Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester (carbendazim)

Evaluation statement

22 December 2022

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AICIS evaluation statement

Subject of the evaluation

Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester (carbendazim)

Chemical in this evaluation

Name	CAS registry number
Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester	10605-21-7

Reason for the evaluation

An evaluation or assessment recommended further evaluation of specific issues related to the chemical(s).

Parameters of evaluation

Carbendazim (CAS RN 10605-21-7) is listed on the Australian Inventory of Industrial Chemicals (Inventory). This evaluation is a human health and environmental risk assessment.

For human health, the chemical was previously assessed under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework (NICNAS 2020). During the public comment period, a report of an extended one generation reproductive toxicity study, together with additional information on the mode of action for reproductive toxicity, and role of substance purity were received. Further evaluation of this information was recommended. In addition, new information on skin sensitisation and developmental toxicity has become available. This evaluation will:

- evaluate the new information that has become available
- consider the impact of substance purity on genotoxicity and whether there is a threshold effect for carbendazim-induced aneuploidy
- re-evaluate the risk to workers and the public from using carbendazim in paints, jointing compounds, and sealants
- consider whether any amendments to the current Schedule 7 entry in the Poisons Standard are warranted.

This evaluation statement should be read in conjunction with the IMAP assessment for carbendazim.

For the environment, this evaluation considers the environmental risks associated with the industrial uses of the chemical. The chemical has been evaluated for risks to the environment according to the following parameters:

- industrial uses listed in the ‘Summary of introduction, use and end use’ section
- exposure to aquatic environments and soil via release to stormwater and sewage treatment plants from these industrial uses.

Summary of evaluation

Summary of introduction, use and end use

In Australia, the chemical is used as a preservative in paints, jointing compounds, and sealants at very low concentrations. The chemical has non-industrial use as a fungicide in agricultural applications.

Internationally the chemical is reported to be used as an industrial biocide in the following applications:

- adhesive and sealant products
- paint and coating products
- construction products such as caulks, grouts, plaster, plastic roofing and concrete additives
- fabric, textile, and leather products
- papermaking and in paper products such as newspaper and toilet paper.

Human health

Summary of health hazards

The critical health effects for risk characterisation include systemic long term effects including mutagenicity and reproductive and developmental toxicity. The major target organs of carbendazim are the testes, liver, kidneys, and thyroid.

Carbendazim is rapidly absorbed, and metabolised following oral exposure and rapidly eliminated within three days of exposure. The primary route of metabolism of carbendazim is oxidation of the phenyl ring, followed by sulfate or glucuronide conjugation. The chemical is poorly absorbed following dermal exposure in rats. In vitro and in vivo dermal absorption studies, using oil-based and water-based paint formulations containing carbendazim, dermal absorption for carbendazim was estimated to be less than 2%.

In repeat dose oral studies reviewed earlier (NICNAS 2020), carbendazim caused increases in relative weights of the thyroid, liver, and adrenals and degenerative changes in kidneys, testes, and ovaries. Changes in spermatogenesis and oogenesis were also noted. The potential for carbendazim to cause reproductive and developmental toxicity has been extensively investigated in laboratory animals including rats, rabbits, and hamsters (NICNAS 2020). Testicular effects and abnormalities in spermatogenesis and foetal malformations, in particular the head and eyes, were the commonly observed effects reported in these studies. The chemical is classified as hazardous with the hazard category ‘Reproductive toxicity – Category 1B’ and hazard statement ‘H360FD (May damage fertility. May damage the unborn child’ in the HCIS (Safe Work Australia). Available data are consistent with this classification.

Dermal exposure to carbendazim for 28 days caused adverse effects on male reproductive organs in Sprague Dawley (SD) rats with effects persisting through a 10-week recovery period. A no observed adverse effect level (NOAEL) of 20 mg/kg bw/day was established based on seminiferous tubule degeneration and hypospermia.

In a modified extended one generation reproductive toxicity study (EOGRTS), no treatment related effects on male or female reproductive organs and tissues or on reproductive

parameters were observed in rats at up to 107 mg/kg bw/day carbendazim (the highest dose tested). Effects in the thyroid were observed, including increased thyroid hormone levels and histopathological changes in parental females. The NOAEL for parental toxicity was 13.9 mg/kg bw/day. There were no effects on live litter size, foetal anomalies (external, visceral, or skeletal), foetal weight, or foetal sex ratio. The F1 and F2 offspring did not show any systemic or developmental neurotoxicity.

In the newly evaluated developmental toxicity studies in rats and rabbits, foetal malformations were consistent with those identified in previously assessed studies.

Carbendazim may induce reproductive and developmental toxicity through alteration of several key events important in spermatogenesis. It has been suggested that the teratogenic and reproductive toxicity effects are observed only when carbendazim is administered as a single large dose. This may explain the absence of any effects on the reproductive system in the EOGRTS was because the study animals were not exposed to high levels of carbendazim, as would be the case with gavage administration. Adverse effects on male reproductive system were observed in a rat dermal study.

Carbendazim is classified as mutagenic with the hazard category 'Germ cell mutagenicity — Category 1B' and hazard statement 'H340 (May cause genetic defects)'. It is a known aneuploidogen, and directly binds to tubulin and inhibits polymerisation of tubulin. In vitro assays with carbendazim demonstrated a threshold effect for carbendazim induced aneuploidy. In vivo, a threshold for aneuploidy induction was observed after gavage administration in mice and rats. The data from some studies indicate that the positive results in bacterial mutation assays may be caused by 2,3-diaminophenazine (DAP) and 2-amino-3-hydroxyphenazine (AHP), present as impurities in technical carbendazim samples. However, even low levels of these impurities (DAP or AHP at levels as low as 5 or 10 ppm, respectively) could produce positive results.

Several long-term studies to evaluate the carcinogenic potential of carbendazim were previously assessed (NICNAS 2020). The results indicated no evidence of carcinogenicity in rats and dogs and some evidence of carcinogenicity in mice. The available data were not sufficient to recommend hazard classification. No new data were identified.

Based on the weight of evidence, the chemical is considered a skin sensitiser.

The chemical has low acute oral, dermal and inhalation toxicity. It is a mild skin and eye irritant (NICNAS 2020).

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
Skin Sensitisation	Skin Sens 1	H317 (May cause an allergic skin reaction)
Genotoxicity	Muta. 1B	H340 (May cause genetic defects)

Reproductive and Developmental toxicity	Repr. 1B	H360FD (May damage fertility; May damage the unborn child)

Summary of health risk

Public

Members of the public may come in contact with the chemical when using paints, jointing compounds and sealants containing the chemical. A quantitative risk assessment assuming maximum 0.35% carbendazim in paints indicated low risks to the public applying paint in domestic scenarios. Margins of exposure (MOE) were calculated for inhalation and dermal exposures. Standard models were used to calculate internal exposure doses for dermal and inhalation exposure during brush/roller and airless spray application. These were compared with effect levels from animal studies. For risk assessment from dermal exposure, a benchmark dose limit estimate of 68 mg/kg bw/day was used. For inhalation risk assessment, the NOAEL of 14 mg/kg bw/day from the rat EOGRTS (oral exposure) was selected, based on alterations in thyroid hormone levels in parental and offspring animals at the LOAEL of 53 mg/kg bw/day. The chosen point of departure value is expected to be protective of other effects including developmental effects and aneuploidy.

Dermal and inhalation MOEs for both methods of paint application (brush and airless spray) were greater than 100, indicating acceptable risk to persons applying paint and other surface coverings containing carbendazim 0.35% or less. The use of jointing compounds and sealants would result in lower exposures and hence have lower associated risk than the use of paint.

At the low concentration proposed to be used, the risk of skin sensitisation to end users is considered to be low. Technical specifications for carbendazim and the low concentration proposed to be used would limit the presence of genotoxic impurities to trace amounts (<0.002 ppm AHP and 0.01 pm DAP).

Workers

During product formulation and packaging, dermal, and inhalation exposure may 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 may vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical local effects and systemic health effects following repeated exposure, 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 risk** 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)
- Toxic (T).

Environmental hazard classification

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) as Acute Category 1 (H400) and Chronic Category 1 (H410):

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short-term)	Aquatic Acute 1	H400: Very toxic to aquatic life
Hazardous to the aquatic environment (long-term)	Aquatic Chronic 1	H410: Very toxic to aquatic life with long lasting effects

Summary of environmental risk

Carbendazim is an industrial biocide that is used in surface coatings (e.g., paints) and in construction materials (e.g., grouts and adhesives) as a dry film preservative.

Carbendazim is not bioaccumulative but resists degradation in environmental waters and is very toxic to aquatic life.

Carbendazim is expected to be released to surface water (both directly and via sewage treatment plant (STP) effluent) and to soils. Releases of carbendazim to STPs may result from both industrial and agricultural uses, and from disposal of products treated with carbendazim to wastewater (e.g., toilet paper). STP processes are only expected to remove approximately 34% of incoming carbendazim via partitioning to sludge. The remaining carbendazim is expected to be released to surface waters. Rainfall events are expected to cause leaching of carbendazim from painted building surfaces, resulting in direct release of carbendazim into surface waters via stormwater infrastructure. International monitoring information indicates that concentrations of carbendazim in stormwaters are typically below levels of concern.

