Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

1,3,5-Triazine-2,4,6-triamine (melamine)

Evaluation statement

30 May 2022

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AICIS evaluation statement

Subject of the evaluation

1,3,5-Triazine-2,4,6-triamine (melamine)

Chemical in this evaluation

Name	CAS registry number
1,3,5-Triazine-2,4,6-triamine	108-78-1

Reason for the evaluation

New information has become available about risks to human health and environment.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health and environment risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

The chemical has reported use in Australia in adhesives and construction materials with an introduction volume between 10 000 and 99 999 tonnes.

Based on international use data the chemical is predominantly used in the manufacture of synthetic resins with formaldehyde. These resins have a wide range of industrial uses including food packaging and tableware. The chemical also has commercial use including as an additive flame retardant (in foam products) and fertiliser and domestic use in paints, coatings, inks, solid cleaning products and laundry detergent pods. Internationally, the chemical is produced in high volumes with over 1 million tonnes manufactured globally.

Human health

Summary of health hazards

The critical health effects for risk characterisation include potential systemic long term effects and carcinogenicity following repeated oral exposure.

The available data suggest that the chemical is readily absorbed in the gastrointestinal tract and is excreted mainly unchanged in urine. The chemical can also transfer to the foetus via the placenta and to pups via breast milk.

Based on the available data, the chemical has low acute toxicity via the oral, dermal and inhalational routes. It is not an irritant to the skin or eye and is not a skin sensitiser.

The urinary tract system, specifically the kidney and the urinary bladder, are the main targets of melamine toxicity following repeated oral exposure. Significant adverse effects documented following repeated oral exposure to melamine in experimental animals include calculus formation in the urinary bladder of male rats, formation of kidney stones, inflammation, renal lesions, transitional cell hyperplasia and dysplasia, tubule dilation and necrosis. The adverse effects of melamine in the urinary tract are dose dependent. Male rats are more susceptible than female rats and mice (both sexes). A value has not been established for the no observed adverse effect level (NOAEL) due to the nephrotoxic effects observed at the lowest concentrations tested. The lowest observed adverse effect level (LOAEL) values of 72 and 84 mg/kg bw/day were in reported for male and female rats, respectively, in 13 week studies conducted by National Toxic Program (NTP) (1983). The kidney stones were composed of melamine and uric acid in equal molar ratios as primary components (61–81%) in one study.

An extensive number of observational studies on melamine toxicity following the milk adulterating incident in China showed similar observations in infants to those in animals exposed to melamine. The main adverse effect in these studies was formation of stones in the urinary tract, predominantly in the kidney (mostly renal pelvis and calyx), and to a lesser extent in in the ureter or the bladder. Other findings included renal lesions, inflammation, dysuria, haematuria, proteinuria, and “sand-like” precipitates in the urine, and in some cases acute obstructive renal failure and mortality. Some studies suggested a correlation between urinary melamine and adverse effects on the urinary tract (contribution to common calcium urolithiasis, impaired renal function) at low dose exposure in human. It is noted that these studies have limitations and given that the effects seen at low doses were similar to those observed in high doses, the low dose effects of melamine are uncertain.

Based on the available data, the chemical is not considered to be genotoxic. Negative results were reported from in vitro bacterial reverse mutation, in vivo micronucleus and chromosomal aberration tests.

In multiple carcinogenicity studies in rats, bladder tumours or papillomas were observed at doses ranging between 263–1090 mg/kg bw/day. Acute and chronic inflammation and hyperplasia of the bladder was reported in animals at doses ≥100 mg/kg bw/day. These studies show a strong correlation between the incidence of calculi and neoplastic incidence in the urinary bladder. Effects were predominantly observed in male rats. The mode of action for melamine associated cancer is thought to be through a non-genotoxic threshold mechanism. It was postulated that the formation of urinary crystals or calculi produces persistent irritation/inflammation and consequently transitional cell epithelium proliferation and urinary tract tumours.

Furthermore, simultaneous administration of melamine and sodium chloride (NaCl) suppresses the formation of calculi and reduces the incidence of bladder tumours in rats. This can be attributable to polyuria induced by NaCl supplementation, which facilitates microcrystal excretion and prevents the formation of larger calculi, and consequently inhibits tumour formation.

In an extended one generation reproductive toxicity study there were histopathological changes to the testes and epididymis and effects on sperm parameters. There were no effects on fertility. The chemical is not expected to cause specific adverse effects on development and neurodevelopment.

Health hazard classification

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Specific Target Organ Toxicity Repeated exposure	STOT Rep. Exp. 1	H372: Causes damage to organs (urinary tract) through prolonged or repeated exposure
Carcinogenicity	Carc. 2	H351: Suspected of causing cancer

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemical:

- by direct skin contact during use of domestic products
- by incidental skin and eye contact with the chemical during use of domestic products.

Due to the negligible vapour pressure of melamine, inhalation exposure to melamine in consumer products is expected to be negligible. Provided normal precautions during use of the chemical are exercised, public exposure from incidental contact during infrequent use of paints and sealants is not likely to pose a risk to the public.

The chemical may be released from various products, including food contact materials and foam products, due to its migration to the surface or via matrix decomposition, aging or mechanical action.

Based on an analysis of several reviews of the risks from migration of melamine from food contact materials this route of exposure is unlikely to pose a risk to the public. All estimates of migration to food resulted in exposures below the 0.2 mg/kg bw/day tolerable daily intake (TDI) derived by the World Health Organisation.

Limited data are available regarding human exposure to melamine in the indoor environment. Internationally, a potential risk for children has also been identified from prolonged contact with foam based products. Dust originating from indoor environments (e.g. houses, offices, stores) are considered as a major source of human exposure to flame retardants. Limited available data indicate that exposure to dust would be below the established TDI level. If additional information becomes available to better characterise exposure and risk, a further evaluation would be required.

The chemical is a persistent and highly mobile contaminant in the environment and; therefore, may contaminate drinking water supplies (see **Environmental exposure** section). However, international monitoring data shows that secondary exposure to melamine through drinking water is low.

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long term health effects, the chemical could pose a risk to workers.

Control measures to minimise dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing any risks** section).

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data the chemical is:

- Persistent (P)
- Not bioaccumulative (not B)
- Not toxic (not T).

Environmental hazard classification

Based on the ecotoxicological data presented in this evaluation, melamine is not expected to be harmful to aquatic organisms. Therefore, the chemical does not satisfy the criteria for classification for acute or chronic aquatic hazard under the Globally Harmonised System of Classification and Labelling of Chemicals (UNECE 2017).

Summary of environmental risk

Melamine is present in a range of industrial and household products worldwide and is likely to have similar industrial and consumer uses within Australia. The substance is expected to be released to wastewater and soil as a result of its use.

Melamine is a persistent and highly mobile contaminant in the environment. Measured concentrations in surface waters are many orders of magnitude below levels of concern, even in industrialised and highly disturbed water bodies. Concentrations in Australian waters are expected to be much lower. Available evidence indicates that melamine may have endocrine activity, but there is no strong evidence suggesting this activity translates into adverse effects in environmental organisms.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this Evaluation Statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from oral exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using this hazardous chemical depend on the physical form and how the chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

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. Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The conclusions of this evaluation are based on the information described in this Evaluation Statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health and environment risks can be managed within existing risk management frameworks. This is provided that all requirements are met under

environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act* 2019 apply.

Supporting information

Rationale

This evaluation considers the human health and environmental risks associated with the industrial uses of melamine. The chemical is used as a synthetic intermediate in the preparation of a wide range of other chemical products, as a flame retardant in polymeric materials and a plasticiser in concrete.

The chemical is used in very high volumes internationally. Over 1 million tonnes of melamine are produced globally per annum.

