compounds, PTBBA, and observations in humans indicate that the chemicals in this group are likely to be harmful following oral exposure.

Cadmium chloride and cadmium sulfate were reported to be acutely toxic in rats with LD50 values ranging from 107–327 mg/kg bw and 280 mg/kg bw, respectively (NICNASa).

PTBBA was reported to have a median lethal dose (LD50) ranging from 550-800 mg/kg in rats and mice. Reported effects included hypoactivity, respiratory congestion, impairment of forelimbs and hypospermatogenesis of the testes (NICNASb).

Cadmium chloride and cadmium sulfate are individually classified as hazardous following acute oral exposure, with the risk phrase 'Toxic if swallowed' (T; R25) in HSIS (Safe Work Australia). Based on similar bioavailability following acute oral exposure, there is sufficient evidence to warrant this classification applying to all chemicals in this group.

Dermal

The chemicals in this group are not individually listed in HSIS and by default, they are covered by the generic 'cadmium compounds' hazard classification with the risk phrase 'Harmful in contact with skin' (Xn; R21) in HSIS (Safe Work Australia).

While there are no experimental dermal toxicity data available for these specific chemicals, a number of soluble cadmium salts are reported to be absorbed through the skin resulting in detectable levels of cadmium in the kidney and liver (see **Toxicokinetics** section).

In the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend the classification for the chemicals in this group.

Inhalation

The chemicals in this group are not individually listed in HSIS. Therefore, by default, they are covered by the generic cadmium compounds hazard classification with the risk phrase 'Harmful if inhaled' (Xn; R20) in HSIS (Safe Work Australia). While there are no experimental data available specific to these chemicals, data from other cadmium compounds support a recommendation to amend the classification for the chemicals in this group.

A median lethal concentration (LC50) for cadmium chloride of $>4.5 \text{ mg/m}^3$ was reported from a 2-hour inhalation study in rats (REACH). Observed effects included pneumonitis (inflammation of lung tissue) and biochemical changes (increased number of alveolar macrophages and decreased lung/body weights). Even after considering the lower percentage of cadmium in these chemicals compared with cadmium chloride, this suggests that the chemicals in this group should be considered toxic.

Observation in humans

Several cases of cadmium poisoning (compound not specified) as a result of ingesting contaminated food or drinks have been documented. Signs and symptoms of toxicity reported include nausea, vomiting, diarrhoea and abdominal cramps.

Eight-hour inhalation exposure to cadmium levels of 5 mg/m^3 is reported to be potentially lethal, while 1 mg/m^3 is considered to be immediately dangerous to life (EU RAR, 2008).

In addition, there are many case studies of acute poisoning following inhalation of cadmium oxide fumes, or fumes produced by heating cadmium-containing materials to high temperatures. Documented signs of toxicity include nausea, fever, difficulties in respiration and severe respiratory irritation. Pulmonary oedema, resulting in mortality, was commonly reported following acute exposure (EU RAR, 2007).

The soluble cadmium salts (cadmium chloride and cadmium sulfate) are classified as hazardous following acute inhalation exposure, with the risk phrase 'Very toxic by inhalation' (T+; R26) in HSIS (Safe Work Australia). There is sufficient information to warrant this classification applying to all chemicals in this group.

Corrosion / Irritation

Respiratory Irritation

While no data are available for the chemicals in this group, based on sublethal symptoms observed in inhalation studies in animals and observations in humans, these compounds are expected to irritate the respiratory tract.

Skin Irritation

While no specific data are available for the chemicals in this group, potential skin irritation was reported following exposure to cadmium chloride (see **Irritation/Corrosivity - Observations in Humans**).

Eye Irritation

No data available.

Observation in humans

Eczema patients were patch-tested with 0.06, 0.5, 1 or 2 % doses of cadmium chloride in distilled water. At the 2 % dose, skin irritation was reported in 25/1502 patients (1.7 %), but no vesicular reactions (skin blisters) were observed. A lowest observed adverse effect level (LOAEL) value of 2 % was reported. No skin irritation was reported at 1 % dose (EU RAR, 2007; REACH).

Sensitisation

Skin Sensitisation

While no data are available for the chemicals in this group, there is limited evidence of skin sensitisation from human observations following exposure to cadmium chloride (see **Sensitisation - Observation in humans section**).