Information made available to the Department indicates that carbendazim concentrations in Australian STP influent and effluent are usually below the level of concern. However, carbendazim concentrations at STPs that receive high proportions of trade waste may have influent and effluent concentrations well above levels of concern. Therefore, emissions of carbendazim in trade wastes from industrial facilities may pose a significant risk to the aquatic environment in waters that receive effluent from STPs that service industrial facilities. Further information to determine the frequency of carbendazim emissions in trade waste and the contribution of non-industrial activities to environmental carbendazim loads is necessary to determine if risk management is required.

While there is uncertainty about the sources of carbendazim releases, the very high aquatic toxicity of carbendazim is well established. As such, the establishment of water quality guidelines may help to communicate potential risks associated with releases of carbendazim to water. Additionally, as there may be potential for carbendazim to be present in liquid trade wastes, revision of trade waste acceptance guidelines to limit carbendazim releases may further reduce potential risks.

Proposed means for managing risk

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling amend the entry in the *Poisons Standard — the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) to allow use of the chemical at higher concentrations in paints and sealants.

Consideration should be given to the following:

- The current schedule entry only exempts use in paints, jointing compounds and sealants containing 0.1 per cent or less of carbendazim.
- The chemical has low volatility and limited dermal absorption.
- The available data indicate that teratogenic and reproductive toxicity effects are observed only when carbendazim is administered as large bolus doses.
- In vitro assays with carbendazim demonstrated a threshold effect for carbendazim-induced aneuploidy. A threshold for aneuploidy induction was observed after gavage administration in mice and rats.
- A quantitative risk assessment assuming maximum 0.35% carbendazim in paints indicated low risk to the public using paint in a domestic setting.

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 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 dermal, and inhalation 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
- work procedures that minimise splashes and spills
- regularly cleaning equipment and work areas
- 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 a hazardous chemical depends on the physical form and the way in which 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

Environment

Recommendation to Department of Climate Change, Energy, the Environment and Water

It is recommended that a water quality default guideline value for carbendazim be established to better communicate the environmental risk of this chemical. Establishing a default guideline value will inform both industrial and non-industrial stakeholders of protective concentrations of carbendazim in surface waters, while assisting the decision making processes of risk managers nationwide.

Recommendation to Australian states and territories

It is recommended that Australian states and territories consult with water management bodies to ensure that trade waste acceptance requirements are protective of the environment. Specifically, the permissible concentrations of biocides, such as carbendazim, in trade wastes should be reviewed to ensure that resulting releases to surface waters are not above concentrations of concern.

Conclusions

The conclusions of this evaluation are based on the information described in this 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 environmental risks associated with the industrial uses of carbendazim. This chemical is used as an industrial biocide to protect construction products, textiles, paper, and as a dry film preservative in paints. The environmental risks resulting from the industrial uses of carbendazim in Australia has not been previously assessed.

The evaluation selection analysis (ESA) of carbendazim found that it may be of concern to the environment based on a potentially high introduction volume, emissive uses in products and high toxicity to aquatic organisms. The European Chemicals Agency (ECHA) has recently determined that some uses of carbendazim as a preservative in industrial products may present an unreasonable risk to the environment (ECHA).

This evaluation will evaluate the potential for emissions of the chemical to the aquatic environment in Australia and whether risk reduction measures are required for industrial uses of this chemical.

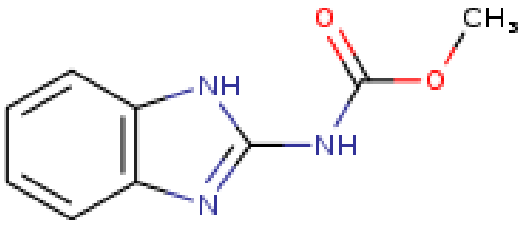
Environmental risks resulting from the use of other dry film preservatives in paints have previously been assessed by AICIS, as well as under the IMAP framework established by the former National Industrial Chemicals Notification and Assessment Scheme (NICNAS). An IMAP environment Tier II assessment for Octylisothiazolinone preservatives and industrial biocides is available and an AICIS evaluation for IPBC (3-iodo-2-propynyl butylcarbamate) has been finalised.

For human health, the chemical was previously assessed under the Inventory Multi-tiered Assessment and Prioritisation Framework (NICNAS 2020). During the public comment period, an extended one-generation reproductive toxicity study, additional information on the mode of action for reproductive toxicity, and role of substance purity were received. Further evaluation of these information sources was recommended. In addition, new information on skin sensitisation and developmental toxicity has become available.

Chemical identity

Carbendazim belongs to a group of chemicals known as benzimidazole carbamates. Chemicals in this group have widespread applications as biocides and pesticides in the agricultural sector as well as pharmacological actives in medicine (NCBI 2022a; 2022b; 2022c). Carbendazim is also a metabolite of thiophanate methyl (CAS RN 23564-05-8) and benomyl (CAS RN 17804-35-2), which are active ingredients in agricultural pesticides. Benomyl is also known to have industrial use as a biocide in surface coatings in Australia but is not subject to this evaluation.

Carbendazim is the simplest of all benzimidazole carbamates. It consists of a heterocyclic benzimidazole core with an amino bound methylcarbamate. It exists in 2 tautomeric forms undergoing amino-imino tautomerism with a 1,3-hydrogen shift between the imino-nitrogen in the heterocyclic ring and the amine in the 2-position (Kasetti and Bharatam 2012). While the tautomerism may affect the protonation of carbendazim, it is not expected to significantly affect its behaviour in the environment:

Chemical name	Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester
CAS No.	10605-21-7
Synonyms	carbendazim 1H-benzimidazole-2-carbamic acid, methyl ester methyl-1H-benzimidazol-2-ylcarbamate 2-(methoxycarbonylamino)benzimidazole
Structural Formula	
Molecular Formula	C9H9N3O2
Molecular Weight (g/mol)	191.2
SMILES	COC(=O)NC1=NC2=CC=CC=C2N1

Relevant physical and chemical properties

Measured physical and chemical property data for carbendazim were retrieved from a report by the Netherland's National Institute of Public Health and Environment (Dang and Smit 2008) and the registration dossiers submitted under the Registration, Evaluation, Authorisation, and restriction of Chemicals (REACH). Additional information was obtained from the Pesticides Properties Database on carbendazim (IUPAC):

Physical Form	White crystalline solid
Melting Point	305−307 °C
Density (20 °C)	1.45 g/cm^3
Vapour Pressure	0.00015 Pa at 20°C (exp.)
Water Solubility	8 mg/L at pH 7 (exp.) 28–36 mg/L at pH 4 (exp.)
Henry's law constant	0.0036 Pa·m^3/mol at 25°C
Ionisable in the environment?	Yes
pKa	4.2 (exp.)
Partition coefficient (log K_{ow})	1.49 (exp.)

Carbendazim is an organic substance that behaves as a weak base in aqueous solution. Based on its measured acid dissociation constant (pKa) it is not expected to be ionised in surface waters above pH 5.

At ambient temperatures, carbendazim is slightly soluble in water at neutral pH and moderately soluble in acidic waters. The chemical has a low volatility from water when in solution and when in its solid form.

Introduction and use

Australia

The chemical has reported domestic uses as a film preservative in paints, jointing compounds, and sealants at very low concentrations (NDPSC 2010).

Carbendazim has non-industrial uses as an active constituent in registered agricultural and veterinary chemical products (APVMA), mainly as a fungicide. This non-industrial use is outside the scope of this evaluation.

International

Available information indicates that carbendazim is an antifungal preservative (biocide) added to many construction and surface coating products worldwide. International products containing the chemical include caulks, building grouts, concrete, roof and outdoor paints,

sealants, adhesives, wood stains, inks, and materials manufactured for use as building facades (ECHA; NCBI 2022a; PMRA 2011).

Carbendazim is also used in papermaking to confer longevity to finished products while in storage, including newspapers and toilet paper (Merel et al. 2018). Other industrial uses include the protection of textiles, clothing, and PVC plastics (Merel et al. 2018; US EPA 2019a).

Based on available information, annual volumes between 1−10 tonnes are registered under REACH for industrial uses (REACH 2019), and between 0.1 and 3.8 tonnes in the Nordic countries (SPIN). In the US, annual estimates are 7 tonnes for use in adhesives/sealants and 77 tonnes in paints and coatings (US EPA 2019a).

Existing Australian regulatory controls

Public

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 7 (TGA 2021).

Schedule 7:
'CARBENDAZIM **except** in paints, jointing compounds and sealants containing 0.1 per cent or less of carbendazim.'

Schedule 7 chemicals are described as 'Substances with a high potential for causing harm at low exposure which require special precautions during manufacture handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely'. Special regulations restricting their availability, possession, storage or use may apply'. Schedule 7 chemicals are labelled with ' Dangerous Poison' (TGA 2021).

Workers

The chemical is listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia) with the following hazard category and statements for human health:

Health hazards	Hazard category	Hazard statement
Genotoxicity	Muta 1B	H341: Suspected of causing genetic defects
Reproductive and Developmental Toxicity	Repr. 1B	H360FD (May damage fertility; May damage the unborn child)

No exposure standards are available for the chemical.

Environment

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

The release of wastewater that contains biocides such as carbendazim, is subject to trade waste acceptance criteria. Limits of contaminants in wastewater are set by the local authorities responsible for wastewater treatment and vary nationwide.

International regulatory status

Canada

Carbendazim is registered as a material preservative for use in aqueous paints and stains, adhesives, caulks and sealants, joint cements, and inks. Under the approved conditions of use, the Pest Management Regulatory Agency (PMRA) found that the product has value and does not present an unacceptable risk to human health or the environment (PMRA 2011).

