Cadmium sulfides: Human health tier II assessment

04 July 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Cadmium sulfide (CdS)	1306-23-6
C.I. Pigment Yellow 37	68859-25-6

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**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group contains cadmium sulfide (CAS No. 68859-25-6) and pigment yellow 37 (CI 77199; CAS No. 68859-25-6). Pigment yellow 37 is included in this group since it is composed of cadmium sulfide, where a controlled calcination process is used to achieve the desired pigment hue (Koleske, 2012). Thus, pigment yellow 37 is considered to be chemically equivalent to cadmium sulfide. There may be differences in the bioavailability depending on the calcination process used in the commercial production of pigment yellow 37. However, no information is available to characterise this. Therefore, the data and recommendations in this assessment apply to both chemicals in this group.

Import, Manufacture and Use

Australian

The chemicals in this group were reported to be manufactured as a pigment in Australia (De Silva & Donnan, 1981).

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the European Chemical Agency (ECHA); Galleria Chemica; International Agency for the Research of Cancer (IARC), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals in this group have reported domestic use including as a pigment in paints, lacquers, emulsion paints, and printing inks.

The chemicals in this group have reported commercial use including:

- as a pigment in polymers, alkyd resin enamels, and rubber;

- as a semi-conductor in photovoltaic applications such as photocells and light-emitting diodes;
- in cathode ray tubes (CRTs) and in LED illumination systems; and
- as a component in plastics and vinyl products.

The chemicals in this group have reported site-limited use including as a stabiliser in producing plastic materials.

The chemicals in this group were also reported to have been used as a component in tattoo inks (Tindall & Smith, 1962).

Restrictions

Australian

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 Australia Work Health and Safety Regulations 2011 for 'use in abrasive blasting at a concentration of greater than 0.1 % as cadmium' (SafeWork Australia).

International

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

In 2013, cadmium sulfide was listed on the candidate list of substances of very high concern (SVHC) for inclusion in Annex XIV (ECHA, 2013). In the EU, companies may have legal obligations if the chemical that they produce, supply, or use is included on the candidate list whether on its own, in mixtures, or present in articles.

Existing Worker Health and Safety Controls

Hazard Classification

Cadmium sulfide (CAS No. 1306-23-6) is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Carc. Cat. 2; R45—May cause cancer.

Muta. Cat. 3; R68—Possible risk of irreversible effects.

Repr. Cat. 3; R62—Possible risk of impaired fertility.

Repr. Cat. 3; R63—Possible risk of harm to the unborn child.

T; R48/23/25—Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.

Xn; R22—Harmful if swallowed.

Exposure Standards

Australian

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

International

For cadmium and cadmium compounds, the following exposure standards are identified (Galleria Chemica): An exposure limit (TWA) of 0.01–0.2 mg/m^3 in different countries such as Canada, the USA, Latvia and Switzerland.

Health Hazard Information

Toxicokinetics

Cadmium sulfide is considered to be water-insoluble. Cadmium oxide and cadmium carbonate are also reported to be relatively water-insoluble but may be able to dissolve at gastric pH, thus it could have similar absorption and toxic effects to soluble cadmiums. While cadmium sulfide is expected to have lower acid solubility, dissociated cadmium ions will act similarly regardless of their source compounds. In addition, it was reported that cadmium sulfide, cadmium carbonate, and cadmium oxide (water-insoluble cadmium compounds) can be changed to water-soluble cadmium salts by interaction with acids or light and oxygen (ATDSR). Additionally, the photochemical decay of cadmium sulfide in aqueous suspensions into cadmium sulfate was implicated in causing lung tumours in rats (Konig et al., 1992).

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, although 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).

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). Dermal absorption is expected to be low due to the ionic nature of the chemical.

Observation in humans

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, the 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).

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).

Acute Toxicity

Oral

Cadmium sulfide is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). While there are limited data available for the chemicals in this group, data from cadmium oxide and observations in humans, support this classification applying to the chemicals in this group.

The oral median lethal dose (LD50) for cadmium sulfide was reported to be in the range 907–1166 mg/kg in mice (Vorob'eva & Shabalina, 1975; Vorob'eva & Shabalina, 1978). Effects reported included dystrophic changes in the heart, liver and kidneys as well as local necrosis of the gastrointestinal mucosa.