In a guinea pig maximisation test, animals (20/dose) were intradermally administered with a 0.007 % cadmium chloride solution in water. After an unreported period, a 5 % solution of cadmium chloride (in petrolatum) was topically applied to the animals. After three weeks, the animals were challenged with 0.05% cadmium chloride solution by intradermal injection and with 7.5% topical application. No contact sensitisation was reported at 24 or 48 hours post challenge application (EU RAR, 2007; REACH).

A negative result was reported for PTBBA in a guinea pig maximisation test (NICNASb).

Overall, there is insufficient evidence to classify the chemicals in this group as skin sensitisers.

Observation in humans

Skin patch tests using cadmium chloride and cadmium sulfate were positive in seven out of approximately 150 patients attending a dermatological department between 1979 and 1981 (EU RAR, 2007).

Repeated Dose Toxicity

Oral

While there are no data available for the chemicals in this group, data from animal studies and observations in humans following exposure to soluble cadmium compounds and PTBBA are provided below as read across.

A chronic exposure study in male Wistar rats using cadmium chloride reported potential damage to the vertebrae. The animals (10/dose) were orally exposed to cadmium chloride for 12 months through drinking water at 1, 5, or 50 mg Cd/L (calculated daily dose ranges were 0.049–0.223, 0.238–0.977, and 2.073–10.445 mg/kg bw/day, respectively). No treatment-related signs were reported at 1 mg/L. At ≥ 5 mg/L, increased lumbar spine deformities and a decrease in lumbar spine mineralisation (measurements included calcium, magnesium, zinc, copper, iron and phosphate) were reported. Decreased mechanical strength of the vertebral column at the fourth lumbar vertebra (L4) was reported at 50 mg/L. The L4 was reported to be fractured in 30 % of animals in this group, while 40 % were reported to have L4 deformities (NICNASa).

In a 90-day oral study, albino Carworth Farm E (CFE) rats (10 animals/sex/group) were orally administered a diet containing doses of 0, 100, 316, 1000, 3160 and 10000 ppm of PTTBA (calculated from food intake 0, 6, 21, and 75 mg/kg bw/d for males; 0, 8, 27, 89 mg/kg bw/d for females, for doses up to 1000 ppm; no calculation was available on the top two doses). Mortality occurred at the top two doses. At 10000 ppm, 90 % of males died by day 34 and 100 % of females by day 53. Bilateral atrophy of the testes, particularly degenerated epithelium of seminiferous tubules, was found in males of all dose groups. Renal tubular necrosis and papillary necrosis were evident in treated male and female rats of all dose groups. At the top two doses, effects were also observed in the liver (sinusoidal congestion and fatty degeneration of centrilobular hepatocytes) and urinary tract (hydronephrosis, hydroureter, ureteral obstructions and haematuria). In addition, effects on the central nervous system (hind limb paralysis) were observed at the top doses. A no observed adverse effect level (NOAEL) could not be established in this study. The LOAEL was identified to be 6 mg/kg bw/d for males and 8 mg/kg for female rats (NICNASb).

Cadmium chloride, cadmium sulfate and PTBBA are classified as hazardous following repeated oral exposure, with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure if swallowed' (T; R48/25) in HSIS (Safe Work Australia).

There is sufficient evidence from animal studies and observations in humans to warrant this classification applying to the chemicals in this group.

Dermal

While there are no data available for the chemicals in this group, data from animal studies following exposure to PTBBA are provided below as read across.

In a 13-week study, groups of 20 male and 20 female Fischer 344 (F344) rats were exposed to PTBBA topically (five days a week), with dosing solutions containing the diethanolamine (DEA) salt of PTTBA. This resulted in daily exposures of 0, 17.5, 35, 70, or 140 mg/kg of the chemical. Although the contribution of DEA (especially on the liver metabolism) cannot be ruled out, the adverse effects observed after repeated oral and inhalation exposure were considered to be attributed to PTBBA treatment. Dose-related significant increases in relative and absolute hepatic and renal weights were seen at all concentrations. Accompanying changes in clinical chemistry suggested altered hepatic and renal function. Histopathological changes in these organs including cytoplasmic vacuolation in the liver, and interstitial nephritis and papillary necrosis of the kidneys were detected at the two highest doses. Signs of microcytic hypochromic anaemia were also observed. Liver cell vacuolation was also evident in female rats only. Males had significantly reduced relative testis weights and sperm counts. Similarly, a decline in LDH-X enzyme activity (a measure of semen integrity) was also reported. Histopathological changes observed in male rats included degeneration and regeneration of distal convoluted tubular epithelium, tubular casts, tubular degeneration with an absence of late spermatids, a reduced number of spermatogenic cell types, and giant cell formation. The LOAEL for this study was 17.5 mg/kg bw/day based on effects in the liver, kidney, testes and peripheral blood (NICNASb).

