Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester: Human health tier II assessment

30 June 2020

CAS Number: 10605-21-7

Preface

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

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

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

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

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

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

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

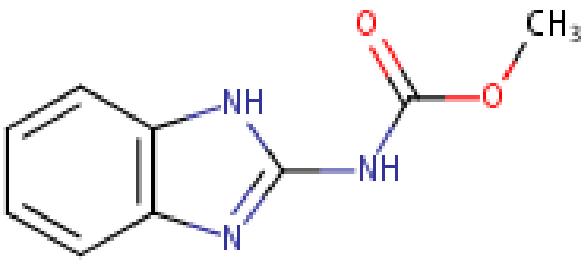
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1H-benzimidazole-2-carbamic acid, methyl ester methyl-1H-benzimidazol-2-ylcarbamate 2-(methoxycarbonylamino)benzimidazole carbendazim
Structural Formula	
Molecular Formula	C9H9N3O2
Molecular Weight (g/mol)	191.19
Appearance and Odour (where available)	Odourless, colourless or light-grey or white powder.
SMILES	c12c(cccc1)N=C(NC(=O)OC)N2

Import, Manufacture and Use

Australian

The chemical is used as a film preservative in paints at very low concentrations (NDPSC, 2010).

The chemical has non-industrial use as a fungicide for agricultural application (APVMA, 2009).

International

The following international uses have been identified through Galleria Chemica, the Substances and Preparations in Nordic countries (SPIN) database, and other publicly available sources.

The chemical has domestic uses, including as:

- a preservative in paints; and
- an active ingredients in fillers, adhesives, binding agents, and in timber treatment.

The use of the chemical as a preservative in paints, textiles, leather and paper has been identified from various online databases.

The chemical has site-limited uses including in impregnation and in construction materials.

The chemical has non-industrial use as a fungicide for agricultural application in other countries (Government of Canada, 2011; JMPR, 2005).

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 7 (SUSMP, 2016).

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'. Schedule 7 chemicals are labelled with ' Dangerous Poison' (SUSMP, 2020).

International

The chemical is listed on the following (Galleria Chemica):

- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;

- Chile List of substances which must not form part of the composition of cosmetic products;
- China List of banned substances for use in cosmetics;
- Costa Rica Prohibited and Restricted Pesticides;
- European Union (EU) Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard - Schedule 4: Components cosmetic products must not contain - Table 1; and
- United Arab Emirates Restricted Chemicals.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is listed on the Hazardous Substances Information System (HCIS) (Safe Work Australia).

Germ cell mutagenicity – Category 1B; H340 (May cause genetic defects)

Reproductive toxicity – Category 1B; H360FD (May damage fertility. May damage the unborn child)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

An occupational exposure limit of 10 mg/m^3 in Germany and Poland. In Russia, the maximum allowed concentration in the air of workplace zone is 0.1 mg/m^3.

Health Hazard Information

The chemical, referred to as carbendazim in this assessment, is a breakdown product of benomyl (CAS No. 17804-35-2) and thiophanate-methyl (CAS 23564-05-8); both chemicals are listed on the Australian Inventory Chemical Substances (AICS). The chemical causes chromosomal damage (JMPR, 2005). During cell division, it interferes with the function of tubulin, a protein responsible for polymerisation of microtubules. In the last step of cell division, microtubules are responsible for the proper segregation of chromosomes (Lodish, 2000). Disruption in this cellular process results in mitotic arrest and faulty chromosomes. The damage is more prominent in rapidly dividing cells. This is suggested to be the underlying mechanism of action for the testicular damage and birth defects caused by carbendazim exposure in laboratory animals (see **Reproductive & Developmental Toxicity** section) (IPCS 1995; JMPR, 2005).

Toxicokinetics

The toxicokinetics of the chemical have been investigated in several studies in humans, rats and mice. Based on the results, carbendazim is rapidly absorbed, metabolised and excreted following oral exposure. The chemical is rapidly eliminated within the first three days from exposure and elimination slowed down after this period. Approximately 60 % of the chemical is excreted in the urine as the conjugated form 2-(methoxy-carbonylamino)-5-hydroxybenzimindazole (5-HBC) and ~35 % eliminated in the faeces as conjugated and free forms of 5-HBC.