European Union

The use of carbendazim has been assessed under the EU Biocidal Products Regulation ((BPR, Regulation (EU) 528/2012)) for three product types: PT7: Film preservatives, PT9: fibre, leather, rubber, and polymerised materials, and PT10: Construction materials preservatives. In February 2021, the European Commission approved carbendazim as an active substance for use in biocidal products of product-types 7 and 10, subject to compliance with certain specifications and conditions. The approval excludes uses of the substance in outdoor paints and plasters that are intended to be used outdoors.

Carbendazim falls within the European Union (EU) Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the composition of cosmetic products.

OECD

Carbendazim is considered a High Production Volume (HPV) chemical by the OECD, which indicates that more than 1000 tonnes of the chemical are used per year in at least one member country (OECD 2007).

United States of America

Carbendazim is listed in the Substance Registry Service for use as a preservative in paints, coatings, plaster, and adhesives (US EPA 2019b).

Following a request from the US EPA Pesticide Re-evaluation Division (PRD), the Health Effects Division (HED) conducted a draft risk assessment (DRA) in support of registration review for the fungicide, thiophanate-methyl (TM) and its metabolite, carbendazim (MBC), which is also an active ingredient.

Exposure standards

The following occupational exposure limits have been recommended internationally:

- Belarus and Russia: Maximum Permissible Concentration (MPC) of hazardous substances in the air of the working area = 3 mg/m^3.
- Germany: Maximum Workplace concentration (MAK) of 10 mg/m^3.
- Kazakhstan MPC of pollutants in the workplace air of 0.1 mg/m^3.
- Switzerland: Occupational Exposure Limit of 10 mg/m^3.

Human exposure

There is potential for workers (painters) and the public to be exposed to carbendazim via dermal and inhalation routes during mixing, loading, and applying paints containing carbendazim.

The major industrial use of carbendazim is in paints and surface coatings. Professional painters and the general public are expected to be exposed to paints during the following activities:

- open pour liquids
- airless spray painting
- brush/Roller Painting.

Dermal and inhalation exposure were estimated for workers and public handling paint.

Parameters used:

- a maximum concentration of 0.35% of carbendazim in paints.
- 50 litres paints applied per day by hand brush
- 100 litres of paint applied by airless spray
- 100% inhalation absorption rate
- 70 kg average body weight.

Dermal and inhalation absorption values (mg chemical absorbed per unit paint applied) are taken from USEPA Pesticide Handlers Exposure Database (PHED) (USEPA 2018; 2019a). The PHED “best fit” measure is the sum of exposure of various individual body parts during paint application. US units (mg/pound) were converted to mg/g by dividing the value by 454 (1 pound=454 grams).

For inhalation exposure, an internal exposure has been estimated to enable comparison with results from oral toxicity studies. For dermal exposure, there is dermal toxicity data estimation for external exposure which is appropriate.

The following table gives relevant estimates of exposure dosing following inhalation and dermal exposure of carbendazim when using paints containing the chemical.

Inhalation and dermal exposure to carbendazim when applying paints

Scenario	Paint applied/day (litres)[a]	Carbendazim handled/day (g)[b]	Unit exposure (mg/g)[c]	Total exposure (mg/day)[f]	Total exposure (mg/kg bw/day)[g]
Inhalation exposure					
Airless Spray Painting	100	350	0.00015[d]	0.0525	0.00075
Brush/Roller Painting	50	175	0.000002[e]	0.00035	0.000005
Dermal exposure					
Airless Spray Painting	100	350	0.096[d]	33.5	0.48
Brush/Roller Painting	50	175	0.252[e]	44.2	0.63

Based on maximum concentration of 0.35% carbendazim in paints was used.
a. Average amount of paint applied in one day
b. Amount of carbendazim handled per day = 0.35% x litres paint applied per day
c. Exposure per gram of carbendazim handled
d. USEPA calculated exposure value from Airless Paint Sprayer Human Exposure Monitoring Study (AEATF II Project ID AEA10: MRID 50879401) (USEPA 2019).
e. USEPA calculated exposure value from Brush/Roller Painting Human Exposure Monitoring Study (AEATF II Project ID AEA09: MRID 50521701). (USEPA 2018).
f. Total exposure (exposure x amount handled per day).
g. Exposure/kg bw/day.

It can be assumed that proper use of personal protective equipment will further reduce occupational exposure to workers involved in the manufacture and use of paints and coatings.

Health hazard information

The newly available studies include an extended one generation reproductive toxicity study (EOGRTS) and a 28 day repeat dose dermal study in rats. Dermal absorption studies using paint formulations containing carbendazim were also conducted.

Detailed information on the toxicokinetics and animal and human health effects of the chemical is provided in a previous assessment (NICNAS 2020). This evaluation reviews toxicity studies identified following publication of the IMAP assessment of carbendazim and previously assessed key data as part of a weight of evidence. Therefore, this assessment should be read in conjunction with the previous assessment (NICNAS 2020).

Toxicokinetics

Carbendazim is well absorbed and extensively metabolised following oral dosing (NICNAS 2020). The chemical is rapidly eliminated within 3 days of exposure. In an oral study in Sprague Dawley (SD) rats (EU BPR 2019), approximately 80% of the applied dose of the chemical was excreted in the urine within 24 hours of dosing. Tissue bioaccumulation was

not observed. The highest tissue levels of carbendazim at 72 hours post-dosing were found in the liver, followed by the kidneys, skin, GI tract, blood, and lungs. The primary route of metabolism was oxidation of the phenyl ring, followed by sulphate or glucuronide conjugation. The major urinary metabolite in males at all dose levels and females at low dose was 5-hydroxy benzimidazole carbamate sulphate (5-HBC-S), while the major metabolite in the faeces was 5-HBC. Subsequent phenyl ring oxidation and N-oxidation at the imidazole nitrogen yielded the metabolite 5,6-hydroxy-oxocarbendazim-N-oxide glucuronide, which was more prevalent in females than in males.

Dermal Absorption

The chemical was reported to be poorly absorbed following dermal exposure in rats (IPCS 1995). In vivo, dermal application of 0.1% carbendazim (14 µg/cm^2) to the back and shoulders of rats for eight hours resulted in an absorbed dose of approximately 1.5-2% (Government of Canada 2011).

In vitro and in vivo dermal absorption studies for carbendazim were conducted with alkyd-based and water-based paints containing carbendazim (De Light and Mass 2009; Mass 2010a, Mass 2010b).

In vitro percutaneous absorption of ^{14}C-carbendazim in alkyd-based and water-based paints was determined in human and rat skin membranes. The test substance was tested at a target concentration of 0.1% (w/w in undiluted paint). The contact time was 8 hours (a normal working day), and the post exposure time was 16 hours. The mean total absorption for alkyd-based paints, defined as the compound related radioactivity present in the receptor fluid, the receptor compartment wash, and the skin membranes (excluding tape strips), was 0.83% of the applied dose in human skin and 2.65% of the applied dose in rat skin. The mean total absorption for water-based paint was 1.27% of the applied dose in human skin and, 1.75% of the applied dose in rat skin. The mean recovery of carbendazim was more that 91% in both studies.

In vivo dermal absorption studies were conducted in rats according to Organisation for the Economic Cooperation and Development (OECD) Test Guidelines 427 (Dotson et al. 2020). The test substance was applied at 0.1% and left on skin for 8 hours (representative in-use concentration). The bioavailability of the residues remaining in/on the skin after washing of the application site as well as the kinetics of percutaneous absorption were observed for 24, 72, and 144 hours following exposure. For the alkyd-based paint, the total absorption was 1% at 24 hours and 1.18% at 144 h after dosing, indicating that absorption was almost complete within 24 hours. For water-based paint, 1.75% of the dose was absorbed within 24 h. The total absorption remained 1.41% at 144 hours after dosing, indicating that absorption was almost complete within 24 hours. Mean recovery of radioactivity in the study ranged from 95% to 107%.

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on the positive results seen in guinea pig maximisation test (GPMT) test.

In the maximisation test, conducted according to OECD Test Guideline 406 (OECD TG 406), intradermal induction was performed on ten male Dunkin-Hartley guinea pigs using 5% carbendazim in the vehicle Alembicol D and Freund’s complete adjuvant and topical

induction with 62.5% of the chemical. The animals were challenged with 62.5% and 31.25% carbendazim in Alembicol D. Reactions were reported in 40% of the animals challenged with 62.5% chemical and 30% of the animals challenged with 31.25% chemical, indicating a sensitisation response (ECHA 2019b).

The chemical was not found to induce dermal sensitisation in two modified Buehler tests and one non-guideline skin irritation and sensitisation study (NICNAS 2020). These tests deviated from guideline protocols with differences in induction and challenge times (ECHA 2019b). These studies were not used for classification purposes because of the non-standard test methods used and because the Buehler test is considered less sensitive than other sensitisation studies.

Observation in humans

One positive reaction to 5% carbendazim suspended in ethanol was reported in a patch test conducted in 47 female fruit workers (apple sorters) with dermatitis. In this patch test, positive reactions were also noted in the two control groups. These groups were comprised of 30 women from the same geographical region and 60 from another. These women were potentially exposed to the chemical while harvesting fruit or during treatment at a dermatological clinic. No further details were provided (MAK 2015).

Repeat Dose Toxicity

Oral

Several studies in rats and dogs were conducted to evaluate toxicity of carbendazim following repeated oral exposure. Adverse effects were seen in the liver, kidneys, and testes (NICNAS 2020) but the observed effects were not sufficient to recommend hazard classification.