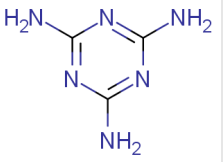
The environment evaluation selection analysis (ESA) found that melamine is potentially of concern to the environment based on its persistent characteristics, and possible endocrine effects. Known industrial uses for the chemical may lead to its release into aquatic and terrestrial environment. Melamine is routinely detected in sewage sludge and the treated effluents produced by sewage treatment plants (STPs). The substance may be released to soil due to its use as a fertiliser or by migration from melamine consumer articles to dust particles.

The human health evaluation selection analysis (ESA) identified new information on the carcinogenicity of the chemical and international activity relating to the risks of the chemical from migration of melamine from articles.

This evaluation will assess:

- the potential for emissions to the aquatic environment in Australia and whether risk reduction measures are required for industrial uses of the chemical
- the risks to workers and public from the introduction and use of the chemical including risks from the migration of the chemical from articles.

Chemical identity

Chemical name	1,3,5-Triazine-2,4,6-triamine
CAS No.	108-78-1
Synonyms	melamine cyanurotriamide cyanuramide
Structural formula	
Molecular formula	C3H6N6
Molecular weight (g/mol)	126.12

SMILES	C1(=NC(=NC(=N1)N)N)N
Chemical description	-

Relevant physical and chemical properties

Measured physical and chemical property data for melamine were retrieved from the registration dossier for the chemical submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the European Union (EU), the EPI Suite experimental database and the relevant scientific literature (Haynes, 2016; REACH; US EPA 2017). Calculated values were estimated using EPI Suite (US EPA 2017).

Physical form	Colourless to white monoclinic crystals or prisms or white powder
Melting point	>300 ºC
Boiling point	No boiling point; decomposes and sublimes at temperatures close to and above the melting temperature
Vapour pressure	1.19 x 10^{-5} Pa at 25 °C
Water solubility	3.48 g/L at 20 °C
Henry's law constant	1.84 x 10^{-14} atm-m^3/mol at 25 °C
Ionisable in the environment?	Yes
pKa	5.39 ± 0.10 at 25 °C [pK_{a1} = 2.6, pK_{a2} = 6.7]
log K_{ow}	-1.37

The first acid dissociation constant (pK_{a1}) for melamine indicates it will be partially ionised in environmental waters where the pH is generally in the range of 4–9.

The logarithmic octanol-water partition coefficient (log K_{OW}) for melamine indicates a low lipophilicity and the chemical will remain in the water compartment following release to surface waters.

Introduction and use

Australia

The chemical was previously reported as being introduced into Australia in the range 10 000 to 99 999 tonnes with the following uses (NICNAS 2006a):

- adhesives: binding agents
- construction material additives.

The chemical has been identified as migrating from bamboo cups exported from Australia.

International

The following international uses have been identified through the:

- European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossier
- Galleria Chemica
- Substances in Preparations in Nordic Countries (SPIN) database
- European Food Safety Authority (EFSA)
- European Chemicals Agency (ECHA) Annex VI, Part 2 – Proposal for Harmonised Classification and Labelling CLH report (ECHA 2019)
- International Agency for Research on Cancer (IARC) Monographs – Volume 119 (IARC 2019)
- Updated Draft Screening Assessment of Certain Organic Flame Retardants Substance Grouping 1,3,5-Triazine-2,4,6-triamine (Melamine) (Government of Canada 2020).

The chemical is predominantly used in the manufacture of synthetic resins with formaldehyde. These have a number of industrial uses including in:

- decorative laminates
- adhesive resin in wood panels, furniture and floorings
- thermally fused melamine paper and shelves
- tableware
- whiteboards and flakeboards
- food packaging.

The chemical also has site limited use in the manufacture of other chemicals such as melamine cyanurate, melamine phosphate, melamine polyphosphate, and melamine pyrophosphate.

The chemical has reported commercial uses, including:

- as an additive flame retardant for polymeric materials, especially polyurethane foams
- as an additive in rubber
- in paints, coatings and inks
- in sealants
- in filters and adhesives
- as a fertiliser
- as a plasticiser in concrete and automobile brake tubes and hoses.

Some of these commercial uses may also have consumer use applications. No consumer uses are registered under REACH; however, consumers uses of paints, coatings and inks were reported under the US Chemical Data Reporting (CDR) under the *Toxic Substances Control Act* (US EPA 2016). The chemical was reported to be used in cleaning pads and sponges and laundry detergent pods in a North American consumer product database (DeLima Associates). Use in paints (concentration 13%) and sealants (concentration 60%) was reported in Canada (Government of Canada 2020). In North America, the chemical was reported as being present in foam seating and bedding at concentrations of up to 29% and in foam based furniture at concentrations of up to 34% by weight (Government of Canada 2020).

The chemical has been used illegally to increase the nitrogen content in foods and animal feeds.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical. There are no restrictions or maximum levels for melamine outlined in the Food Standards Code.

Workers

The chemical is not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (Safe Work Australia).

Environment

The use of melamine is not subject to any specific national environmental regulations.

International regulatory status

Exposure standards

No specific exposure standards were identified.

United Nations

The chemical is not currently identified as Persistent Organic Pollutants (UNEP 2001), ozone depleting substances (UNEP 1987), or hazardous substances for the purpose of international trade (UNEP & FAO 1998).

OECD

The chemical was sponsored by Austria for assessment under the 8th Screening Information Dataset (SIDS) Initial Assessment Meeting (SIAM 8). The SIDS Initial Assessment Report (SIAR) concluded that melamine is a low potential risk and low priority for further work (OECD 1998).

Canada

An updated draft screening assessment proposes to conclude that melamine is harmful to human health under *Section 64 of the Canadian Environmental Protection Act (CEPA) 1999* because it is entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. The exposure source of concern, identified in the updated draft screening assessment, is dermal exposure

to melamine from products made with polyurethane foam (PUF), a type of polymeric foam. Specifically, the potential concern is for children who have prolonged skin contact with certain manufactured products made from PUF that contains melamine (Government of Canada 2020).

European Union

Listed in the *List of Authorised Substances: Annex I, Plastics Food Contact Regulation 10/2011/EU* with a specific migration limit of 2.5 kg/kg (Chemwatch).

EFSA established a TDI of 0.2 mg/kg body weight for melamine (EFSA 2010).

Melamine is currently being examined under the public activities coordination tool (PACT) (ECHA 2022a). The chemical is listed on ECHA's persistence, bioaccumulation and toxicity (PBT) assessment list for investigation into the chemicals PBT or vP/vB properties (ECHA 2022b).

United States of America

US FDA Indirect Food Additives: Adhesives and Components of Coatings - Substances for Use Only as Components of Adhesives – Adhesives (Chemwatch).

Asia

China GB 9685-2016 *National Food Safety Standard: Standard for the Use of Additives in Food Contact Materials and Articles* - A1: permitted additives for plastic food contact materials and articles (Chinese) (Chemwatch).

China GB 9685-2016 *National Food Safety Standard: Standard for the Use of Additives in Food Contact Materials and Articles* - A5: permitted additives for adhesives for food contact use (Chinese) Legs & Regs (Chemwatch).

China GB 9685-2016 *National Food Safety Standard: Standard for the Use of Additives in Food Contact Materials and Articles* - A6: permitted additives for paper and board for food contact use (Chinese)Legs & Regs (Chemwatch).

Other

Many countries have introduced limits for melamine in infant formula (1 mg/kg) and other foods (2.5 mg/kg) (FSANZ 2008; WHO 2009a).

Human exposure

Public

The public may be exposed to melamine in food as a result of uses in food contact materials, including articles made of melamine-formaldehyde plastics, can coatings, paper and board and adhesives.