Cadmium oxide was reported to be acutely toxic in rats following oral exposure, with oral LD50 values in the range 72–296 mg/kg bw (EU RAR, 2007; NICNAS). The difference in the LD50 values between cadmium sulfide and cadmium oxide may be considered to indicate the difference in availability of cadmium ions between the two compounds.

Dermal

No data are available.

Inhalation

Although there are no data available for the chemicals in this group, data from animal studies exposed to pigments related to cadmium sulfide are reported in the relevant sections below, as read-across.

Sprague-Dawley rats (26 animals/sex/dose) were exposed to aerosolized cadmium red (equivalent to cadmium sulfoselenide) and cadmium yellow (equivalent to cadmium zinc sulfide) at concentrations of approximately 100 mg Cd/m^3 for 2 hours. No mortalities were observed in both chemical groups. For both chemicals, excessive lacrimation was observed 4-hours post-exposure. In addition, there was also a higher incidence of kidney discolouration in the cadmium red group compared to the controls or cadmium yellow group. The LC50 value for both chemicals was determined to be > 100 mg/m^3 (Rusch et al., 1986; REACH).

In a non-guideline experiment, CdZnS (5.0 mg in 0.5 mL saline solution) was administered to anaesthetised male F344 rats (30 animals/group) by intratracheal instillation. Ten animals were sacrificed for bronchoalveolar lavage fluid (BALF) and histopathology on day 1, week 1, and week 14 after dosing with CdZnS. The animals showed signs of dyspnoea and lethargy which were reversible within 1 hour. At day 1 post-treatment, the following parameters were found to be significantly higher in the CdZnS group compared with the control group: alkaline and acid phosphatases, mean protein level, β-glucuronidase, and white blood cell (WBC) and macrophage count. It was also reported that the levels of Cd and Zn in the blood and liver were comparable. High concentrations of Cd and Zn were found in the lung which declined over the post-treatment period. At week 14 post-treatment, a statistically significant amount of Cd and Zn was found in the kidney. Histopathology on the CdZnS group showed interstitial inflammation of the trachea that consisted of lymphocyte and neutrophil infiltration in the mucosa and submucosal tissues. The study concluded that intratracheal instillation of CdZnS causes an acute inflammatory response in the lungs and that the bioavailability of CdZnS was poor as evidenced by the small amount found in the kidneys (Bergmann et al., 2000).

Additionally, intratracheal administration of cadmium sulfoselenide (15 mg/animal) in rats caused pneumonia, pneumosclerosis, and lung emphysema (Vorob'eva & Shabalina, 1975; Vorob'eva & Shabalina, 1978).

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.

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).

Corrosion / Irritation

Respiratory Irritation

While no specific data are available for the chemicals in this group, based on the sublethal symptoms observed in inhalation studies in animals and observations in humans from exposure to cadmium compounds, chemicals in this group are expected to be irritating to the respiratory tract.

Skin Irritation

Although there are no data available for the chemicals in this group, it was reported that no dermal effects were observed when cadmium zinc sulfide (CdZnS), a pigment related to cadmium sulfide, was intradermally applied to rabbits at a dose of 9.4 g/kg for 24 hours (National Academy of Sciences, 1997).

Eye Irritation

Although there are no data available for the chemicals in this group, it was reported that rabbits treated with a mixture containing approximately 35 % CdZnS by instillation produced negligible corneal effects. (National Academy of Sciences, 1997).

Sensitisation

Skin Sensitisation

While there are limited experimental data available for the chemicals in this group, data from observations in humans have shown dermal effects when cadmium sulfide, based on its use in tattoo inks, is exposed to light (see **Observations in humans**). However, there is insufficient evidence to warrant classifying the chemical as a skin sensitiser.

Observation in humans

Cadmium sulfide was historically been used as the main constituent of yellow pigments used in tattooing. In a 1962 report, case studies on humans who were tattooed using cadmium sulphide pigments showed localised skin swellings around the tattooed skin upon exposure to sunlight (Tindall & Smith, 1962).