Sub-chronic and chronic oral exposure at lower doses of carbendazim caused increased absolute weights of the liver, and relative weights of the thyroid and adrenals (in both males and females). Tubular dilation and hydropic degeneration (accumulation of water) in kidneys were observed in males.

Dermal

In a 28 day dermal toxicity study conducted according to US EPA Regulations for Good Laboratory Practice, pure carbendazim (99.8%) in corn oil vehicle was applied to the clipped skin of Sprague-Dawley rats (10/sex/dose) at dose levels of 0, 20, 120, 480, or 720 mg/kg bw/day for 6 hours/day, 5 days per week, for 4 weeks. To assess recovery following exposure, rats (10 sex/dose) were treated similarly at 0 or 720 mg/kg bw/day for 4 weeks and then held without dosing for an additional 10 weeks (Ehman 2008).

There was no mortality or any clinical signs of adverse effects. Clinical chemistry and gross pathology parameters were normal. Mild to severe (dose related) hypospermia was observed in the epididymis caput, cauda, and corpus at 120 (1/10), 480 (2-4/10) and 720 mg/kg bw/day (4/10) compared to controls (0/10). Moderate to severe seminiferous tubule degeneration was observed at 120 mg/kg bw/day and higher doses (2-5/10 treated vs 0/10 controls). These effects were considered treatment related. Sperm granulomas were also noted in the epididymis of 1/10 at 480 mg/kg bw/day (moderate severity) and 3/10 at 720 mg/kg bw/day (severe).

Increased thyroxine (T4) levels were observed in female rats at 480 and 720 mg/kg bw/day, (40%, and 31%, respectively). The significance of this finding is uncertain, but it was considered treatment related.

Cauda epididymal sperm concentration was significantly decreased at 480 and 720 mg/kg bw/day. The percentage of abnormal sperm was increased from 1.45% in controls to 12.41% at 720 mg/kg bw/day, but this finding was not statistically significant because of the extreme variation observed (due to one 720 mg/kg bw/day animal). Decreases (18-22%) were also noted in motile sperms, spermatid head concentration and daily sperm production per testis.

Following a 10 week recovery period, the microscopic changes generally persisted in the 720 mg/kg bw/day group. Mild to moderate hypospermia was observed in the epididymis caput, cauda, and corpus (3/10 treated vs 0/10 controls), and moderate seminiferous tubule degeneration was also noted (4/10 treated vs 0/10 controls). All sperm parameters in the treated groups were similar to controls, except the percent abnormal sperm was slightly increased at 720 mg/kg bw/day (p less than or equal to 0.01).

The NOAELs from this study were 20 mg/kg bw/day for males based on seminiferous tubule degeneration and hypospermia, and 120 mg/kg bw/day for females based on increased thyroxine levels.

In other dermal studies reviewed earlier, treatment of rabbits with up to 250 mg/kg bw/day carbendazim for 21 days did not cause any systemic toxicity (NICNAS 2020).

Inhalation

No data are available for the chemical.

Genotoxicity

Based on weight of evidence carbendazim is classified as mutagenic with the hazard category 'Germ cell mutagenicity — Category 1B' and hazard statement 'H340 (May cause genetic defects)'. Carbendazim gave positive as well as negative results in both in vitro and in vivo tests (NICNAS 2020). Several studies reported micronuclei formation in NMRI and B6D2F1/Cr-1BR mouse bone marrow and Swiss mouse colon epithelial cells following oral exposure to carbendazim (JMPR 2005). In the bone marrow of Wistar rats and spermatids of SD rats, micronuclei formation was observed at 150 and 100 mg/kg bw/day carbendazim, respectively (JMPR 2005). In a mouse micronucleus formation assay, a positive result was obtained following intraperitoneal injection of ≤6000 mg/kg bw of carbendazim, but in another similar study, the chemical gave negative results at ≤500 mg/kg bw (IPCS 1995).

The chemical does not bind directly to DNA and there is no evidence for the induction of gene mutations in vitro, or structural chromosomal damage in vitro or in vivo. No interaction with DNA was seen in liver cells of rats dosed in vivo with carbendazim. However, carbendazim, is a known aneuploidogen. Carbendazim directly binds to tubulin, a protein that is essential for the segregation of chromosomes during cell division and inhibits polymerisation of tubulin (Lim & Miller 1997). As a result, formation of spindles during cell division is prevented and this affects the segregation of chromosomes (JMPR 2005). Through this mechanism carbendazim induces numerical changes in chromosomes (aneuploidy) in mammalian cells (Lim & Miller 1997). This aneuploidogenic mechanism of action is likely to be responsible for the testicular toxicity and teratogenicity of carbendazim

observed in animal studies. Carbendazim also inhibited mitosis in *Saccharomyces pastorianus* and *Aspergillus nidulans* (Government of Canada 2011).

A review of literature supports the notion that there is a threshold effect for carbendazim-induced aneuploidy (Can and Albertini 1997). However, no absolute consensus for the specific concentration threshold has been reached. The inhibition of tubulin polymerisation by carbendazim modifies the formation of the mitotic spindle in cultured mammalian cells. Concentrations of carbendazim below those which completely eliminate mitotic spindle formation in mammalian cells lead to the formation of "imperfect" mitotic spindles resulting in abnormal segregation of chromosomes. The abnormal segregation of chromosomes results in the production of aneuploid progeny cells including those with both reduced and increased chromosome numbers i.e., monosomic and trisomic cells (Bentley et al. 2000). Since multiple copies of tubulin molecules are present in proliferating cells, at low concentrations of the chemical, only a limited number of tubulin molecules may be affected, and it may not adversely affect the cells. Experiments undertaken with benomyl and carbendazim have demonstrated No Observed Effect Levels (NOELs) for aneuploidy induction using in vitro assays (Marshall et al. 1996; Bentley et al. 2000; Elhajouji et al. 1995). Although data from these studies and from mathematical models do not allow the determination of specific thresholds for chemical-induced aneuploidy in vitro, the dose response curves obtained provided convincing evidence for in vitro NOELs. Consequently, a clear No Adverse Effect Level was recognisable. Thus, interactions of carbendazim with biological material is of a nature that is entirely consistent with a dose level being identifiable as having no toxicological effect (SCP 2001). Further studies are required to establish an acceptable daily intake (ADI) and an acceptable operator exposure level (AOEL).

An in vivo study was conducted with the aim of confirming that the formation of micronuclei in bone marrow polychromatic erythrocytes (PCE) was the result of aneuploidy, rather than clastogenecity. BDF1 mice (5 animals/sex/dose) were orally administered carbendazim at 0, 66, 1646, or 3293 mg/kg bw. Bone marrow cells were harvested from animals 48 hours after dosing and micronuclei were assessed for the presence or absence of centromeres or centromere-associated proteins (kinetochores). Kinetochore positive (KC+) micronuclei were presumed to contain intact chromosomes and were indicative of aneuploidy. Carbendazim induced statistically significant increases in the frequencies of total micronucleated PCEs and kinetochore+ micronucleated PCEs in female mice at 1646 and 3293 mg/kg bw and in male mice at 3293 mg/kg bw. Greater than 80 % of the total MN-PCEs contained kinetochores. Aneuploidy in Syrian hamster oocytes was observed following a single gavage dose of 1000 mg/kg bw. In a study conducted to assess the ability of carbendazim to induce numerical chromosome aberrations in sperm and micronuclei in peripheral blood erythrocytes, groups of three to five Wistar rats received carbendazim (purity not reported) as single oral doses at 0, 50, 150, 450, or 800 mg/kg bw in corn oil. An increase in hyperploid sperm was observed at doses of 150 mg/kg bw and greater (JMPR 2005). Further studies are required to establish a definitive threshold value in vivo.

In addition to its aneugenic activity, carbendazim was believed to cause mutation by incorporating into the DNA during DNA replication by acting as a purine base analogue. However, Sarrif et al. (1994) reported that the mutagenic activity associated with carbendazim was due to contaminants. This was supported by the fact that mutagenic activity was not detected in all carbendazim preparations, and mutations were induced only at very high concentrations. Also, if carbendazim was acting as a purine base analogue, activity would be expected in base-pair substitution strains. The activity was evident only in the frame-shift strains.

In addition, data from some studies indicate that the positive results in bacterial mutation assays may be caused by 2,3-diaminophenazine (DAP) and 2-amino-3-hydroxyphenazine (AHP), present as impurities in technical carbendazim samples (Sarrif et al. 1994)). These chemicals are known mutagens (Wagner et al. 1996). Their mutagenicity was found to be greatly enhanced with mammalian hepatic microsomal activation resulting in a preferential induction of frameshift mutations. Concentrations of DAP and AHP as low as 0.025 and 0.05 µg/plate, respectively, were reported to be positive in the Salmonella/AMES test with activation (Sarrif et al. 1994). Consequently, carbendazim samples containing DAP or AHP at levels as low as 5 or 10 ppm, respectively, would be positive in the Salmonella/Ames test with metabolic activation when tested at 5000 micrograms/plate.

Many investigations comparing different carbendazim batches and preparations with variable amounts of impurities indicated that the positive mutagenic effects could be traced to two mutagenic impurities, namely 2,3-diamino-phenazine (DAP) and 2-amino-3-hydroxyphenazine (AHP). Carbendazim technical containing ≥1.8 ppm DAP was found to be mutagenic whereas a batch containing 0.6 ppm DAP and less than 4 ppm AHP was negative.

A new Ames test with a batch containing 2.3 ppm DAP and 0.3 ppm AHP was performed in the context of this evaluation. No increased numbers of revertants were observed in TA 1535, TA 1537, TA 98 and TA 100 and E. coli strain WP2 uvrA. (EU BPR, 2019).