Estimates of daily exposure to melamine are:

- 13 µg/kg bw/day from the migration from tableware products such as cups, bowls, plates, or utensils (WHO 2009a)
- <0.35 µg/kg bw/day from the migration from melamine-containing adhesives
- 0.0019 µg/kg bw/day from the migration from melamine-containing paper and paperboard
- 30–80 µg/kg bw/day (mean) 50–120 µg/kg bw/day (95th percentile) from the migration from tableware (children aged 1–2 years and 3–6 years, typical migration levels) (EFSA 2010)
- 40–110 µg/kg bw/day (mean), 70–230 µg/kg bw/day (95th percentile) from the migration from tableware (children aged 1–2 years and 3–6 years, high migration levels) (EFSA 2010)
- 34 µg/kg bw/day from the migration from coatings on metal cans and closures (infants aged 6 months) (EFSA 2010)
- 92 µg/kg bw/day from the migration from coatings on metal cans and closures (children aged 1.5 years) (EFSA 2010)
- 25 µg/kg bw/day from the migration from coatings on metal cans and closures (adults) (EFSA 2010).

The estimates are based on conservative scenarios (EFSA 2010). The public could also be exposed to the chemical through use of domestic products such as paints and sealants and due to migration from the chemical from other consumer products such as foam products. Due to the negligible vapour pressure of melamine, inhalation exposure to melamine in consumer products is expected to be negligible.

Exposure may occur from prolonged contact with foam mattresses and furniture. Oral exposure in infants mouthing foam could also occur. Estimates of dermal exposure to melamine via prolonged dermal contact with foam mattresses or furniture were 0.02 to 0.36 mg/kg bw/day and 0.08 to 1.02 mg/kg bw/day in adults, and infants, respectively (Government of Canada 2020). The estimates of oral exposure to melamine via mouthing of a foam object are 0.00051 to 0.0118 mg/kg bw/day for infants and 0.0049 to 0.0114 mg/kg bw/day for toddlers. The chemical has also been detected in human breast milk. The daily intake estimates in infants (0 to 6 months) to melamine presence in breast milk are 0.0027 and 0.0076 mg/kg bw/day for mean and maximum concentrations, respectively (Government of Canada 2020).

The chemical has been detected in dust in indoor environments. From an analysis of samples 12 countries (not including Australia) reported a global median concentrations of 1800 ng/g and maximum of 17000 ng/g. The median EDIs of MEL were in the ranges of 1.04–34.3, 1.37−80.0, 0.448−18.8, 0.245−9.38, and 0.206−7.50 ng/kg bw/day for infants, toddlers, children, teenagers, and adults, respectively, for the 12 countries studied (Zhu and Kannan 2018). In another study analysing dust from childcare centres in the USA reported mean and max concentrations were 6920 and 66000 ng/g respectively. Estimated daily intake from combined dust ingestion and dermal absorption was 67.4 ng/kg/day (95th percentile) (Zheng et al. 2020).

Health hazard information

Toxicokinetics

Melamine has a low molecular weight (126.12 g/mol) with low log K_{ow} value (-1.37). Therefore, it is expected to be readily absorbed following oral administration.

Toxicokinetic studies in rats, monkeys, pigs, sheep and humans demonstrate that the chemical is readily absorbed from the gastrointestinal tract and is excreted mainly unchanged in urine. The chemical can also transfer to the foetus via the placenta and to pups via breast milk.

Absorption

The chemical was rapidly absorbed from the gastrointestinal tract in rats following a single dose via oral gavage. The peak plasma concentration of the chemical was reached within 1–2 hours. In monkeys, maximum concentration was reached within 2.6 hours with plasma half life of 4.41 hour. Structurally similar compounds show only maximum dermal absorptions of 10–16% in human skin (Government of Canada 2016).

Distribution

Several animal studies (rat, monkey, pig and sheep) suggest that the chemical is distributed via blood or extracellular fluid to most tissues including kidney, liver, stomach, spleen, heart, uterus, ovaries, testes, brain, bladder and lungs. In one oral study in rats, radiolabelled melamine was found in liver, kidney and bladder at different time points (0.5–96 hour) with highest concentrations detected in the kidney and the urinary bladder (ECHA 2019; IARC 2019).

Placental transfer of melamine and distribution in the foetus was reported in rat studies. The chemical passed the placental barrier in a dose dependent manner when administered at daily doses of 40 or 400 mg/kg bw/day by gavage on days 13–20 of gestation in pregnant female F344 rats. In another study, pregnant (days 16–18 of gestation) and lactating Sprague Dawley (SD) rats were treated with a single oral dose of 21.4 mg/kg bw by gavage. Within 0.5 hours of administration 80% of the chemical was found in dam's serum. Peak levels in foetuses (ca. 30%) were reached after 2 hours and in amniotic fluid (ca. 20%) after 3 hours of maternal intake. Peak concentration (ca. 40%) was found in breast milk in lactating animals after 3 hours of oral intake. In an in vitro human placental perfusion study, 34–45% of the dose tested (10 µM or 1 mM) was transferred to foetal circulation through the placenta by mechanisms independent of efflux transporters (ECHA 2019; IARC 2019).

Metabolism

Animal studies demonstrate that the chemical is not metabolised in mammalian tissues. While no specific toxicokinetic studies in humans are available, the unmetabolised chemical was detected in urine of paediatric patients exposed to melamine tainted milk products. The chemical may be metabolised to several compounds including cyanuric acid by bacteria. However, metabolism of melamine via gut microbial activity has not been established in humans (ECHA 2019; IARC 2019).

Elimination

Urinary excretion is the main route of elimination in animals and humans although excretion in faeces may increase at higher doses. After administration of a single oral dose of approximately 1.3 mg [^{14}C]-melamine to adult male Fischer 344 (F344)/N rats, 90% of the administered dose was excreted in the urine within the first 24 hours. After administration of a single oral dose of 1000 mg/kg bw/day to SD rats, 61% and 25% of the administered dose was excreted in the first 24 hours in the faeces and urine, respectively. Very low levels of melamine were detectable in plasma, urine, and faeces on day 7 after dosing. In a randomised crossover human study (migration from melamine resin plastic bowls), an

estimated urinary elimination half-life was reported to be ~6 hours following low dose melamine exposure (ECHA 2019; IARC 2019).

Acute toxicity

Oral

Based on the available data, the chemical has low acute toxicity following oral exposure.

In an acute oral toxicity study in F344 rats (5/sex/dose), the reported median lethal doses (LD50) were 3161 and 3828 mg/kg bw for males and females, respectively. No details on sub-lethal effects were reported (NTP 1983; REACH).

In an acute oral toxicity study in B6C3F1 mice (5/sex/dose), the reported median lethal doses (LD50) were 3297 and 7014 mg/kg bw for males and females, respectively. No details on sub-lethal effects were reported (NTP 1983; REACH).

Dermal

Based on the limited available data, the chemical has low acute toxicity following dermal exposure.

The reported LD50 in rabbits is >1000 mg/kg bw. No details on sub-lethal effects were available (REACH).

Inhalation

Based on the available data, the chemical has low acute toxicity following acute inhalation exposure.

In a Good Laboratory Practice (GLP) compliant acute inhalation toxicity study conducted in accordance with Organisation for Economic Co-operation and Development (OECD) TG 403, Wistar rats (5/sex/dose) were exposed to the chemical as an aerosol (nose only) for 4 hours at 5.19 g/m³ concentration. The mass median aerodynamic diameter was 6.6 µm. The reported median lethal concentration (LC50) was >5.19 g/m³ for both sexes. Sub-lethal effects included changes in breathing pattern and eye lid twitching (REACH).

The chemical also has a reported LC50 in rats of 3248 mg/m³. No further details are available (REACH).