PTBBA is classified as hazardous following repeated dermal exposure, with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure in contact with skin' (T; R48/24) in HSIS (Safe Work Australia). However, it cannot be assumed that the bioavailability of the ionic cadmium salts will be the same as that of PTBBA, but dissociation of the chemicals in sweat is expected to produce some PTBBA.

This information indicates that the chemicals in this group should be classified as harmful by the dermal route.

Inhalation

While there are no data available for the specific chemicals in this group, data from animal studies and observations in humans following inhalation exposure to other cadmium compounds and PTBBA are provided below as read-across.

Effects observed in animal studies following repeated-dose exposure to cadmium oxide are reported to be similar to those observed in acute inhalation exposure studies including rales (abnormal respiratory sounds), laboured breathing and pneumonia, seen at low doses (EU RAR, 2008).

In a 13-week repeated-dose inhalation study in rats exposed to cadmium oxide, the NOAEL was reported to be 0.025 mg/m³. At higher doses (≥ 0.05 mg/m³), treatment-related lesions in the lungs, including inflammation and fibrosis, were observed. A dose-related increase in hyperplasia (elevated cell production) in the lungs was also reported (EU RAR, 2007).

In an 11-day inhalation study, F344 rats (eight animals/sex/dose) were repeatedly exposed to PTBBA (dust) at mean concentrations of 0, 12.5, 106 and 525 mg/m³ for six hours a day, for four days followed by three days' (males) or four days' (females) rest period and another three days of exposure. Microscopically, treatment-related lesions were seen in the livers, spinal cord, testis, epididymides, and thymus of rats from mid and high dose groups. In animals exposed to 106 mg/m³ PTBBA, severe tubular changes were observed, consisting of absence of late spermatids, reduction in spermatogenic cell types, atrophy and inflammation of epididymides. Female rats exposed to high doses exhibited abnormalities in blood count. Significant loss of body weight was noted in both sexes. The LOAEC was 12.5 mg/m³ (six hours a day, seven exposure days) based on a dose-related reduction in the mean number of sperm in each testis and treatment-related lesions seen in the kidneys of rats from all dose groups. Neurotoxicity was noted at concentrations of ≥ 106 mg/m³. Behavioural anomalies were observed in the exposed males, including limb paralysis, hunched posture, convulsions, hypoactivity, prolapsed penis and abnormal respiration.

Neurodegenerative changes such as degeneration and loss of neurons, vacuolation, microgliosis and congestion were localised in the central area of the grey matter lesions and in the ventral funiculi region of white matter. These animals also showed clinical signs of paraplegia (NICNASb).

Cadmium chloride, cadmium sulfate and PTBBA are classified as hazardous following repeated inhalation exposure, with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure through inhalation' (T; R48/R23) in HSIS (Safe Work Australia). Availability of cadmium and PTBBA are expected to be similarly high on inhalation exposure.

There is sufficient evidence from animal studies and observations in humans to warrant this classification applying to the chemicals in this group.

Observation in humans

Exposure to low levels of cadmium over a long period of time has been linked to chronic cadmium poisoning. The effects of cadmium on specific target organs following exposure in humans are summarised below.

Respiratory effects

There are a number of documented case studies of workers chronically exposed to the chemical fumes (EU RAR, 2007). Effects reported included fatigue, respiratory irritation, shortness of breath, decreased lung function and recurrent bronchitis.

It is suggested that an increase in residual levels of the chemical in lungs may lead to chronic obstructive airway disease and (in some cases) mortality, all of which have been documented following exposure (EU RAR, 2007). A lowest observed adverse effect concentration (LOAEC) of 0.0031 mg/L, based on lung effects (increased residual levels of the chemical), was derived from a study on workers exposed to the chemical fumes at <0.5 mg/m³ over several years.