The BPR report concluded that carbendazim is devoid of gene mutagenic or clastogenic activities, despite the occasional positive findings in *in vitro* tests. Positive findings have been traced to aminophenazine by-product impurities which are reduced in present manufacturing processes to amounts ≤3.5 ppm, not inducing gene mutations in *Salmonella typhimurium* strains.

The Food and Agriculture Organisation of the United Nations (FAO) specification for carbendazim sets maximum levels of 0.0005 g/kg AHP and 0.003 g/kg for DAP (EFSA 2020).

Reproductive and Development Toxicity

The potential for carbendazim to cause reproductive and developmental toxicity has been extensively investigated in laboratory animals including rats, rabbits, and hamsters (APVMA 2009; Government of Canada 2011; IPCS 1995; JMPR 2005). The chemical is classified as hazardous with the hazard category ‘Reproductive toxicity – Category 1B’ and hazard statement ‘H360FD (May damage fertility. May damage the unborn child’ in the HCIS (Safe Work Australia). The available data support this classification.

Reproductive toxicity

Results from several previously assessed studies (acute, sub-acute, repeat dose and multigeneration) conducted in Wistar rats, mice and Syrian hamsters showed that carbendazim was toxic to reproduction. These studies used the oral route of exposure (gavage and dietary) and tested a wide range of doses from 0.5 mg/kg bw/day to 17,000 mg/kg bw/day. Testicular effects and abnormalities in spermatogenesis were the most commonly observed adverse effects. Additionally, carbendazim has androgenic activity and caused alterations in hormones associated with reproduction (NICNAS 2020).

Extended one-generation reproductive toxicity study

In a newly submitted modified extended one generation reproductive toxicity study (EOGRTS), conducted according to OECD TG 443, carbendazim (99.5 % pure) was administered to Wistar Hanover Crl:WI(HAN) rats (30/sex/dose) in the diet (Gilmore 2014). Dose levels were 0, 250, 1000, or 2000 ppm (equivalent to average daily doses of 0, 13.9, 53.2, or 106.7 mg/kg bw/day in males and 0, 16.2, 67.6, and 136.8 mg/kg bw/day in females) for at least 4 weeks prior to mating, during the 14-day mating period, throughout gestation, and through lactation until weaning. Dietary adjustments of doses were not made during any in-life phase of the study. As a result, test compound intake in females during lactation was up to 2-fold greater than other dose groups. The study protocol also included evaluation of circulating thyroid hormone levels and a statistical semi-quantitative microscopic evaluation of thyroid colloid area and follicular cell height in parental animals and some offspring cohorts as recommended in the OECD guidelines. Study design and cohort assignment are summarised below:

P Generation: Parental (P) males were exposed to carbendazim in diet until postnatal day (PND) 85 and P females were exposed until lactation day (LD) 22.

F1 Generation: Each set of F1 offspring was maintained on the test diet from the time of weaning until termination. F1 offspring were divided into five different groups (Cohorts 1a, 1b, 2a, 2b, and 3) at weaning on PND21, and evaluated for potential effects on the nervous system, reproductive and endocrine systems, thyroid function, and other systemic toxicity parameters, as follows:

Cohort 1a (22/sex/group) and their F2 offspring: assessment of reproductive and systemic toxicity which included oestrous cycle evaluation and post-mortem evaluations that focused on thyroid hormones, reproductive organs, sperm assessment, and ovarian follicle counts.

Males and females were mated on PND 90, and males were sacrificed on PND 148. Females were sacrificed on gestation day 20 and caesarean parameters evaluated. The F2 foetuses from this mating were examined for external, visceral, and skeletal anomalies.

Cohort 1b (20/sex/group) and their F2 offspring: assessment of reproductive toxicity which included oestrous cycle evaluation and post-mortem evaluations that focused on clinical chemistry, hormones (testosterone and thyroid), hematology, reproductive organs, sperm assessment, ovarian follicle counts, and histopathology. Males and females were mated on PND 90, and males were sacrificed on PND 175. Females were sacrificed on LD 20. The F2 offspring were sacrificed on PND 21 (n=12/sex/group for necropsy, perfusion of the nervous system, and gross brain measurements), PND 23 (n=12/sex/group for thyroid hormone analysis, necropsy, and target organ pathology), and PND 45 (20 females/group for vaginal patency and thyroid hormone analysis).

Cohort 2a (10/sex/group): developmental neurotoxicity assessment, which included clinical signs, body weight, ophthalmology (~PND 45) functional observational battery (FOB, PND 52-55), motor activity (PND 63-66), and acoustic startle response (PND 58-61). On PND 70, animals were perfused for central nervous system and peripheral nerve neuropathology evaluation and brain morphometry.

Cohort 2b (12/sex/group): developmental neurotoxicity assessment, which included clinical signs, terminal body weight and brain measurements, perfusion for central nervous system and peripheral nerve neuropathology evaluation, and brain morphometry on PND 21.

Cohort 3 (12/sex/group): assessment of systemic toxicity which included thyroid hormone analysis, necropsy, and target organ pathology on PND 23.

There were no treatment related effects on P or F1 parental mortality, clinical signs, body weight, body weight gain, hematology, or clinical chemistry parameters, urinalysis, and macroscopic findings. In some F1 female rats, significantly increased white blood cell counts (40%) and absolute lymphocytes (46%) and segmented neutrophils (35%) were observed but were within historical control and therefore not considered adverse effects.

In P females, statistically significant increases in plasma T4 and thyroid stimulating hormone (TSH) levels compared to controls were noted, but there was no dose response. The hormonal changes were associated with modest increases in thyroid follicular cell height and decreases in colloid area as identified by morphometric analysis. The combined findings of changes in T4 and TSH in female rats, along with slight thyroid hypertrophy and increased follicular cell height/decreased follicular colloid area, were considered indicative of perturbation of thyroid homeostasis and therefore determined to be an adverse effect. No thyroid effects were observed in P males.

Changes in thyroid hormone levels, colloid area and follicular cell height were seen in F1 and F2 offspring at higher doses but were not consistent across cohorts or life stages. In F1, at PND 23, both male and female offspring showed increased T4 at 2000 ppm, but only females showed increased TSH. Decreased colloid area/increased follicular cell height was observed in both sexes at this dose and time point. At 1000 ppm, male offspring showed significant increases in T4 and TSH, and significant colloid area/follicular cell height changes, but females had only higher T4. F2 female pups, on PND 45, showed increased T4 and TSH and altered colloid area and follicular cell height at 2000 ppm.

Plasma testosterone levels in P males were minimally reduced at 1000 and 2000 ppm (25%) but were not statistically significant and there were no effects on male sperm or other reproductive parameters. Testosterone levels were also unaffected in F1 males by the treatment.

In adult F1 offspring (Cohorts 1a and 1b), a slight but significant decrease in triiodothyronine (T3) at 1000 and above was observed in males, but no other effects were seen on thyroxin or thyroid histopathology. In F1 females, significant increases in absolute/relative thyroid weight (18%/25%) and decreased colloid area/increased follicular cell height were observed at 2000 ppm. Analysis of follicular cell height and T4 or TSH levels did not show a consistent positive correlation among the different cohorts/generations of treated animals.

The NOAEL for parental toxicity was 13.9 mg/kg bw/day based on increased thyroid hormones and histopathological changes in P females. There were no treatment related effects on reproductive organs, reproductive indices (mating, fertility, or gestation) or other effects including sperm parameters in either P-generation or F1 cohort 1a or 1b. The reproductive NOAEL was 106.7 mg/kg bw/day in males and 136.8 mg/kg bw/day in females, the highest dose tested.

Developmental toxicity

Increased resorption rate, reduction in foetal weight and increased frequency of skeletal variations are common embryo/fetotoxic effects of carbendazim observed in rats and rabbits. The lowest reported NOAEL was 10 mg/kg bw/day. For maternal toxicity, the following were reported: NOAEL of 30 mg/kg bw/day in rats and 20 mg/kg bw/day in rabbits (NICNAS 2020).

Extended one-generation reproductive toxicity study

In the EOGRTS described above, there were no treatment related effects on live litter size or pup viability, anogenital distance, developmental landmarks, organ weights, or histopathology of the F1 and F2 offspring. At the highest dose, the number of litters with dead pups (6/27) was higher compared to control. At this dose 15 pups died during lactation compared to only one from the control group. The majority of the dead pups during lactation was from one litter (10/15 deaths). No deaths occurred in other dose groups, or in any of the F2 offspring. Body weight gain of F1 male pups at 2000 ppm was significantly decreased from PND 4−18 by 10%, correlating with absolute mean body weights decreases of 6-7% (not significant) from PNDs 14-21. After weaning, body weights of F1 male offspring in both Cohorts 1a and 1b remained decreased, compared with controls (7−10 %), but were not significantly decreased at later time points. Mean body weights of F2 females were significantly decreased by 8-11% on PNDs 24−28.

Developmental neurotoxicity was not apparent in any of the cohorts. There were no effects of treatment on clinical signs, ophthalmology, FOB parameters, motor and locomotor activity, auditory startle parameters, brain weights, gross brain measurements, microscopic brain measurements and brain neuropathology, or other neuropathological findings. Statistically significant differences in brain morphometric measurements were of small magnitude and did not show a dose-response and were therefore not considered treatment-related.

Prenatal Developmental Toxicity Study - Rat

The US EPA has reviewed two new developmental studies (Dotson et al. 2020).