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is not considered to be a skin irritant.

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, New Zealand White (NZW) rabbits (n=6) were treated with the chemical for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48 and 72 hours after patch removal. No skin irritation was observed in the study (mean primary dermal irritation index=0) (REACH).

In 2 non-guideline skin irritation studies, application of the chemical at up to 50% in water to shaved skin of rabbits resulted in no irritation. Observation period was up to 14 days (NCBI 2001; REACH). No further details of the studies are available.

Eye irritation

Based on the limited data available, the chemical is not expected to be an eye irritant.

In a non-guideline eye irritation study, the chemical was applied undiluted or as a 10% suspension in 0.5% methyl cellulose solution to one eye of rabbits (3/dose). Mild irritation was observed for undiluted chemical, and the effect was fully reversible after 24 hours. No other irritation scores were reported (NCBI 2001; REACH).

In a non-guideline eye irritation study, the chemical was instilled into one eye of Vienna White rabbits (n=2). Observations were recorded at 1, 24 hours and 8 days after the application. Slight redness (conjunctivae score = 1) was observed, and the effect was fully reversible after 24 hours (REACH).

In another non-guideline study, the chemical (500 mg) was reported to cause slight irritation at 24 hours in rabbits (REACH). No further details are available.

Sensitisation

Skin sensitisation

Based on the available data, the chemical is not considered to be a skin sensitiser.

In a GLP compliant guinea pig maximisation test (GPMT) conducted according to OECD TG 406, epicutaneous inductions were performed on day 1 and 7 using the chemical at 50% in petrolatum. Challenge with the chemical at 50% in petrolatum resulted in no skin reactions in any of the animals (REACH).

Observation in humans

In a human patch test, positive reactions were observed in 1 out of 208 human subjects treated with the chemical. The chemical was considered to be a non-sensitiser (REACH). No further details are available for this study.

Repeat dose toxicity

Significant adverse health effects have been observed in the urinary tract system of humans orally exposed to melamine and in multiple guideline and non-guideline studies in rats, mice, monkeys and other animals. Hazard classification is warranted.

Oral

Rats

In two 13 week sub-chronic repeated dose studies similar to OECD TG 408, F344 rats (12/sex/dose) were administered the chemical in the diet at concentrations of 750–18000 ppm (equivalent to ~72–1700 mg/kg bw/day for males; and ~84–1600 mg/kg bw/day for females), 7 days/week for 13 weeks. Urinary bladder stones were observed in a dose

dependent manner in all males tested and in females at doses of ≥1400 mg/kg bw/day. Hyperplasia of the transitional epithelium of the bladder was only observed in males and at doses ≥300 mg/kg bw/day. However, calcareous deposits were observed in the proximal renal tubules of all females tested in a dose dependent manner. The lowest observed adverse effect level (LOAEL) established from these studies were 72 and 84 mg/kg bw/day for male (urinary bladder stones) and female (calcareous renal deposits) rats, respectively (NTP 1983; ECHA 2019).

In a 13 week sub-chronic study, acidification of urine (by the addition of 1% NH_4Cl in drinking water) did not affect bladder stone formation in rats fed high doses of melamine (NTP 1983, ECHA 2019; IARC 2019).

Histopathological re-evaluation of the studies described above revealed a range of kidney injuries including tubule dilation and tubule basophilia. The incidence and severity of these injuries were higher in males than females (Hard et al. 2009).

In a GLP-compliant sub-acute repeated dose study similar to OECD TG 407, SD rats (6/sex/dose) were administered the chemical (99% purity) by gavage at 140, 700 and 1400 (lowered to 1000 due to mortality) mg/kg bw/day for 14 consecutive days. Slight crystal depositions in the papillary renal area were observed in 33% of females at 140 mg/kg bw/day dose. No other treatment related effects were observed at the low dose. Severe renal pathologies including dilation of distal nephron tubule, degeneration and necrosis of tubular epithelium, and regeneration of the tubular epithelium were reported in addition to reduced renal function (increased blood serum urea and creatinine) and crystal depositions in both sexes at 700 mg/kg bw/day. In addition to the kidney injuries, pathophysiological effects in the heart and immune system and high mortality were observed at 1000 and 1400 mg/kg bw/day. Although the original study reported a no observed adverse effect level (NOAEL) of 140 mg/kg bw/day (Early et al. 2013), nephrotoxic effects (crystals) were observed in the kidney of female rats at this concentration. Renal crystal formation is regarded as initial key event in the mode of action culminating in severe epithelial damages and cancer (ECHA 2019).

In a non-guideline repeated dose toxicity study, male F344 rats (20/dose) received melamine in the diet at concentrations of 3000, 10000, or 30000 ppm (equivalent to ~100, 330 or 1090 mg/kg bw/day) for 36 weeks followed by 4 weeks with basal diet. The effects of melamine administration included dose-related incidences of calculi in urinary bladder (≥100 mg/kg bw/day), renal pelvis (≥330 mg/kg bw/day) and ureters (1090 mg/kg bw/day), as well as inflammation, fibrosis, necrosis, degeneration and regeneration of renal tubules, and transitional cell hyperplasia (ECHA 2019; Okumura et al. 1992).

In a non-guideline study designed to examine the effect of urine volume on urinary bladder stone formation, male F344 rats were fed a diet containing 1 or 3% melamine (approximately 350–1030 mg/kg bw/day) or 1 or 3% melamine supplemented with 5 or 10% NaCl for 36 weeks. The study period was followed by 4 weeks with basal diet. Following exposure to melamine without NaCl supplementation calculi in the urinary bladder and histopathological findings in the kidney were observed at all doses. Co-administration of NaCl (5 or 10%) with melamine suppressed calculus formation and histopathological findings in the low dose group (350 mg/kg bw/day). Examination of the calculi showed that melamine and uric acid in equal molar ratios as primary components (61–81%) (ECHA 2019; Ogasawara et al. 1995).

In several non-guideline repeated dose toxicity studies ranging from 5–28 days, renal crystal formation, tubular dilatation and necrosis, inflammation, transitional cell hyperplasia and pale and pitted kidneys were observed in rats administered the chemical by gavage or in feed at

doses ≥100 mg/kg bw/day in a dose dependent manner. One study reported differential regulation of marker genes associated with kidney injuries (ECHA 2019).

Additional 3 non-guideline 14-day repeated dose toxicity studies supported melamine related toxicity in the urinary system, mainly the kidney and bladder (ECHA 2019; IARC 2019).

Mice

In a 13 week sub-chronic repeated dose study similar to OECD TG 408, B6C3F1 mice (10/sex/dose) were administered the chemical in the diet at concentrations of 6000–18000 ppm (equivalent to ~1400–4700 for mg/kg bw/day male; and ~1800–5900 mg/kg bw/day for females), 7 days/week for 13 weeks. Dose dependent urinary stone and other adverse urinary tract effects were observed at concentrations ≥2800 mg/kg bw/day (NTP 1983; ECHA 2019). The incidence and severity of retrograde nephropathy and scarring of the kidney was lower in mice compared to rats (Hard et al. 2009).

In a chronic combined repeated dose and carcinogenicity study similar to OECD TG 451, B6C3F1 mice (50/sex/dose) were administered the chemical in the diet at concentrations of 2250 or 4500 ppm for males (equivalent to ~327 or 688 mg/kg bw/day for male; and ~523 or 1065 mg/kg bw/day for female), 7 days/week for 103 weeks. A high incidence of urinary stone formation associated with acute/chronic inflammation and mild epithelial hyperplasia was reported in males at both doses (40/47 at 327 and 41/44 at 688 mg/kg bw/day) and to a lesser extent in females at high dose (4/50 at 1065 mg/kg bw/day) (ECHA 2019; IARC 2019; NTP 1983).