The main urinary metabolite identified in an oral study in Sprague Dawley (SD) rats was 5-HBC in males and methyl(5-hydroxy-6-oxo-6H-benzimidazol-2-yl)carbamate (5,6-HOBC) N-oxide in females (MAK, 2015). Other minor metabolites identified include sulfuric and glucuronic acid conjugates of methyl (5,6-dihydroxy-1H-benzimidazol-2-yl)carbamate and 2-amino-benzimidazole) (Government of Canada, 2011; MAK, 2015).

The metabolism of carbendazim in rats involves oxidation and conjugation at the phenyl ring to form sulfate and glucuronide conjugates of 5-hydroxy- and 5,6-dihydroxy-carbendazim. These metabolic processes are followed by phenyl ring oxidation and N-oxidation (more prominently in female rats) (Government of Canada, 2011).

The concentration of the chemical in the blood of rats peaks within 15-40 minutes after administration. Seven and 14 days after the last treatment, the liver contained 0.3 % and 0.08 % of the administered dose, respectively. In other tissues, including the kidneys, blood, fat, muscle and gonads, 0.01 µg/kg of carbendazim residues were identified (IPCS, 1995). In another rat study, the majority of carbendazim was excreted in the urine and only 1 % was eliminated in the faeces (Government of Canada, 2011).

In a radiolabelling study in mice, carbendazim was found in the liver and kidney 10 minutes after oral exposure (Government of Canada, 2011). Approximately 80 % of the chemical was excreted in the urine within 24 hours of dosing. Compared to rats, the metabolism of the chemical is slower in mice.

In humans, the level of the metabolite 5-HBC excreted in the urine following oral, dermal and intravenous administration was proportional to the administered dose (IPCS, 1995).

The chemical is poorly absorbed following dermal exposure in rats (IPCS, 1995). In vivo, dermal application of 0.1 % weight per weight (w/w) carbendazim (12 or 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). The reported in vivo dermal absorption of carbendazim is approximately 4.5 % within four hours (APVMA, 2009).

In Wistar rats and Swiss mice, carbendazim (~200 to 1000 mg/kg bw/day) induced activity of the following enzymes: 7-ethoxycoumarin-O-deethylase; biphenyl-4-hydroxylase; aniline hydroxylase; 4-methoxybiphenyl-N-demethylase; cytochrome c reductase; and glucuronyl transferases I and II (MAK, 2015).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bw. Observed sub-lethal effects include histopathological changes in the testes and epididymides. Following oral exposure to 1000 mg/kg bw of carbendazim, the testes appeared small, soft and discoloured. The rats showed degenerated tubules (more than 70 %) and reduced sperm count in the epididymides (IPCS, 1995).

Dermal

The chemical has low acute toxicity based on the results from animal tests following dermal exposure. The LD50 in rats is >2000 mg/kg bw (IPCS, 1995). No further details were provided.

Inhalation

The chemical has low acute toxicity based on results from animal tests following inhalation exposure for one or four hours. The median lethal concentration (LC50) in rats is >5 mg/L (IPCS, 1995). No further details were provided.

Corrosion / Irritation

Skin Irritation

The chemical causes at most slight, transient dermal irritation based on studies in New Zealand White (NZW) rabbits and guinea pigs.

In NZW rabbit study, 5 g of the chemical, administered as Benlate C (50 % wettable carbendazim powder), was applied to intact, clipped skin for four hours. The animals were monitored and scored, using the Draize scale, for treatment-related effects including erythema and oedema four, 24, 48, and 72 hours after carbendazim exposure. Under the conditions of the test, no dermal irritation was reported (IPCS, 1995). In another rabbit study, slight transient irritation was observed following application of 75 % wettable carbendazim powder formulation to the intact and abraded skin. No further details were reported (IPCS, 1995).