In the first developmental toxicity study, groups of 25 presumed pregnant Crl:CD BR rats were administered 0, 5, 10, 20 or 90 mg/kg bw/day carbendazim (technical, 98.8%) by gavage in 0.5% aqueous methyl cellulose vehicle. Doses were administered from days 7 through 16 of gestation, inclusive. Pregnant rats were sacrificed on gestation day 22.

At the highest dose (90 mg/kg bw/day), the number of litters with viable foetuses was reduced. The low number of dams that delivered pups at 90 mg/kg bw/day was due to a combination of lower pregnancy rate (19/25 dams, an effect unrelated to treatment), and three dams with total litter resorptions. The total litter resorptions are considered to be potentially attributable to maternal toxicity. The maternal NOAEL was 20 mg/kg bw/day based on increased total litter resorptions observed in the 90 mg/kg bw/day group.

At the top two doses the mean percentage of foetuses with variations related to retarded development was significantly increased. The total incidence expressed as a mean percent of foetuses was 42% and 53%, at 20 or 90 mg/kg bw/day, respectively. At 20 mg/kg bw/day vertebrae showed increases in bipartite ossification (21 foetuses in 8 litters) and dumbelled centrum (44 incidents in 13 litters) along with misaligned sternebrae and extra ossification of the ribs. At 90 mg/kg bw/day, malformations included a variety of conditions, mainly of the head (exencephaly, domed head), eyes (anophthalmia, microphthalmia or eye bulge), clubbed paws and the skeleton (fused vertebrae, ribs and sternum or malformed scapula). A significant decrease in foetal body weight was also observed at the top two doses. At 90 mg/kg bw/day decreases in mean live foetuses per litter (24%) and an increase in early and late resorptions, including three total litter resorptions were observed. The developmental NOAEL in this study was 10 mg/kg bw/day based on decreased foetal body weight and an increased incidence of skeletal variations seen at 20 mg/kg bw/day (LOAEL).

Prenatal Developmental Toxicity Study - Rabbit

In the second reported developmental toxicity study (EPA - MRID 00154466), carbendazim (98.7%) was administered to pregnant Hra(NZW)SPF rabbits (20/dose) by gavage in 0.5% aqueous carboxymethyl cellulose vehicle. The doses were 0, 10, 20 or 125 mg/kg bw/day, and the dosing was from days 7 through 19 of gestation. Does were sacrificed on gestation day 29.

At 20 mg/kg bw/day, an increase in mean percentage resorptions (3.8-fold above controls), including one total litter resorption, and a slight decrease in implantations (-22% below controls) were observed. These changes were not statistically significant when compared to controls.

At 125 mg/kg bw/day, two does aborted (GD 22 and 25) and a marked increase in the incidence of mean percentage resorptions (13 fold above controls), including loss of 7/16 litters and resorptions/dam (15 fold above controls) was observed. A decrease in implantations (-23% below controls) and reduced corpora lutea/dam (-17% below controls were also observed. The maternal NOAEL in this study was 20 mg/kg bw/day based on decreased implantations per dam and an increased incidence in resorptions (including total litter resorptions) at 125 mg/kg bw/day.

At 20 mg/kg bw/day, increased mean percentage resorptions (3.8 fold above controls), including one total litter resorption were observed, which resulted in a decreased number of live foetuses/dams. Since the resorptions were largely seen in a single litter, the effect was not considered to be treatment related. At 125 mg/kg bw/day, these effects were more pronounced, with 7 litters completely resorbed and decreased live foetuses/dam (−28% below controls) in the remaining 9 litters. Incidences of fused ribs and malformed cervical vertebrae (including hemivertebra, fused centra/arches and vertebrae that were asymmetric, bifid, unilaterally ossified or unossified) were increased in litters and individual foetuses at levels that exceeded historical control ranges. The total foetuses with skeletal malformations were slightly increased, consisting primarily of malformed cervical vertebrae and interrelated malformations of the ribs (fused) and proximate thoracic vertebrae. The developmental NOAEL was 20 mg/kg bw/day based on increased resorptions and reduced live foetuses/dam.

Overall conclusion

Short and long term repeat dose studies with carbendazim gave conflicting results on reproductive and developmental toxicity. Several published studies reported significant adverse effects in rats and rabbits. Sakr and Shalaby (2014) observed decrease in testes weight, diameter, and germinal epithelial height of the seminiferous tubules in rats administered carbendazim by gavage. Histological results revealed degeneration of seminiferous tubules and loss of spermatogenic cells. In this study, carbendazim also caused elevation of testicular malondialdehyde (MDA), a marker of lipid peroxidation, and reduction in superoxide dismutase and catalase activities.

Two published studies evaluated toxicity from single gavage doses to MBC (Nakai *et al.* 1992) or to benomyl (Hess et al. 1991) and a third evaluated testicular effects following 2 or 7 gavage doses (Breslin et al. 2013). The two single dose studies identified LOAELs of 100 mg/kg bw based on minimal sloughing of immature testicular germ cells and seminiferous tubule histopathology. The two dose study identified epididymal toxicity at 20 mg/kg bw/day, the lowest dose tested.

The EOGRT study reviewed above (Gilmore 2014), did not show any effect of carbendazim on male or female reproductive parameters or on the tissues and organs of the reproductive system. No effects on live litter size, foetal anomalies (external, visceral, or skeletal), foetal

weight, or foetal sex ratio were observed. The F1 and F2 offspring did not show any systemic or developmental neurotoxicity.

Similarly, in a 1 year dog oral (dietary) study, carbendazim (98% pure) did not have any adverse effects on reproductive parameters, urinalysis, organ weights or liver histopathology (Dotson et al. 2020).

It has been suggested that the teratogenic and reproductive toxicity effects are observed only when carbendazim is administered as single large doses by gavage (APVMA 2012; US EPA 2020). Large loads of the chemical given by this method are not effectively detoxified by the liver and cross the placenta in high concentrations and potentiate the observed effects. Low dietary doses, on the other hand, are rapidly metabolised and cleared by the body. This is supported by the toxicokinetic data from a range-finding study where carbendazim levels in the plasma reached a peak of 16-17 µ/mL 0.4 to 4 hours after gavage administration, whereas they remained fairly constant over a period of 16 hours following dietary intake. It was inferred from these results that the absence of any effects on reproductive system in the EOGRTS was because the study animals were not exposed to high levels of carbendazim, as would be the case with gavage administration. Adverse effects on the male reproductive system were observed in the rat dermal study. More studies would be required to evaluate this further.

Carbendazim is believed to induce reproductive and developmental toxicity through alteration of several key events important in spermatogenesis (Rama et al, 2014). Microarray analysis of rats treated with carbendazim and another model testicular toxicant, 2,5-hexanedione, identified several altered sperm mRNA transcripts when compared to control. Some transcript alterations remained significantly altered after the three months recovery period (Pacheco et al. 2012).

It is unlikely that the observed adverse effects of carbendazim are due to the impurities, 2-amino-3-hydroxyphenazine (HAP) and 2, 3- diaminophenazine (DAP), present in the technical grade carbendazim. There is no evidence that these two chemicals cause reproductive or developmental toxicity in laboratory animals. Moreover, in the rat dermal study, pure carbendazim (99.8%) showed adverse effects on male reproductive system and thyroid levels. Developmental effects (increase in bipartite ossification of vertebrae and dumbelled centrum) were also observed in Crl:CD BR rats from 98.8% pure carbendazim doses as low as 20 mg/kg bw/day in the developmental toxicity study in rats (Dotson et al. 2020).

Human health risk characterisation

Critical health effects

The critical health effect for risk characterisation is testicular toxicity.

Risk assessment

Selection of Point of Departure for risk characterisation

A risk assessment of dermal exposure selected an NOAEL from a 28 day dermal study. The NOAEL from this study was 20 mg/kg bw/day. Due to the large dose-spacing in this study, a benchmark dose (BMD) analysis of several reproductive endpoints in this study was performed to determine whether a higher dose could be estimated for use as a point of departure (POD) in dermal risk assessment. The analysis concluded that a BMDL10

estimate of 68 mg/kg bw/day, established for seminiferous tubule degeneration, is suitable for use as a point of departure in dermal risk assessments for short and intermediate term dermal exposure scenarios (Reiss 2008). The USEPA reviewed the analysis and concluded it to be appropriate for risk assessment.

Vapour pressure of carbendazim is very low. Inhalation exposure in this scenario derives mainly from aerosol formation during brushing. A default 100% inhalation absorption is assumed. For inhalation risk assessment, the NOAEL of 14 mg/kg bw/day from the rat EOGRTS (oral exposure) was selected, based on alterations in thyroid hormone levels in parental and offspring animals at the Lowest Observed Adverse Effect Level (LOAEL) of 53 mg/kg bw/day.

The chosen point of departure values is expected to be protective of other effects including developmental effects and aneuploidy.

Risk characterisation for workers and the general public using carbendazim in paints

Scenario	Paint handled/day (litres)	Inhalation exposure (mg/kg bw/day)	Dermal exposure (mg/kg bw/day)	MOE Inhal.	Dermal
Open Pour Liquids	200	0.000005	0.02	v. high	3400
Airless Spray Painting	100	0.00075	0.48	v. high	142
Brush/Roller Painting	50	0.000005	0.63	v. high	108

Paint application rate is 100 litres paint per day by airless spray and 50 litres by hand brush or roller.