Other animals

In a GLP compliant sub-chronic repeated dose study similar to OECD TG 409, cynomolgus monkeys (3/sex/dose) were administered the chemical (99% purity) by nasal-gastric gavage at 60, 200, and 700 mg/kg bw/day for 91 days followed by 28 days recovery. No treatment related histopathological findings were reported at 60 mg/kg bw/day. Nephrotoxicity was reported in 2 out of 3 males at 200 mg/kg bw/day, while kidney hypertrophy, renal tubular degeneration, regeneration, tubular dilatation and necrosis was reported in all animals at the highest dose. The nephrotoxicity effects were not reversible after 28 days. Some effects on other organs including the heart, bone marrow, spleen, thymus, liver and adrenals were also observed. The NOAEL was determined to be 60 mg/kg bw/day for the chemical based on the effects on the kidney (ECHA 2019).

Mixed results were reported in studies using different species of pigs. No signs of nephrotoxicity were found in two different studies where the animals were treated orally with the chemical at concentrations of 200 or 400 mg/kg bw/day for 3–28 days. Small numbers of crystals were found in the kidney of 1 of 2 weanling cross-bred barrow when orally administered 200 mg/kg bw/day for 7 days. Mass spectral analysis revealed that the crystals were composed of melamine and cyanuric acid at an approximately equal molar ratio (ECHA 2019; IARC 2019).

Nephrotoxicity, as well as accumulation of renal crystals in some cases, has also been observed after exposure to melamine in other species, including sheep, broiler chickens, and Jinding laying ducks. In contrast, cats (up to 181 mg/kg bw/day in feed for 11 days), and fish treated with melamine showed no signs of nephrotoxicity under the experimental conditions used (IARC 2019).

Observation in humans

In a milk adulteration incident in China, approximately 300000 infants were adversely affected by melamine-containing formula resulting in 50000 hospitalisations and 6 confirmed deaths. Based on the reported mean (1212 mg/kg) and maximum (4700 mg/kg) concentrations of melamine found in 111 samples of infant formula, the estimated daily intake was 8.6–110.2 mg/kg bw/day depending on the age of the children (WHO 2009a). The main adverse effect in the studies was formation of stones in the urinary tract, predominantly in the kidney (mostly renal pelvis and calyx) and to a less extent in in the ureter or the bladder. Other reported effects included renal lesions, inflammation, dysuria, haematuria, proteinuria, and passage of “sand-like” precipitates in the urine, and in some cases acute obstructive renal failure and death. The incidence of kidney stones and kidney swelling were ~3 times higher in male infants compared to female infants (age group <1 year). The kidney stones had variable proportions of melamine (0.2–339 mg/g) with 8 of the 10 stones consisting of the crystal forms of urate. The kidney stones and renal abnormalities persisted in 8–10% of the cases. The available data show strong correlation between urinary melamine and its adverse effects on the urinary tract following melamine exposure (ECHA 2019; IARC 2019).

Some studies suggested a correlation between urinary melamine and adverse effects on the urinary tract (contribution to common calcium urolithiasis, impaired renal function) at low-dose exposure in human. However, these low-dose effects cannot be fully established as there are major limitations concerning the relevance and validity of the data (ECHA 2019).

Genotoxicity

Based on the available data, the chemical is not considered to be genotoxic.

In vitro

Negative results were reported in the following in vitro genotoxicity studies (ECHA 2019):

- Two bacterial reverse mutation assays (OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, with and without metabolic activation (S9) at concentrations of 0–5550 µg/plate.
- A bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 and *Escherichia coli* WP2 uvrA, with and without metabolic activation (S9) at concentrations of 0–500 µg/plate.
- A chromosome aberration study (OECD TG 473) in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations 0–300 µg/mL.
- A mammalian cell gene mutation study (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (Hprt) locus in CHO cells with and without metabolic activation at concentrations up to 1000 µg/mL.
- A mammalian gene mutation assay (OECD TG 490) in mouse lymphoma L5178Y cells with and without metabolic activation at concentrations 0–160 µg/mL.

In vivo

In a GLP compliant mammalian erythrocyte micronucleus test similar to OECD TG 474, CD1 mice (4/sex/dose) were administered the chemical by gavage at single doses of 0 and 1000 mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity (ECHA 2019).

In a non-GLP compliant mammalian erythrocyte micronucleus test similar to OECD TG 474, male B6C3F1 mice (5/dose) were treated with the chemical by intraperitoneal injection at single doses of 0, 500, 1000 and 2000 mg/kg bw/day. The incidence of micronuclei in bone marrow and peripheral blood polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity (ECHA 2019).

In a non-GLP compliant mammalian bone marrow chromosomal aberration test similar to OECD TG 475, male B6C3F1 mice (8/dose) were administered the chemical by a single IP injection at doses of 0, 150, 300 and 600 mg/kg bw. The incidence of chromosome aberrations in bone marrow increased in the mid dose group; however, did not increase in the low and high dose groups. Therefore, the chemical was reported non-clastogenic under the test conditions (ECHA 2019).

Carcinogenicity

Based on the weight of evidence of available data, the chemical is suspected to be a carcinogen, warranting hazard classification. This is based on the evidence of benign and malignant tumours in the urinary bladder of male rats through a non-genotoxic mode of action secondary to the formation of calculi. An analysis of the various key events related to melamine mediated carcinogenesis concluded that although species specific anatomical and physiological factors may play a role regarding the response to calculus formation, species independent key events, common to both rodents and humans, can be clearly identified (ECHA 2019).

The IARC concluded that the chemical is possibly carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals for the carcinogenicity of melamine and inadequate evidence in humans for the carcinogenicity of melamine (IARC 2019).

Oral

In a chronic combined repeated dose and carcinogenicity study similar to OECD TG 451, F344 rats (50/sex/dose) were administered the chemical in the diet at concentrations of 2250 or 4500 ppm for males (equivalent to ~126 or 263 mg/kg bw/day) and 4500 or 9000 ppm for females (equivalent to ~262 or 542 mg/kg bw/day), 7 days/week for 103 weeks. The incidence of urinary bladder stones and transitional cell carcinomas were significantly increased in male rats receiving the high dose. Other observations at highest dose included transitional cell papillomas and hyperplasia. Urinary bladder stones and transitional epithelial cell hyperplasia were also observed in 1/50 males receiving the low dose. There was a statistically significant correlation ($p<0.001$) between bladder stones and the occurrence of transitional cell carcinomas at the high dose. Out of 10 male rats with stones, 8 (16%) had transitional cell carcinomas. No carcinomas were observed in the kidneys of female rats; however, the incidence of chronic inflammation was significantly increased in females; 34% at low dose and 82% at high dose (NTP 1983; ECHA 2019). A histopathological re-evaluation revealed dose dependent incidence of fibrotic scarring associated with dilatation and hyperplasia in the inner medulla, and loss of tubules and atrophy in both sexes, although female rats were more affected (Hard et al. 2009).

In a GLP compliant chronic combined repeated dose and carcinogenicity study similar to OECD TG 451, F344 rats (65/sex/dose) were administered the chemical in the diet at concentrations of 100, 500 or 1000 ppm (equivalent to ~4, 20 and 40 mg/kg bw/day) for males and 100, 1000 or 5000 ppm (equivalent to ~5, 50 and 80 mg/kg bw/day) for females. No urinary bladder calculi or significant adverse effects were reported. However, an increased incidence of preneoplastic transitional epithelial cell hyperplasia was reported in male rats at the highest concentration (ECHA 2019).