In an experiment conducted on human skin, the chemical was applied as a tattoo and exposed to different wavelengths of light. It was shown that swelling, lasting 2–72 hours, appeared when the skin was exposed to wavelengths of 380–450 nm. Histological examination of skin biopsies from the application site revealed slightly dilated capillaries surrounded by sparse infiltrates of lymphocytes. However, a negative result was found in a patch test where the chemical was superficially applied to skin for 48 hours and subsequently irradiated with identical wavelengths of light (Bjornberg, 1963).

Repeated Dose Toxicity

Oral

Cadmium sulfide is classified as hazardous with the risk phrase ‘Toxic: danger of serious damage to health by prolonged exposure if swallowed.’ (T; R48/25) in HSIS (Safe Work Australia). While there are no data available for the specific chemicals in this group, data from animal studies and observations in humans exposed to cadmium compounds support this classification applying to the chemicals in this group.

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 (ATSDR).

Cadmium chloride and cadmium sulfate are also 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).

Dermal

No data are available.

Inhalation

Cadmium sulfide is classified as hazardous with the risk phrase ‘Toxic: danger of serious damage to health by prolonged exposure if inhaled.’ (T; R48/23) in HSIS (Safe Work Australia). The available data support this classification applying to the chemicals in this group.

In an experiment conducted on Han:NMRI mice (48 females/dose/group), cadmium sulfide was administered by inhalation at concentrations of 90, 270, or 1000 µg/m^3 for eight or 19 hours/day, five days/week, for 69 weeks. The mass median aerodynamic diameter (measurement of chemical particle size) was reported to be 0.2−0.6 µm (geometric standard deviation of 1.6). The survival rates of animals in the 90 and 270 µg/m^3 groups were similar to controls. Effects that were observed include alveolar enlargement, thickening and scarring of the lung tissues, and tumours of the trachea. These effects were also observed in an experiment conducted on Hoe:SYHK hamsters at the same doses (IARC, 1993).

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 fumes of cadmium oxide (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 cadmium oxide 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 cadmium oxide), was derived from a study on workers exposed to the fumes of cadmium oxide at <0.5 mg/m^3 over several years.

Renal effects

The kidneys are considered to be the main target organ for cadmium toxicity following repeated oral or inhalation exposure (EU RAR, 2007; ATSDR, 2012). Initial signs of kidney effects following cadmium exposure include tubular dysfunction, 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 µg/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 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 hypercalcinuria (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

Cadmium sulfide is classified as hazardous (Category 3 mutagenic substance) with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) in HSIS (Safe Work Australia). The available data for cadmium sulfide and results for other cadmium compounds indicate that absorbed cadmium is a possible mutagen.

In vitro

Cadmium sulfide was reported to induce DNA strand breaks in Chinese hamster ovary (CHO) cells and chromosome aberrations in human lymphocytes (IARC, 1993; REACH).

Other cadmium compounds

Cadmium salts have been shown to induce genotoxic effects in both in vitro (reduction in colony-forming ability and DNA strand breaks in *Escherichia coli*) and in vivo studies (sister chromatid exchange and chromosomal aberration in mice, and DNA strand breaks in rats) (EU RAR, 2007; IARC, 2012).

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.

Carcinogenicity

Cadmium sulfide is classified as hazardous (Category 2 carcinogenic substance) with the risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). The available data support this classification applying to the chemicals in this group.

In an experiment conducted on Wistar rats (20–40 males or 20 females per dose group), cadmium sulfide was administered by inhalation at doses of 90, 270, 810, or 2430 µg/m^3 for 22 hours/day, seven days a week, for 18 months. The incidence of primary pulmonary tumours was increased in all dose groups compared with the controls. The observed tumours were mostly adenomas, adenocarcinomas, bronchioalveolar adenomas, and squamous-cell carcinomas (IARC, 1993; REACH CdS).

In another experiment, intratracheal administration of cadmium sulfide in Wistar rats (40 females/dose) at doses of 630, 2500, or 10 000 µg induced dose-related increase in the incidence of lung tumours, primarily adenocarcinomas (IARC, 1993).