MOE = POD/exposure; dermal POD = 68 mg/kg bw/day; inhalation POD = 14 mg/kg bw/day

Mixing of carbendazim into paints is done in industrial scale under closed conditions and by professional trained personnel. During the incorporation process, minimal exposure to workers is expected as closed automated systems are employed. The assessment of inhalation and dermal exposure to 0.35% carbendazim during the application of paints is based on actual exposure data obtained from PHED model (US EPA 2018).

Margins of exposure (MOE) were calculated for inhalation and dermal exposures. Dermal and inhalation MOEs for both methods of paint application (brush and airless spray) were above the safety factor (100, accounting for inter- and intra-species differences), indicating acceptable risk to persons applying paint and other surface coverings containing carbendazim 0.35% or less. For workers the risks will be lower if appropriate personal protective equipment is worn. For members of the public, the risk will be lower due to the irregular use of paint and the comparatively low volumes applied.

Environmental exposure

Industrial uses of carbendazim are expected to result in both diffuse and point source emissions into the environment.

Carbendazim may slowly leach from painted surfaces and some treated construction materials, such as roofing plastic exposed to the weather through the action of rainfall (Bollmann et al., 2014; Klamer M, 2014; Klamer M, 2014a). In these products, the functional use of the chemical is as dry film preservative which means it is intended to continuously leach out of the painted surface over time, to provide long term protection from microbial degradation (Florio and Miller 2004). The surface run-off containing this chemical can be discharged directly onto soil and into surface waters through the stormwater drainage systems. These sources may contribute to cumulative diffuse emissions of carbendazim into the environment.

Carbendazim may enter municipal STPs via emissions to wastewater from factories that manufacture industrial products, such as paint formulation facilities. The release of trade waste in this way is regulated by local council, state authorities and water management

utilities and typically requires permits prior to the disposal of such residues. Depending on degradation and partitioning processes of carbendazim in STPs, emissions of the chemical in treated effluent to rivers or oceans are expected, as are emissions to soil through application of biosolids to agricultural land (Struijs 1996). Further releases of the chemical to STPs occurs from residential sources such as washing of carbendazim treated clothing and textiles or from treated toilet paper disposed to sewage (Merel et al. 2018). The domestic use of paints and adhesives may also contribute to releases of carbendazim to STP through washing and disposal processes.

Large volumes of carbendazim are used as an agricultural pesticide for the protection of various crops and pastures from fungal infection. Release from these sources will occur to soil and groundwater after application of these chemicals to crops. Runoff from treated fields will result in releases to surface waters. Therefore, a significant proportion of the chemical released to the environment may originate from these non-industrial sources.

Carbendazim is also a degradation product of other benzimidazole carbamates, such as benomyl or thiophanate-methyl (APVMA 2010; NCBI 2022b). Some proportion of carbendazim detected in the environment may be due from the degradation of these chemicals.

Environmental fate

Partitioning

Carbendazim will partition to soil and the water compartments after release into the environment.

Carbendazim is slightly soluble in water at neutral and basic pH. However, it is charged and moderately soluble in acidic waters. The chemical has a low volatility and is not expected to appreciably volatilise to air from surface water or soils.

Measured organic carbon absorption coefficients (K_{oc}) for carbendazim range from 122–2805 vary depending on pH, organic carbon content and clay content (ECHA 2019; NCBI 2022a). Carbendazim may be expected to be mobile in soils with low levels of organic matter (Paszko 2014). In a water/sediment system, carbendazim is expected to partition mostly into the aqueous fraction rather than absorb to sediments.

Calculations with a standard multimedia partitioning (fugacity) model assuming equal and continuous distributions to water and soil compartments only (Level III approach) predict that carbendazim will mainly partition to the soil compartment (75.5%), with a substantial partitioning to the water compartment (24.3% in aqueous phase and 0.29% in sediment) and negligible amounts (0.001%) into the air compartment (US EPA 2017). Fugacity calculations assuming distribution to water only suggest that carbendazim will predominately stay in the water compartment (98.8%) with minimal partitioning to sediments (1.2%).

Degradation

Carbendazim is resistant to biodegradation in environmental waters but may not persist in sediments and soil.

The main primary degradation pathway identified in various degradation tests appears to involve the loss of the carbamate moiety to produce 2- aminobenzimidazole (2-AB, CAS RN 934-32-7) (ECHA 2019; US EPA 2019b; US EPA 2020).

Carbendazim undergoes limited degradation under standard biodegradation screening tests. In a study performed by the Japanese Chemicals Inspection & Testing Institute, with conditions comparable to OECD 301C, 0% degradation was observed after 28 days according to O2 consumption (NITE). In a study according to OECD guideline 301 B, <20% degradation was observed according to measured CO2 production (ECHA 2019).

The degradation of carbendazim under water/sediment systems is variable but indicates potential for persistence. The primary half-life for carbendazim in a European water/sediment study was determined to be 15.1–76.8 days at 20°C (ECHA 2019). Water/sediment studies available to the US EPA suggest primary half-lives for carbendazim of 23–61 days (pH 7.3–8.6) and 356–554 days (pH 5.2–5.8) in various sediment types (US EPA 2020).

Carbendazim can be slowly biodegraded by aerobic soil micro-organisms. Primary metabolism half lives in aerobic soils range from 12–320 days (ECHA 2019; US EPA 2019b; 2020). Field dissipation studies available to the US EPA, with minimal leaching of carbendazim, demonstrated dissipation of carbendazim with half-lives of 22–94 days (US EPA 2020). Similarly, field dissipation studies in Germany found dissipation half-lives ranging from 11–78 days (ECHA 2019).

Carbendazim is stable to photolysis and to hydrolysis at pH 5 and 7 but can be slowly hydrolysed in alkaline waters. In one hydrolysis study, 30% of the parent compound was transformed to 2-aminobenzimidazole over 164 days at pH 9 (ECHA 2019).

Bioaccumulation

The chemical is not expected to bioaccumulate in aquatic organisms.

The measured log K_{OW} obtained for carbendazim is below the domestic threshold for bioaccumulation potential. A bioconcentration factor (BCF) of 27 in fish has been reported for this chemical (INERIS 2017), which indicates a low potential to bioaccumulate in aquatic organisms.

However, carbendazim has been found in terrestrial organisms and in plants growing on treated soil. Given its systemic properties, carbendazim residues in soil are absorbed through the roots and transferred to plant tissues, including nectar (up to 27 µg/kg) and pollen (range 13-1800 µg/kg), thus contaminating the food sources of pollinators (Johnson et al. 2010; Stoner and Eitzer 2013). Residues of carbendazim up to 29 ng/g body weight were found in 24% of bumblebees collected from urban East Sussex (UK), with lower levels up to 1.2 ng/g in bees from the surrounding arable land, suggesting the main source of contamination is industrial uses (Botías et al. 2017).

Environmental transport

While carbendazim has some potential to undergo long range environmental transport, detections of carbendazim in remote regions have not been identified during this evaluation.

The chemical is persistent in the aquatic environment and is highly mobile in soils. This indicates that carbendazim may have potential for long range transport in water, as the chemical will be resistant to degradation and limited proportions of the chemical will settle out to sediments and with particulates. However, no information has been identified that suggests that carbendazim has been detected in remote regions of the world far from sources of release.

Carbendazim is not volatile and has a short calculated atmospheric half-life (0.6 hrs). These properties limit the potential for this chemical to undergo long-range transport through the atmosphere.

Predicted environmental concentration (PEC)

In various waters and soil PECs for carbendazim have been selected based on domestic STP effluent concentrations and international monitoring of soils and stormwaters.

A study report commissioned by the former Department of Agriculture, Water and Environment (DAWE 2022) indicates that concentrations of carbendazim in effluents from many Australian STPs are typically below 83 ng/L. However, in pooled samples taken over several days at one STP in a major Australian city, the carbendazim concentrations in influent and effluent were 7620 ng/L and 5030 ng/L respectively (34% removal). A measured concentration of 2210 ng/L was found in another influent sample, pooled from samples from this STP taken over an 11month period. As this STP services an industrial zone of a major city, these elevated carbendazim concentrations in influents and effluents may be due to the STP receiving trade waste from one or more facilities that handle, process, or apply carbendazim. Values of 5030 ng/L and 83 ng/L are taken as the riverine PECs for release from industrial and residential STPs respectively in this evaluation.

Internationally, carbendazim is one of the most prevalent biocides detected in wastewaters, often occurring at high concentrations. In Europe, effluent concentrations of carbendazim are in the range 9−530 ng/L with similar influent concentrations (Paijens et al. 2020a). Higher concentrations of carbendazim, up to 693 ng/L, have been detected in drainage waters from agricultural uses (Masiá et al. 2015). Residues in groundwaters up to 40 ng/L have been reported (Pitarch et al. 2016).

Biosolids obtained from sewage treatment plants contain residues of carbendazim in the range 0.6−84 µg/kg dry weight (dw) (Campo et al. 2013). The calculated carbendazim concentrations in soil amended with biosolids is 3 µg/kg dw, based on measured international biosolids concentrations, typical biosolids application rates and a soil bulk density of 1500 kilograms per cubic metre (kg/m^3) (EPHC 2009).

Concentrations of carbendazim in stormwater runoff indicate the potential for leaching of this chemical from building facades and surfaces.