In a non-GLP compliant carcinogenicity study conducted similar to OECD TG 451, albino rats (10/sex/dose) received the chemical in diet at concentrations of 1000 or 10000 ppm (equivalent to ~30 and 350 mg/kg bw/day for males; and ~40 and 470 mg/kg bw/day for females) for 7 days/week, 103 weeks. Sporadic calculus formation was reported at the low concentration; however, no treatment related incidence of cancerous lesions was observed at this concentration. Preneoplastic transitional cell hyperplasia were increased in males. (ECHA 2019; IARC 2019).

In a non-guideline sub-chronic repeated dose toxicity study (see **Repeated dose toxicity: oral** section), high incidences of transitional cell carcinomas, papillomas, and papillomatosis in the urinary bladder were reported in male rats administered the chemical in diet at ~1090 mg/kg bw/day) for 36 weeks. Strong correlations ($p<0.0065$) between tumour incidence and stone formation were established in these studies (ECHA 2019; Okumura et al. 1992).

In a non-guideline sub-chronic repeated dose toxicity study (see **Repeated dose toxicity: oral** section), no transitional cell carcinomas were observed at low concentration (350 mg/kg bw/day) when co-administered with NaCl (5 or 10%) or at high concentration (1030 mg/kg bw/day) co-administered with NaCl (10%). It was concluded that polyuria induced by NaCl supplementation promoted microcrystal excretion and, consequently, inhibited tumour formation. It was postulated that the proliferative lesions were due to the irritative stimulation of the calculi, and not to molecular interactions between melamine or its metabolites with the bladder epithelium (ECHA 2019; IARC 2019; Ogasawara et al. 1995).

Based on the above studies, the following dose−response relationship of melamine associated tumour formation in the urinary bladder of male rats was established by ECHA (2019).

Table 1. Dose-response relationship regarding tumour formation in the urinary bladder of male rats (ECHA 2019).

Dose (mg/kg bw/day)	Incidence of hyperplasia (# of animals examined)	Incidence of papillomas (# of animals examined)	Incidence of carcinomas (# of animals examined)	Reference
ca. 4–40	0% (0/65)	0% (0/65)	0% (0/65)	Hazleton (1983)
ca. 100	5% (1/20)	0% (0/20)	0% (0/20)	Okumura et al. (1992)
ca. 126	2% (1/50)	0% (0/50)	0% (0/50)	Melnick et al. (1984) and NTP (1983)
ca. 263	4% (2/49)	2% (1/49)	16% (8/49)	Melnick et al. (1984) and NTP (1983)
ca. 330	30% (6/20)	5% (1/20)	5% (1/20)	Okumura et al. (1992)
ca. 350	47% (9/19)*	42% (8/19)	21% (4/19)	Ogasawara et al. (1995)

Dose (mg/kg bw/day)	Incidence of hyperplasia (# of animals examined)	Incidence of papillomas (# of animals examined)	Incidence of carcinomas (# of animals examined)	Reference
ca. 1030	75% (15/20)*	50% (10/20)	90% (18/20)	Ogasawara et al. (1995)
ca. 1090	63% (12/19)	63% (12/19)	79% (15/19)	Okumura et al. (1992)

*multiple papillomatous hyperplasias

Dermal

In a non-guideline carcinogenicity study, female CD1 mice (n=20) received a single topical application of the chemical (1 µmol in 0.2 mL of acetone) on shaved back skin, followed by twice weekly applications of 10 nmol of 12-O-tetradecanoylphorbol 13-acetate in 0.2 mL of acetone for 31 weeks. No significant increases in the incidence of skin papilloma were reported in melamine treated mice (19%) when compared with controls (14%) (IARC 2019).

Observation in humans

Follow up studies were conducted in children (n<200) who developed urinary stones after exposure to melamine as a contaminant in infant milk formula (melamine content, 0.1–2500 ppm) in China. No tumours were reported in clinical examinations carried out during 4 years of observations including ultrasound screening for cancer of the urinary system. However, these data are not completely reliable due to short follow-up period and small group size (IARC 2019).

Reproductive and development toxicity

Although observed effects are not sufficient to warrant classification, potential adverse effects of the chemical on sexual function following repeated oral exposure cannot be excluded.

In a GLP compliant extended one generation reproductive toxicity study conducted in accordance with OECD TG 443, Wister rats (28/sex/dose) were administered the chemical in diet at concentrations 1000, 4000 and 12500 ppm (equivalent to 65, 268 and 833 mg/kg bw/day in F0 males; 87–1124 mg/kg bw/day in F0 females; 89, 370 and 1200 mg/kg bw/day in F1 males; and 93–1227 mg/kg bw/day in F1 females) continuously daily including 2 weeks prior to mating (F0 and F1 parents). The doses were reduced by 50% for females during the lactation period to accommodate increased food intake. Offspring were weaned at day 21 and administered the chemical in diet from day 22. Treatment time of F1 animals varied from 5–19 weeks in different cohorts. Adverse kidney effects were observed in both males and females of F0 and F1 generations at concentrations 4000 and 12500 ppm.

Increases in the number of sperm cells with detached head and tubular atrophy (including degeneration, vacuolation, exfoliation and sperm retention) in testes with related minimal cellular debris in the epididymis were observed in F0 males at 12500 ppm and F1 males at 4000 ppm. Fertility of the F0 males or any of the F1 cohorts was not affected. No developmental toxicity was observed in both F1 and F2 generations. The following NOAEL values were determined from this study: parental systemic toxicity 1000 ppm (equivalent to 65 and 87 mg/kg bw/day for F0 generation males and females, 89 and 93 mg/kg bw/day for

F1 generation males and females, respectively); reproductive toxicity 4000 ppm for F0 generation (equivalent to 268 mg/kg bw/day for males) and 1000 ppm for F1 generation (equivalent to 370 mg/kg bw/day for males); developmental toxicity 12500 ppm (equivalent to 1200 and 1227 mg/kg bw/day for F1 generation males and females, respectively) (REACH).

In sub-chronic and chronic repeated dose studies in rats and mice by NTP (1983) (see **Repeated dose toxicity: oral** section for the details of these studies), no adverse effects on the reproductive organs were reported following macroscopic and microscopic investigation of mammary glands, ovaries, uterus, testes, prostate and seminal vesicle (NTP 1983).

Several non-guideline sub-acute and sub-chronic repeated dose studies reported adverse effects in the testes in male mice orally administered the chemical for 5–65 days. These include altered sperm morphology and damage to testicular DNA (412 mg/kg bw/day), effects on seminiferous tubules (sperm development, production and morphology), spermatogenic cells, testosterone synthesis, testicular enzymes and protein levels (50 mg/kg bw/day) (Government of Canada 2020).

Developmental Neurotoxicity and Immunotoxicity

Based on the available data, the chemical is not expected to cause specific adverse effects on neurodevelopment following oral exposure.

In a GLP compliant extended one generation reproductive toxicity study conducted in accordance with OECD TG 443 in Wister rats (see **Reproductive and development toxicity** section), no developmental neurotoxicity or immunotoxicity was observed in F1 generation. Based on this, the developmental neurotoxicity or immunotoxicity NOAEL was 12500 ppm (equivalent to 1200 and 1227 mg/kg bw/day for F1 generation males and females, respectively) (REACH).

Human health risk characterisation

Public risk

Food contact materials

Several reviews of the risks from migration of melamine from food contact materials have been conducted. A TDI for melamine has been established as 0.2 mg/kg bw/day (EFSA 2010; WHO 2009a).

A WHO (2009a) assessment concluded that estimates of exposure to baseline levels of melamine from all sources (up to 13 µg/kg body weight per day) were well below the TDI. It also concluded that limits for melamine in powdered infant formula (1 mg/kg) and in other foods (2.5 mg/kg) would provide a sufficient margin of safety for dietary exposure relative to the TDI.