Renal effects

The kidneys are considered to be the main target organ for cadmium toxicity following repeated oral or inhalation exposure (ATSDR, 2012; EU RAR, 2007). Initial signs of kidney effects following cadmium exposure include tubular dysfunction, a decreased glomerular filtration rate, and increased proteinuria and enzymuria. Renal dysfunction is considered to occur when renal cortex cadmium concentrations reach 200 ppm (equivalent to 5–10 mg/g creatinine) (EU RAR, 2007).

Increased incidence of kidney stones has also been reported in workers exposed to cadmium (18 %), compared with unexposed workers (3 %) (EU RAR, 2007).

Skeletal effects

Oral cadmium exposure is reported to cause bone disease in humans (EU RAR, 2008). While the underlying mechanism is not clearly understood, it is thought that cadmium-induced kidney damage and the resulting hypercalcaemia (elevated levels of calcium in the urine) may promote osteoporotic effects in bone (EU RAR, 2007).

In a case study in Japan, a high incidence of Itai-Itai disease was diagnosed in patients from specific geographical locations. It was found that farms in these areas were irrigated by a river being polluted by cadmium sludge from an upstream mine, and the patients may have been exposed to cadmium for over 30 years. Samples of rice taken from those areas were reported to contain cadmium at 0.68 mg/kg, compared with 0.066 mg/kg in other areas (EU RAR, 2007). Itai-Itai disease is characterised by osteomalacia (softening of the bones), osteoporosis, severe renal tubular disease, and is associated with severe pain (WHO, 2011). A limited number of case reports have also documented clinical bone disease in workers exposed to cadmium compounds (EU RAR, 2007).

Genotoxicity

While there are no data available for the chemicals in this group, data from other soluble cadmium salts (cadmium chloride and cadmium sulfate) and observations in humans are provided below.

In vitro

Cadmium chloride was reported to not be mutagenic in *S. typhimurium* bacterial strains TA 98, TA100, TA 1535 and TA 1537 with and without metabolic activation (REACH). However, cadmium ions have been shown to induce genotoxic effects in vitro (reduction in colony-forming ability and DNA strand breaks in *Escherichia coli*) (EU RAR, 2007).

In another test using CHO cells, cadmium acetate was reported to induce large genomic deletions, base substitutions and splice mutations (HSDB).

Cadmium chloride and cadmium sulfate were clastogenic in tests using mammalian cells. An increase in sister chromatid exchanges was reported in male and female mouse splenocytes exposed to cadmium chloride, and in human lung fibroblasts exposed to either cadmium chloride or cadmium sulfate; chromosomal aberrations were observed in male and female Swiss mouse splenocytes following exposure to cadmium chloride; and DNA strand breaks and mutations at the K-ras gene were reported in human lung fibroblasts exposed to cadmium sulfate (REACH).

In vivo

Cadmium chloride was reported to be mutagenic in vivo in male albino rats that were injected intraperitoneally with a 4 mg/kg bw dose of the chemical. Single strand DNA breaks were observed following exposure, notably in the kidney (EU RAR, 2007).

Cadmium chloride was reported to be mutagenic in vivo where micronucleus induction and sister chromatid exchanges in mouse bone marrow and chromosomal aberration were investigated, after a single intraperitoneal (ip) treatment at doses of 1.9, 5.7 or 7.6 mg/kg bw. A dose-dependent increase of peripheral erythrocytes with micronuclei was reported in this study. Doses of 5.7 and 7.6 mg/kg bw induced bone marrow toxicity demonstrated by a significant increase in the percentage of polychromatic erythrocytes relative to normal chromatic erythrocytes when compared with the control. The chemical was also reported to induce chromosomal aberrations (excluding metaphases with chromosome or chromatid gaps). The effects were dose-dependent with the maximum effect observable at 24 hours post-treatment. A dose-dependent increase in the frequency of sister chromatid exchanges was reported at the two highest doses (EU RAR, 2007).

Observations in humans

Chromosomal aberrations, increased frequency of micronuclei, and sister chromatid exchanges have been detected in humans environmentally exposed to cadmium (EU RAR, 2007). However, the specific cadmium compounds involved are not identified.

Cadmium chloride and cadmium sulfate are classified as hazardous—Category 2 mutagens—with the risk phrase 'May cause heritable genetic damage' (T; R46) in HSIS (Safe Work Australia).

There is sufficient evidence to warrant this classification applying to the chemicals in this group.