In guinea pigs (strain unspecified), application of 75 % wettable carbendazim powder formulation in dimethyl phthalate to intact shaved skin of albino guinea pigs resulted in mild irritation (IPCS, 1995). No further details were provided.

Eye Irritation

The eye irritation potential of carbendazim was investigated in NZW rabbits. The available data are not sufficient to recommend hazard classification.

Based on the publicly available data from studies predating Good Laboratory Practice (GLP), the chemical at 50 % wettable powder formulation is a slight to moderate eye irritant in NZW rabbits. Slight corneal opacity, mild or moderate conjunctival redness, and slight or mild conjunctival oedema were observed in six male rabbits. Moderate inflammation of the iris (iritis) was noted in 3/6 rabbits and one animal displayed minimal discharge containing blood. No corneal damage was seen during microscopic examination. Effects were reversible in two rabbits within 72 hours after exposure (IPCS, 1995).

The chemical was not considered an eye irritant in rabbits when applied as 75 % wettable powder (IPCS, 1995). In this study, transient corneal opacity was noted in 6/6 unwashed and in 2/3 washed eyes. Mild to moderate corneal opacity and conjunctival irritation were also reported following application of the chemical. However, these effects were reversible within four days. The report indicated that the observed response was likely due to the 'inert ingredient' in the powder formulation used in the study (IPCS, 1995).

Sensitisation

Skin Sensitisation

The chemical was not found to induce dermal sensitisation when tested in guinea pigs up to 75 %.

Two Buehler tests were undertaken in 20 Hartley guinea pigs. Inductions were performed by applying 40 or 50 % carbendazim to skin sites, three times a week for three weeks. Dermal reactions were scored 24 hours after each induction exposure. The challenge exposure used either 40 or 50 % carbendazim, administered two weeks after the last induction. Effects were scored 24 and 48 hours after each challenge exposure. The results of the tests indicated that the chemical was not a skin sensitiser (APVMA, 2009).

In another study, 75 % wettable powder formulation or technical grade carbendazim did not produce skin reactions following intradermal administrations or repeated exposures to intact, shaved skin of 10 albino guinea pigs (IPCS, 1995). No further details were provided.

The chemical did not produce a reaction in a maximisation test in Hartley guinea pigs (n=10). The intradermal and topical induction used 5 % or 25 % of the chemical in water. Epicutaneous challenge was performed using 1 % or 5 % carbendazim in water (MAK, 2015).

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 in contact with the chemical while harvesting fruit or during treatment at a dermatological clinic. No further details were provided (MAK, 2015).

Repeated Dose Toxicity

Oral

A number of studies in rats and dogs were conducted to evaluate the repeat dose toxicity of carbendazim following oral exposure. The observed effects are not sufficient to recommend hazard classification.

In a 90-day oral toxicity study, Wistar rats (n=10/sex/group) were administered 0, 16, 32, 64 mg/kg bw/day of carbendazim by gavage. The results showed changes in the kidney in caused by carbendazim at all doses. Tubular dilation and hydropic degeneration (accumulation of water) in kidneys were observed in males at 16 mg/kg bw/day (lowest dose) (Government of Canada, 2011). Fibrosis and congestion of the kidneys and reduction of blood urea levels were reported in males at 32 mg/kg bw/day. Elevated bilirubin levels in the serum were seen in males at 32 mg/kg bw/day and females at 64 mg/kg bw/day. Hyalinisation, extensive vascular congestion and significant increase in alkaline phosphatase (ALP) activity were observed in males at 64 mg/kg bw/day. The study was poorly reported with no clear no observed adverse effect level (NOAEL) (IPCS, 1995; Government of Canada, 2011).

In a 90-day oral study, rats (n=16/sex; strain not specified) were exposed to a diet containing 0, 50, 150, 450 or 1350 ppm of carbendazim (approximately equivalent to 0, 12, 35 and 106 mg/kg bw/day for males and 0, 13, 39 and 116 mg/kg bw/day for females). The results showed slight increase in the liver weight in females at 39 mg/kg bw/day. Males showed increase in kidney weight at 106 mg/kg bw/day. Females exhibited increase in spleen and thyroid weights, reduced total serum protein and food consumption during the recovery phase at 116 mg/kg bw/day. No adverse treatment-related effects were observed in this study. The NOAEL values reported for this study were 106 and 116 mg/kg bw/day, for males and females, respectively (Government of Canada, 2011).