An EFSA (2010) opinion concluded that exposure from background levels of melamine and cyanurate that can occur in food and feed from approved sources does not represent a risk to the human consumer or to animals. Exposure in children due to migration from food contact materials would be below or in the region of the TDI.

Using an oral BMDL of 35 mg/kg bw/day derived by the WHO (2009a) the Government of Canada calculated a margin of exposure of 313 for toddler exposure from use of melamine

tableware. This MOE was considered to be adequate to account for uncertainties in the exposure and health effects data (Government of Canada 2020).

A FSANZ (2008) risk assessment concluded that melamine may be detected in beverages at levels of 0.5, 0.7, 1.4 and 2.2 mg/kg in coffee, orange juice, fermented milk and lemon juice respectively. These levels originate from migration of melamine from the cup, made of melamine-formaldehyde resin, into the beverage under experimental hot and acidic conditions (95 °C for 30 min). Given the extreme use conditions used to generate these data it is considered that a level of 2.5 mg melamine/kg food would represent the upper levels likely to be legitimately found in foods.

The FDA (2008) concluded that levels of melamine and melamine related compounds below 2.5 ppm do not raise public health concerns in food other than infant formula. It noted that melamine does not migrate from melamine-formaldehyde tableware into most foods although can migrate under some conditions (acidic foods at high temperatures).

Other consumer products

Using an oral BMDL of 35 mg/kg bw/day derived by the WHO (2009a) and extrapolated migration rates, the Government of Canada estimated dermal and oral exposure to melamine from foam based products (Government of Canada 2020). Oral exposure, such as mouthing of foam based products by a child was not identified as a concern (calculated margins of exposure >2900). However, dermal exposure from prolonged contact with foam based products such as upholstered furniture mattresses, mattress toppers, and other foam based products was identified as a concern for infants, and toddlers and young individuals (up to 18 years) (calculated margins of exposure were <100 for some exposure estimates).

The MOEs derived from human biomonitoring data for 12–19 year old age group (85400) are significantly higher than the calculated dermal exposures to melamine from lying on foam containing mattresses or furniture. However, it was noted that biomonitoring data were considered insufficient to derive MOEs for age groups younger than 12 years. In addition, the MOE for biomonitoring data was based on samples collected in 2003.

Literature available providing information on levels of melamine in dust in indoor environments indicate exposure to the chemical are orders of magnitude below the established TDI (Zheng et al. 2020; Zhu and Kannan 2018).

The chemical is a persistent and highly mobile contaminant and may contaminate drinking water supplies. However, international monitoring data shows that the risk to humans via secondary exposure to melamine through drinking water is very low.

Environmental exposure

The high international production volume and widespread usage of melamine suggests the chemical is likely to be present in Australian soil and aquatic environments. Multiple monitoring studies indicate that the chemical has been detected in international water, soil and sewage. Melamine may also be present in the atmosphere through adhesion to dust and particulate matter based on its occurrence in rainwater monitoring studies (Zhu and Kannan 2020).

The predominant use of melamine is as an intermediate in the production of melamine resins, melamine based flame retardants and adhesives. The manufacture of resins may lead to localised release of the chemical to soil and release of small amounts to wastewater

through the disposal of aqueous residues or in the clean up of plant and equipment. Treatment of this wastewater in sewage treatment plants will remove a fraction of the quantity of these chemicals from influents. Depending on the efficiency of various degradation and partitioning processes, a fraction of the quantity of chemicals in wastewater entering STPs can be emitted to rivers or oceans in treated effluent, or to soil by application of biosolids to agricultural land.

Melamine may be added to fertilisers which are used to increase nitrogen content of domestic and agricultural soils to aid plant growth (Zhu et al. 2019). Melamine is highly water soluble and highly mobile in soils and may move to ground or surface waters by runoff from rainfall.

Melamine is expected to migrate from melamine resin household products to sewage and dust. Melamine resins are used to make or coat many household products, such as tableware, fabrics, laminates and furniture. Evidence indicates that under some conditions (acid pH, high heat) melamine can migrate from tableware (Lund and Petersen 2006). Monitoring data supports melamine as a common dust borne contaminant in households internationally (Zhu and Kannan 2018). This is expected to also occur in Australian households. Migration of melamine out of household products may occur during washing and subsequent discharge of wastewaters to STP which can contribute to the release of melamine to surface waters (Schreder and La Guardia 2014).

Some melamine emissions to the environment may be due to non-industrial applications. Melamine is a metabolite of some triazine pesticides which may be used in agriculture in Australia (WHO 2009b).

Environmental fate

Partitioning

Melamine partitions to surface water after release to the environment.

Melamine is not expected to volatilise to air from moist soil or surface waters based on the calculated Henry's Law constant. The chemical is highly polar and readily soluble in water. It is ionised in environmental surface waters at acidic to neutral pH. Melamine is not lipophilic with a measured log K_{OW} value of -1.37.

The chemical is highly mobile in soil based on a calculated soil adsorption coefficient (K_{OC}) of 32.28 L/kg (US EPA 2017). Highly mobile chemicals are likely to leach into groundwater or run off to surface water bodies such as lakes and rivers.

Degradation

Melamine is expected to be resistant to degradation in the environment.

The chemical has no hydrolysable functional groups and is expected to be resistant towards hydrolysis under environmental conditions (PubChem 2022).

The chemical is not expected to undergo biodegradation in water and sediment systems. In a Modified MITI Test screening test (OECD Test Guideline (TG) 301C), no degradation occurred over 28 days. A TG 302B inherent biodegradability test result of 16% in 20 days indicates that melamine is not inherently biodegradable.

Degradation of melamine studied in 2 different soil types was found to be less than 20% in a time frame of 6–28 weeks (REACH 2021).

Pure culture studies using *Pseudomonas* strain A and 3 mM of melamine indicate the degradation pathway of melamine involves the conversion of melamine to ammeline (CAS No. 645-92-1) and eventually cyanuric acid (CAS No. 108-80-5) (NCBI 2001).

Bioaccumulation

Melamine is not expected to bioaccumulate in aquatic life.

Experimentally determined and calculated bioconcentration factors (BCFs) and measured log K_{ow} values are below the domestic categorisation threshold for bioaccumulation (EPHC 2009).

A bioconcentration study (2 ppm w/v melamine) with 6 weeks exposure using European carp (*Cyprinus carpio*) reported a BCF of 0.38 L/kg (NITE 2022). Correspondingly, calculated values show a range of 0.9–3.2 L/kg wet-wt (US EPA 2017). In fish, melamine exhibits low biomagnification (Pacini et al. 2013), and relatively short depuration half lives in the range of 1–4 days (Stine et al. 2012).

Environmental transport

Melamine has properties conducive to long range transport but has not been detected in locations far from possible release sources. More information is required to determine whether the chemical exhibits long range transport behaviour.

The chemical is persistent and highly mobile in the aquatic environment and may be transported long distances in water. However, detections of melamine in remote regions have so far only been linked with discharges from local human settlements (Duarte et al. 2021).

Melamine has been detected in household dust and may be distributed by atmospheric particulates. Dust bound persistent contaminants can also exhibit long range atmospheric transport. The potential for melamine to be transported by suspended particles is supported by the detection of the chemical in precipitation (Zhu and Kannan 2020). However, the chemical has a low measured log K_{OC} coefficient, indicating it may not strongly bind to dust particles. The transport of the chemical by particle adhesion is likely to be restricted by rainfall events.

Predicted environmental concentration (PEC)

The predicted environmental concentration of melamine in the Australia is 213 µg/kg in soil and 10 µg/L in surface waters.

Australian environmental monitoring data are not available for melamine.