Carcinogenicity

While there are no data available for the chemicals in this group, data from other soluble cadmium salts (cadmium chloride and cadmium sulfate) are provided below as read across.

Oral administration of cadmium chloride to Wistar rats increased the incidence of large granular lymphocytes, leukaemia, prostate tumours, and testicular tumours. Prostate hyperplasia was also reported in Noble (NBL/Cr) rats orally exposed to the chemical (NTP, 2011; REACH).

A non-guideline inhalation study reported an increase in lung tumours in male and female Wistar rats (20/sex/dose) exposed to aerosolised cadmium chloride, cadmium sulfate, cadmium oxide dusts, cadmium oxide fumes or cadmium sulfide (REACH).

In separate studies, rats were exposed to cadmium chloride (0.03 and 0.09 mg/m³) and cadmium sulfate (0.09 mg/m³ for 22 hours a day, seven days a week for 18-months. Effects reported included: lung bronchioalveolar adenomas (benign glandular tumour of the lung), adenocarcinomas (malignant glandular tumours) and squamous cell carcinomas (cancer of the outer layer of the lining of the airways). A LOAEL for carcinogenicity of 0.03 mg/m³ air was reported for cadmium chloride. In a follow-up study using cadmium sulfate, a significant incidence of lung tumours was observed following chronic inhalation exposure to 0.09 mg/m³ over a 29-30 month period (NICNASa).

Observations in humans

There are many case studies that explore the link between exposure to cadmium and increased incidences of cancer in workers (NTP, 2011; IARC, 2012).

Significantly increased mortalities due to lung cancer were reported in workers in cadmium-processing plants, cadmium recovery plants and those who worked in the nickel-cadmium battery production industry (IARC, 2012). An increased risk of lung cancer was identified in workers with long-term employment in high cadmium-exposure jobs.

A few cases of cancer of the prostate, pancreas and kidney have also been reported following exposure to cadmium (either from occupational exposure or by contamination).

In some of these cases, workers may have been exposed to other chemicals, including arsenic and nickel. Both IARC and the US NTP concluded that the increase in lung cancers could not be solely due to coexposure to other chemicals (NTP, 2011; IARC, 2012). However, the Agency for Toxic Substances and Disease Registry (ATSDR) disputed that the interpretation of these observations in humans is complicated by co-exposure with other metals, and that there is a 'lack of significant relationship between cadmium exposure and duration' (ASTDR, 2012). These data suggest that there may be limited evidence of cancer of the prostate, pancreas and kidney occurring from exposure to cadmium compounds in these studies.

The International Agency for Research on Cancer (IARC) has classified cadmium and cadmium compounds as 'Carcinogenic to humans (Group 1)' based on sufficient evidence in humans and experimental animals (IARC, 2012). Additionally, the US National Toxicology Program (NTP) has also classified cadmium and cadmium compounds as 'Known to be human carcinogens' (NTP, 2011).

Cadmium chloride and cadmium sulfate are classified as hazardous—Category 2 carcinogens—with risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). Based on the available data, there is sufficient evidence from animal studies and observations in human to warrant this classification applying to the chemicals in this group.

Reproductive and Developmental Toxicity

While there are no experimental data available for the chemicals in this group, data from other soluble cadmium salts (cadmium chloride and cadmium sulfate) and PTTBA are provided below as read across.

Reproductive toxicity

In a study in female Wistar rats, animals were exposed to cadmium chloride by oral gavage at 0.04, 0.4, 4 and 40 mg/kg bw/day for 14 weeks. Increased oestrous cycle lengths and decreased body weights compared with the control group were reported in the highest dose group (40 mg/kg bw/day) after six weeks of treatment; this was not reported for the other dose groups. A reproductive NOAEL of 4 mg/kg bw/day and LOAEL of 40 mg/kg bw/day were reported for this study (EU RAR, 2007; NICNASa).

In a fertility study using Wistar rats, males were fed diets containing 0, 20, 100 or 500 ppm PTBBA for a 70-day period before mating trials. Successful impregnation of at least one of the two females was used as fertility indicator. Unsuccessful males from the first mating trial were kept for another 70 days, but without exposure to PTBBA. These males were mated again (second mating trial) to two non-exposed female virgins for one week. The results showed that, in the first mating trial, the lowest levels of dietary PTBBA (20 ppm) did not cause fertility impairment. However, one male from the 100 ppm group was not successful in impregnating and no pregnancies occurred in the 500 ppm dosing group. The impairment was reversed in the second mating trial, although minor lesions were found in the germinal epithelium and were confined to a few tubules only at 500 ppm. A NOAEL for male fertility of 20 ppm (1.6 mg/kg/bw) was reported from this study (NICNASb).