A stormwater monitoring study from a residential area in Denmark detected carbendazim in stormwater at concentrations up to 306 ng/L, with median detected concentration of 45 ng/L (Bollmann et al. 2014). The study estimated that on average 50 µg of carbendazim was leached from each house per rain event. The study also demonstrated that releases of carbendazim were mostly continuous and proportional to rainfall mass, indicating that higher masses of carbendazim would be released with higher rainfalls. A French study found no significant difference in carbendazim storm water concentrations between residential and industrial sites, with reported 20th−80th percentile concentrations of carbendazim in stormwater of 7–195 ng/L (Gasperi et al. 2014). In another study in Paris, carbendazim was found at concentrations of 40–49 ng/L in an underground stormwater storage pond and at 52–170 ng/L in sewerage overflow (from high flow events) (Paijens et al. 2020b).

A study investigating pesticide concentrations in soils from surface leaching found concentrations of carbendazim in soil below 5 µg/kg in samples adjacent to painted residential walls (Bollmann et al. 2017).

While Australian products and Australian weather may not be completely comparable to European products and conditions, these findings indicate that releases of carbendazim during rain events may occur in Australia and contribute to environmental carbendazim loads. Nevertheless, the PEC for carbendazim in stormwater is assumed to be 50 ng/L in line with the average concentrations from two good quality monitoring studies (Bollmann et al. 2014; Paijens et al. 2020b). The higher bound concentration of carbendazim detected in European soils adjacent to residential areas, 5 µg/kg, is taken as the worst-case PEC for carbendazim in soils.

Environmental effects

Carbendazim causes toxic effects at low concentrations in aquatic organisms across multiple trophic levels.

Effects on Aquatic Life

Acute toxicity

Acute toxicity data are available for many species of aquatic organisms, including amphibians, fish, crustaceans, insects, molluscs, worms, fungi, and algae. The following are the most sensitive acute median lethal concentrations (LC_{50}) for fish and median effect concentrations (EC_{50}) for invertebrates and algae as reported in the literature (Canton 1976; Dang and Smit 2008; Ferreira et al. 2008; Palawski and Knowles 1986):

Taxon	Endpoint	Method
Fish	96 h LC_{50} = 0.012 mg/L	Experimental *Ictalurus punctatus* (channel catfish) static, nominal
Invertebrate	48 h EC_{50} = 0.15 mg/L	Experimental *Daphnia magna* (water flea) static, nominal OECD TG 202
Algae	48 h ErC_{50} = 0.34 mg/L	Experimental *Chlorella pyrenoidosa* (green algae) static, measured
	72 hr ErC_{50} = 1.3 mg/L	Experimental *Pseudokirchneriella subcapitata* static, nominal OECD TG 201

Carbendazim is a systemic fungicide with protective and curative action. It inhibits fungal mitotic microtubule formation, which prevents the migration of chromosomes during the process of cell division. This toxic mode of action is expected to also occur in aquatic organisms exposed to carbendazim.

Carbendazim is very toxic to all aquatic organisms, particularly to fish and invertebrates. Acute LC_{50} values for fish are in the range 0.012 mg/L (*Ictalurus punctatus*) to 80 mg/L (*Cyprinus carpio*). Aquatic crustaceans have acute LC_{50} values ranging from 0.150 mg/L in *Daphnia magna* to 16.8 mg/L in the shrimp *Macrobrachium ferreirai*.

Chronic toxicity

Chronic toxicity data are available for 24 species of aquatic organisms. The following measured no-observed-effect concentrations (NOEC) for model organisms across three trophic levels were obtained from the literature and from international risk assessments (Dang and Smit 2008; ECHA 2019; US EPA 2019b):

Taxon	Endpoint	Method
Fish	79 d NOEC = 0.011 mg/L	Experimental *Oncorhynchus mykiss* (rainbow trout) Flow-through, measured
Invertebrates	21 d NOEC = 0.0015 mg/L	Experimental *Daphnia magna* (water flea) Renewal, nominal
Algae	72 h NOEC = 0.5 mg/L	Experimental *Pseudokirchneriella subcapitata* static, nominal OECD TG 201

Effects on terrestrial Life

Carbendazim is toxic to soil dwelling invertebrates and has some toxicity to mammals and birds.

Carbendazim is very toxic to earthworms. Mortality studies on *Eisena andrei* and *Eisena fetida* gave LC_{50} values of 5.7 and 9.3 mg/kg dry soil respectively (OECD TG 207, artificial soil) (Van Gestel et al. 1992). The study on *E. andrei* showed significant effects on growth and reproduction (reproduction EC_{50} = 2.9 mg/kg dry soil). NOECs for growth and reproduction were 1.9 and 0.6 mg/kg respectively (Van Gestel et al. 1992).

The chemical does not appear to be toxic to bees (Apis mellifera) by acute exposures (US EPA 2020).

Carbendazim is moderately toxic to rats, with a 21 day NOEL of 100 mg/kg body weight (bw) for reproduction endpoints (ECHA 2019; IUPAC). The chemical is also moderately toxic to birds by chronic exposure with a reported NOEL of 26.4 mg/kg bw for Mallard duck (IUPAC) but is not expected to cause toxic effects to Mallard duck or bobwhite quails through acute oral exposures (US EPA 2020).

Effects on sediment dwelling life

Carbendazim is moderately toxic to benthic insect larvae, with NOEC = 0.013 mg/L for the midge *Chironomus riparius* (European Food Safety Authority 2010).

Predicted no-effect concentration (PNEC)

Based on the lowest endpoint value of 1.5 µg/L for Daphnia magna and an assessment factor of 10, the PNEC for aquatic organisms in this assessment is 150 ng/L as reliable chronic ecotoxicity data are available for three trophic levels (EPHC 2009). This value also applies to sediment dwelling organisms.

A PNEC of 6 µg/kg for soil was derived from the lowest measured chronic endpoint for earthworms (NOEC = 0.6 mg/kg dry soil), using an assessment factor of 100.

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 its stability and half-life in water at environmental conditions, carbendazim is categorised as Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on log K_{OW} and BCF values below domestic thresholds, carbendazim is categorised as Not Bioaccumulative.

Toxicity

Toxic (T). Based on available ecotoxicity values below 1 mg/L and evidence of high chronic toxicity to aquatic and terrestrial organisms, carbendazim is categorised as Toxic.

Environmental risk characterisation

Carbendazim is an industrial fungicide used widely as a dry-film preservative in architectural paints and as a preservative in other construction products such as grouts and adhesives. These uses will result in releases of the chemical to the aquatic environment via stormwater runoff and discharges to the sewage system.

The chemical is expected to leach from painted or treated surfaces into stormwater during rainfall events. Any discharges of carbendazim into stormwater drains are expected to reach surface waters in full, as the chemical is resistant to degradation in aquatic environments and stormwaters are not treated prior to release.

Carbendazim may also be released to sewage as trade waste from formulation and blending activities during the manufacture of paints and other industrial products that contain the chemical. Releases of trade waste to STP is expected to occur under the conditions of a licence or permit that establishes acceptable limits. STP processes are expected to remove

approximately 40% of carbendazim from influents (Juksu et al. 2019; Kupper et al. 2006). Most of the removed carbendazim will be captured by sludge and the remainder of the carbendazim will be released to surface waters. If the sludge is processed in a furnace the carbendazim will be destroyed, but carbendazim will remain in untreated sludge and may be released to soil if the sludge is used as a soil treatment.

Carbendazim is highly resistant to degradation in the aquatic environment and is very toxic to aquatic organisms. As such, carbendazim that is released to surface waters through stormwater or via STP has the potential to cause adverse effects to aquatic organisms.

Based on the PEC and PNEC values determined above, the following Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for release of carbendazim into the aquatic and soil environments:

Compartment	Source	PEC	PNEC	RQ
Surface water	Industrial STP effluent	5030 ng/L	150 ng/L	33.5
	Residential STP effluent	<83 ng/L	150 ng/L	<0.55
	Stormwater leachate	50 ng/L	150 ng/L	0.33
Soil	-	5 µg/kg	6 µg/kg	0.83

An RQ value greater than 1 for surface waters receiving industrial STP effluent indicates that carbendazim may pose a risk to the aquatic environment in these locations.

Information available to the Department indicates that carbendazim concentrations may be elevated in some Australian STP effluents where the STPs receive high proportions of trade waste. The concentrations of carbendazim indicate that these effluents may be high enough to cause adverse effects to aquatic organisms in the receiving river and in downstream marine environments.

An RQ less than 1 for surface waters that receive residential STP effluent indicates that carbendazim is not expected to pose a risk to the aquatic environment under typical use scenarios. Additionally, carbendazim concentrations in soils amended with sludge from STPs are not expected to be at levels of concern.

An RQ less than 1 for stormwaters indicates that the concentrations of carbendazim in stormwaters are expected to be below levels that could cause a risk to the environment. While the maximum detected concentration in stormwater (306 ng/L) was comparable to the PNEC (150 ng/L), the median concentration from the European studies was approximately 50 ng/L and was deemed more representative. A study that considers Australian paint and Australian weather events would be required to better understand how the risk of carbendazim in stormwater runoff under Australian conditions compares to the risk under European conditions.

Uncertainty

This evaluation was conducted based on a set of information that may be incomplete or limited in scope.

The available monitoring data for carbendazim in Australia may overestimate the risks from industrial uses. Effluents from STPs will contain residues from both industrial uses and agricultural sources, including metabolites of other fungicidal products. Consequently, the environmental risks from industrial uses alone of this chemical cannot be determined with certainty without further information.

The stormwater monitoring studies discussed above were conducted in Europe. Australian paints and Australian weather may differ considerably compared to the paints and weather relevant to the studies. Australian specific information, including volume of use information, would provide greater clarity regarding the risk of this environmental exposure pathway under Australian conditions.

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