International monitoring studies indicate that melamine is a widespread contaminant in soils and surface waters. The chemical is released to water from STP effluent and manufacturing waste streams. Release to soil may result from release at manufacturing sites, the migration of melamine out of melamine products into dust and particulates or direct application from its use in fertiliser.

A survey of different water bodies the US A found melamine at up to 3.65 µg/L in surface waters, 2.68 µg/L in effluent wastewater, 0.181 µg/L in rain water and 0.086 µg/L in sea water (Zhu and Kannan 2020). A survey of house dust in California found melamine at concentrations of 3.16 µg/g (Shin et al. 2020).

Melamine has been detected in river water downstream from an STP, at concentrations of 10 µg/L (Liu et al. 2021). The chemical has also been detected at levels of up to 5.8 µg/L at drinking water intake points in Dutch rivers (Smit 2018). A different study found surface water concentrations in the Netherlands of 3.5 µg/L and drinking water concentrations of 2 µg/L (Kolkman et al. 2021).

Analysis of groundwater in India found the chemical at a concentration of up to 0.095 µg/L (Richards et al. 2021).

Soils adjacent to melamine production sites in China contained the chemical at up to 41 136 µg/kg (Qin et al. 2010). This is unlikely to reflect environmental concentrations from industrial activity in Australia as the chemical is not produced in this country.

A different study quantifying melamine present in farmland soils from fertiliser use found an average of 213 µg/kg dw (peak 2020 µg/kg) of melamine in 98 sample locations. Melamine was detected in 16 different fertilisers sampled in China (Zhu et al. 2019).

Environmental effects

Effects on Aquatic Life

Melamine has a low toxicity to aquatic organisms. Toxic effects are only observed at high exposure concentrations.

Acute toxicity

The following measured median lethal concentration (LC_{50}) and median effect concentration (EC_{50}) values for model organisms across 3 trophic levels were retrieved from the registration dossiers for melamine under *EU REACH legislation* (REACH) and from a draft screening assessment published by the Government of Canada (Government of Canada 2020; REACH):

Taxon	Endpoint	Method
Fish	48 h LC_{50} = 1000 mg/L	*Oryzias latipes* *(Japanese rice fish)* *mortality* *test guideline not reported*
Invertebrate	48 h EC_{50} = 200 mg/L	*Daphnia magna* *(water flea)* *mobility* *static conditions* *EPA OPP 72-2*
Algae	72 h EbC_{50} = 196 mg/L	*Pseudokirchneriella subcapitata* *(green algae)* *static conditions* *PRO/FT Algae-AC090-6*

Chronic toxicity

The following measured median effect concentration (EC_{10}) and no observed effect concentrations (NOEC) for model organisms across three trophic levels were retrieved from the registration dossiers for melamine under EU REACH legislation (REACH), water quality standards for melamine published by the Dutch National Institute for Public Health (Smit 2018) and the Environment and from a draft screening assessment published by the Government of Canada (Government of Canada 2020; Smit 2018):

Taxon	Endpoint	Method
Fish	36 d NOEC = 5.25 mg/L	*Pimephales promelas* (fathead minnow) length, mortality flow-through conditions OECD TG 210
Invertebrates	21 d EC10 = 32 mg/L	*Daphnia magna* *(water flea)* *static* *NEN 6502*
Algae	72 h NOEC = 31 mg/L	*Pseudokirchneriella subcapitata* *(green algae)* *Static conditions* *PRO/FT Algae-AC090-6*

Effects on terrestrial Life

Limited data are available for the effects of melamine exposure to terrestrial life. Available endpoints indicate a low toxicity to plants, microbes and mammals.

Melamine has shown inhibitory effects on the unicellular eukaryotic organism *Tetrahymena pyriformis* (EC_{50} = 820 mg/L). The study further demonstrated that melamine exerts a toxic effect that is accumulated over several generations (Wang et al. 2011). Melamine shows low toxicity to soil microorganisms (165 day respiration inhibition EC_{50} = 490 mg/kg) (REACH).

Melamine has low toxicity to plants. A 14 day NOEC of 170 mg/kg was obtained for the germination of string beans, and a 4 day EC_{50} of 1100 mg/L was found for the root growth of garden cress (Government of Canada 2020).

Melamine has low acute toxicity to mammals (see human health effects section).

Endocrine effects/activity

Melamine may cause endocrine mediated effects in terrestrial mammals. At this time, more data is needed to confirm whether these effects contribute to the environmental hazard.

A recent scoping review highlighted three areas that have sufficient evidence to review the potential hazard: neurophysiological, anthropometric and reproductive effects (Bolden et al. 2017). Several studies indicate that melamine has endocrine disruptive and neurotoxic properties that could impact on early development and growth. However, in a GLP compliant one generation reproductive toxicity study (see **Reproductive and development toxicity** section) rat fertility and neurodevelopment was not adversely affected. Additionally, there is no strong evidence that melamine causes endocrine-mediated effects in aquatic organisms.

Predicted no-effect concentration (PNEC)

A freshwater PNEC for melamine of 530 µg/L was derived from the measured fish chronic ecotoxicity endpoint (28 d NOEC = 5.25 mg/L) using an assessment factor of 10. This assessment factor was selected as reliable chronic ecotoxicity data are available 3 trophic levels (EPHC 2009).

A soil PNEC of 3.4 mg/kg was derived from the measured chronic ecotoxicity endpoint for plant seed germination (14 d NOEC = 170 mg/kg). An assessment factor of 50 was selected because chronic ecotoxicity data are available for 2 taxa (EPHC 2009).

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to domestic environmental hazard thresholds is presented below:

Persistence

Persistent (P). Based on measured degradation studies that show melamine is not readily or inherently biodegradable, the substance is categorised as Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on low measured and calculated bioconcentration factors (BCF), melamine is categorised as Not Bioaccumulative.

Toxicity

Not Toxic (Not T). Based on available ecotoxicity values above 1 mg/L and evidence of low chronic toxicity, melamine is categorised as Not Toxic.

GHS classification of environmental hazard

Based on the ecotoxicological data presented in this evaluation, melamine is not expected to be harmful to aquatic organisms. Therefore, the chemical is not formally classified for acute or chronic aquatic hazard under the Globally Harmonised System of Classification and Labelling of Chemicals (UNECE 2017).

Environmental risk characterisation

Based on the PEC and PNEC values determined above, the following Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for release of melamine into rivers and soils:

Chemical	PEC	PNEC	RQ
River	10 µg/L	530 µg/L	0.019
Soil	0.22 mg/kg	3.4 mg/kg	0.065

For rivers and soils, an RQ less than 1 indicates that melamine is not expected to pose a risk to the environment, as environmental concentrations are below levels likely to cause harmful effects.

Melamine is a persistent and highly mobile contaminant in the environment. Measured concentrations in surface waters are many orders of magnitude below levels of concern, even in industrialised and highly disturbed water bodies. Concentrations in Australian waters are expected to be much lower.

Available evidence indicates that melamine may have some endocrine activity; however, the available evidence does not demonstrate that this activity causes adverse effects.

Uncertainty

This evaluation was conducted based on a set of information that may be incomplete or limited in scope. Some relatively common data limitations can be addressed through use of conservative assumptions (OECD 2019) or quantitative adjustments such as assessment factors (OECD 1995). Others must be addressed qualitatively, or on a case by case basis (OECD 2019).

The most consequential areas of uncertainty for this evaluation are:

- There are no domestic monitoring data for melamine in surface waters or soil. The risk profile may change should monitoring data become available to indicate that the chemicals are present in Australian environmental compartments at concentrations above the level of concern.
- Insufficient information is available to determine the extent of endocrine activity of melamine. Further evaluation may be required if information becomes available to indicate that melamine exposure can cause endocrine-mediated adverse effects.

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