Furthermore, repeated exposure to PTBBA by oral, skin and inhalation routes, and acute inhalation exposure has been shown to induce testicular abnormalities. The effects were primarily characterised by the degeneration of germinal epithelium resulting in disrupted spermatogenesis, damage in the epididymides, including atrophy and inflammation. The reported effect levels for testis toxicity were 6 mg/kg bw/day (oral LOAEL), 35 mg/kg bw/day (dermal NOAEL) and 12.5 mg/m³ (inhalation LOAEC) (see **Repeated dose toxicity**).

Developmental toxicity

Effects of cadmium exposure on maternal and foetal zinc metabolism were reported to be investigated in a non-guideline developmental toxicity study. SD rats were orally exposed to cadmium chloride in drinking water at daily doses of 0, 5, 50 and 100 ppm on GD 6-20. Exposure-related reductions in maternal weights and weight gains were reported at the two highest dose groups (50 and 100 ppm) but not in the 5 ppm group. In the 100 ppm dose group, reduced foetal weights were reported to be a secondary effect to decreased maternal weights (attributed to maternal reduced food and water intake). A significant difference in the foetal weight to maternal weight ratio (compared with controls) was only observed in the 50 ppm group.

It was reported at the 50 ppm dose that cadmium-induced zinc retention was the cause of impaired foetal growth, as zinc retention in maternal liver and kidney and decreased concentration of zinc in the foetal liver were observed. A maternal and developmental NOAEL of 5 ppm (0.63 mg/kg bw/day) and a maternal and developmental LOAEL of 50 ppm (4.7 mg/kg bw/day) were reported (EU RAR 2007; REACH).

In another study, cadmium chloride was administered intragastrically at 2, 12 and 40 mg/kg bw/day, to pregnant rats. At the two highest dose groups, reduced foetal body weights and reduced skeletal ossification, compared with controls, were reported. Reduced body weight gains of treated females at all dose levels during pregnancy were also reported. NOAEL or LOAEL estimates were not reported for this study (EU RAR 2007).

Cadmium chloride is listed in the HSIS and is classified as hazardous – as Category 2 reproductive and developmental toxins – with the risk phrases 'May impair fertility' (T; R60) and 'May cause harm to the unborn child' (T; R61) in HSIS (Safe Work Australia). PTTBA is also listed in the HSIS and is classified as hazardous – as Category 2 reproductive toxins – with the risk phrase 'May impair fertility' (T; R60) in HSIS (Safe Work Australia). There is sufficient evidence to adopt the classification of cadmium chloride for the chemicals in this group for developmental toxicity, while the toxicity to fertility classification should be based on PTBBA.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, mutagenicity, reproductive toxicity and developmental toxicity), and toxic effects (renal, skeletal, respiratory and neurotoxic effects) resulting from repeated exposure. The chemicals are also expected to cause acute adverse health effects from all routes of exposure.

Public Risk Characterisation

Given the uses identified for the chemicals in this group, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical health effects, the chemicals in this group may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemical are implemented. The chemicals in this group should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

NICNAS Recommendation

Assessment of the chemicals in this group is considered to be sufficient, provided that the recommended amendment to the classification are adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing any of the chemicals in this group should be labelled in accordance with state and territory legislation (SUSMP).

Work Health and Safety

The chemicals in this group are recommended for classification and labelling under the current Approved Criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

The classification proposed below is based on read across principles (see **Health Hazard Information**) and the existing classifications for cadmium chloride (CAS No. 10108-64-2), cadmium sulfate (CAS No. 10124-36-4), and PTTBA (CAS No. 98-73-7). If empirical data become available for any member of the group indicating that a lower (or higher) classification is appropriate for the specific chemical, these may be used to amend the default classification for that chemical.