It was also shown that subcutaneous injections of 10 % aqueous suspension (25 mg cadmium sulfide suspended in 0.25 mL saline) in both sides of the dorsal midline of Wistar rats induced fibrosarcomas at the site of injection. The same effect was observed upon intramuscular injections of 10 % aqueous suspension (50 mg cadmium sulfide suspended in 0.5 mL saline) (IARC, 1993; REACH CdS).

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).

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).

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 co-exposure 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.

Reproductive and Developmental Toxicity

Cadmium sulfide is classified as hazardous (Category 3 substance toxic to reproduction) with the risk phrases ‘Possible risk of impaired fertility’ (Xn; R62) and ‘Possible risk of harm to the unborn child’ (Xn; R63) in HSIS (Safe Work Australia). While there are no experimental data available for the chemicals in this group, results from cadmium chloride (by oral exposure) and cadmium oxide (by inhalation exposure) indicate that reproductive effects (fertility and developmental effects) were detected at dose levels that also caused general toxicity and maternal toxicity. In the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend the existing reproductive and developmental toxicity classifications for cadmium sulfide. The available data support this classification applying to the chemicals in this group.

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 other dose groups. However, increased mortality and other signs of toxicity (animals became emaciated, aggressive with ruffled hair coat) were also observed at the highest dose. 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; REACH).

In another study, female rats were treated with 0.1, 1 and 10 mg/kg bw/day cadmium chloride by gavage. Male rats treated with the same dose for nine weeks were mated with the treated female rats. Adverse effects including less copulating and fewer pregnant females were reported at 10 mg/kg bw/day. Female rats in this group also showed decreased body and organ weights. A reproductive NOAEL of 1 mg/kg bw/day and LOAEL of 10 mg/kg bw/day were reported for this study (EU RAR, 2007).

In a study in male and female F344/N rats and male and female B6C3F1 mice, animals were exposed to cadmium oxide by inhalation at 0.025, 0.5, 0.1, 0.25 or 1 mg/m^3 for 13 weeks. Decreased spermatid counts and increased oestrous cycle lengths were reported in rats in the highest dose groups, as well as decreased body weight gain and increased mortality. No treatment-related histopathological changes of the reproductive organs were seen. In mice, there was no reproductive toxicity reported at any exposure level (NTP, 1995). A reproductive LOAEL of 1 mg/m^3 was reported for this study based on the effects observed in rats (EU RAR, 2007).

Developmental toxicity

In a developmental toxicity study in Sprague Dawley (SD) rats, animals were exposed to cadmium oxide by inhalation at 0.05, 0.5 or 2 mg/m³ on gestation days (GD) 4–19. Exposure-related foetal skeletal variations (reduced ossification of the pelvis and the sternebrae) and reduced foetal weights (statistically significant in the highest dose group) were reported. However, significantly decreased maternal body weights and reduced absolute liver and kidney weights were also recorded at the highest dose, in addition to one mortality at GD 17. Signs of toxicity were observed in dams in all treatment groups. The effects included dyspnoea (difficult or laboured breathing) and hypoactivity (NTP, 1995). A maternal NOAEL of <0.05 mg/m^3 and a developmental NOAEL of 0.5 mg/m^3 were reported for this study (EU RAR, 2007).

In another study, Swiss mice were exposed to cadmium oxide by inhalation at 0.05, 0.5 or 2 mg/m^3 on GD 4–17. An increased frequency in reduced ossification of the sternebrae was reported in foetuses (statistically significant at the highest dose), while significantly reduced foetal weights were reported at ≥0.5 mg/m^3. Signs of toxicity, including dyspnoea and hypoactivity, were observed in dams from all treatment groups, in addition to significantly reduced maternal body weights and five mortalities (euthanised moribund) from the highest dose group (NTP, 1995). A maternal NOAEL of <0.05 mg/m^3 and a developmental NOAEL of 0.05 mg/m^3 were reported for this study (EU RAR, 2007). Placental and lactational transfer of cadmium to the offspring (see **Toxicokinetics**) are also considered to be adverse to development.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity; reproductive toxicity; skeletal, respiratory and renal effects from oral and inhalation exposure). The chemicals in this group are also harmful following acute oral exposure.