Hazard	Approved Criteria (HSIS) ^a	GHS Classification (HCIS) ^b
Acute Toxicity	Harmful if swallowed (Xn; R22) Harmful in contact with skin (Xn; R21)* Very toxic by inhalation (T+; R26)	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Fatal if inhaled - Cat. 1 (H330)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure in contact with skin (Xn; R48/21) Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23) Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373) Causes damage to organs - Specific target organ tox, single exp Cat. 1 (H370) Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)	May cause genetic defects - Cat. 1B (H340)

Hazard	Approved Criteria (HSIS) ^a	GHS Classification (HCIS) ^b
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)	May cause cancer - Cat. 1B (H350)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May impair fertility (T; R60) Repro. Cat 2 - May cause harm to the unborn child (T; R61)	May damage fertility. May damage the unborn child - Cat. 1B (H360FD)

^a Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

^b Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

* Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing any of the chemicals in this group should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from exposure to the chemicals in this group should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemicals has not been undertaken as part of this assessment.

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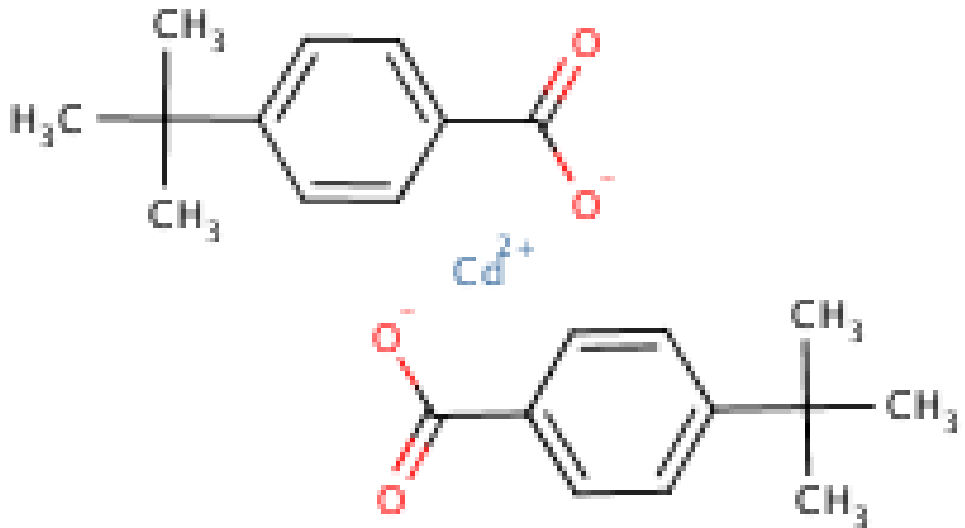
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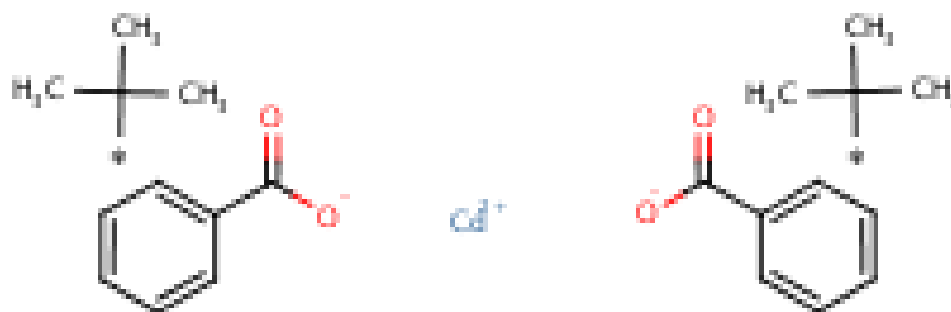
Chemical Identities

Chemical Name in the Inventory and Synonyms	Benzoic acid, 4-(1,1-dimethylethyl)-, cadmium salt Benzoic acid, p-tert-butyl-, cadmium salt p-tert-Butylbenzoic acid, cadmium salt Cadmium, p-tert-butylbenzoate
CAS Number	4167-05-9
Structural Formula	



Molecular Formula	C ₁₁ H ₁₄ O ₂ ·1/2Cd
Molecular Weight	466.85

Chemical Name in the Inventory and Synonyms	Benzoic acid, (1,1-dimethylethyl)-, cadmium salt Benzoic acid, tert-butyl-, cadmium salt Cadmium, tert-butylbenzoate
CAS Number	31215-94-8
Structural Formula	



Molecular Formula	C ₁₁ H ₁₄ O ₂ .1/2Cd
Molecular Weight	

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