Public Risk Characterisation

Cadmium sulfide is listed on Schedule 6 of the SUSMP under the chemical group 'cadmium and cadmium compounds' (SUSMP, 2013). For the majority of potential public exposure routes, this schedule entry is expected to be appropriate.

Given that there has been documented use of cadmium sulfide in tattoo inks, additional regulatory controls could be required should information become available to indicate that the chemical is continued to be used in tattoo inks.

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 chemicals 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

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory, and the recommended classification is adopted.

Given that there has been documented historical use of cadmium sulfide in tattoo inks, additional regulatory controls could be required should information become available to indicate that the chemical continues to be used in tattoo inks. Formulators and importers of tattoo inks should ensure current products do not contain cadmium sulfide. Unless information becomes available to indicate continuing use of cadmium sulfide in tattoo inks, no further assessment is required.

Regulatory Control

Public Health

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

Work Health and Safety

The classification listed below is the existing classification for cadmium sulfide (CAS No. 1306-23-6). This classification is applicable to pigment yellow 37, unless substantial information can demonstrate that the bioavailability of cadmium from specific grades of pigment yellow 37 is sufficiently low to mitigate toxicity.

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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
Repeat Dose Toxicity	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)*	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)* Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)*	Suspected of damaging fertility or the unborn child - Cat. 2 (H361fd)

[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 the chemicals in this group should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from exposure to the chemicals in this 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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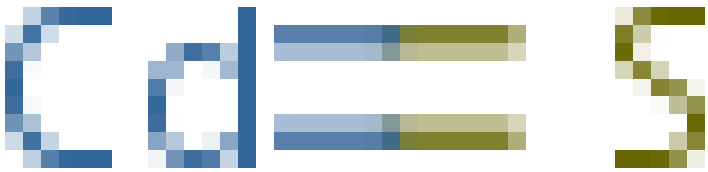
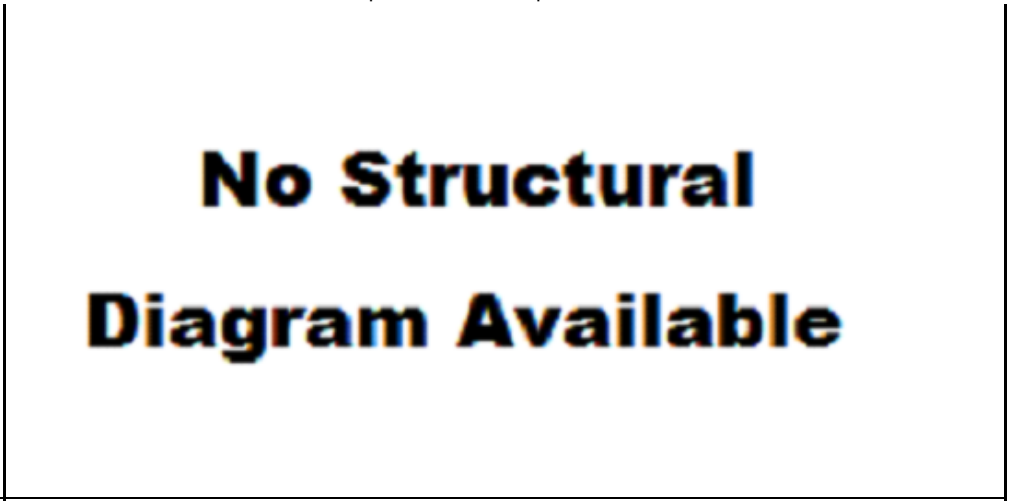
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Cadmium sulfide (CdS)** cadmium monosulfide cadmium orange cadmium yellow 37 CI 77199 cadmium sulphide
CAS Number	1306-23-6
Structural Formula	
Molecular Formula	CdS
Molecular Weight	144.47

Chemical Name in the Inventory and Synonyms	**C.I. Pigment Yellow 37**
CAS Number	68859-25-6
Structural Formula	

	
Molecular Formula	Unspecified
Molecular Weight	

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