In a similar repeat dose oral study, Wistar rats were given diet containing 0, 80, 400, 2000 ppm and 10000 ppm of carbendazim (equivalent to approximately 0, 6.5/6.9, 32/36, 163/174, 780/847 mg/kg bw/day, males/females respectively) for 93 days. The results indicated a transient increase in relative liver weight at 6.9 mg/kg bw/day in females and 163 mg/kg bw/day in males. At 780 mg/kg bw/day, one male had small testes and showed atrophy of the seminerous tubules. Reduced body weight was reported at the highest dose. The NOAELs derived from this study were 163 and 174 mg/kg bw/day, for males and females respectively (JMPR, 2005).

Subchronic and chronic oral toxicity studies (90 days to one year) were conducted to examine the effects of carbendazim in beagle dogs. The concentrations tested ranged from approximately 3 mg/kg bw/day to 800 mg/kg bw/day, administered either through diet or oral gavage (IPCS, 1995; Government of Canada, 2011). The lowest NOAEL values reported were 9.7 (males) and 10.2 mg/kg bw/day (females) for the 90-day studies and 6.4 (males) and 7.2 mg/kg bw/day (females) for the one-year study. Effects observed in higher doses in the 90-day studies include the following:

- increase in relative weights of the thyroid, liver, and adrenal glands and decrease in the relative heart weight at 45 mg/kg bw/day;
- histopathological findings in the liver in one female at 177.4 mg/kg bw/day; and

- dose-related decrease in red blood cell counts, microscopic lesions in the stomach, alterations in the spleen and liver and degenerative changes in kidneys, testes and ovaries from 80 mg/kg bw/day.

Dogs treated with carbendazim at doses 16.5 (males) and 17.1 mg/kg bw/day (females) for one year showed increased liver weight and changes in haematological parameters (Government of Canada, 2011).

Findings in the same organs were reported in the 28-day oral studies in rats and dogs. In rats, liver weight increase was observed at 100 mg/kg bw/day and degeneration of testicular tissue was observed at 200 mg/kg bw/day. At this dose, changes in spermatogenesis and oogenesis were also noted. At 2500 mg/kg bw/day, rats exhibited pathological changes in the liver and kidneys. In dogs, treatment with 96 mg/kg bw/day of carbendazim elevated liver enzymes (alanine transaminase (ALT) and ALP), and disseminated focal lesions in the liver of male dogs. Female dogs showed increased liver weight and slightly swollen hepatocytes at 19 mg/kg bw/day (Government of Canada, 2011).

Dermal

Based on the treatment-related effects reported in sub-chronic toxicity studies in rabbits and rats, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a 21-day dermal study in rabbits (strain not specified), 0, 10, 50 and 250 mg/kg bw/day of carbendazim, in an aqueous solution, was applied to the skin of the animals for six hours a day, five days a week. Although treatment-related dermal effects (erythema, dryness at the scarified sites and thickening) were observed, no systemic toxicity was reported (Government of Canada, 2011). In another 21-day study in NZW rabbits, the chemical did not cause any treatment-related effects on mortalities, clinical and haematological parameters and bodyweight at doses of up to 10000 mg/kg bw/day (APVMA, 2009).

The potential repeat dose dermal toxicity of the chemical was also investigated in rats (strain not specified). In this study, rats were exposed to 0, 20, 120, 480, and 720 mg/kg bw/day of carbendazim, suspended in corn oil, six hours a day, five days a week for approximately four weeks (Government of Canada, 2011). At $\geq$ 120 mg/kg bw/day, the following effects were reported: mild to severe degeneration of seminiferous tubules and mild to severe hypospermia in the lumen of the epididymal tubules in males; and increased liver weight in females. Other effects reported in males at the higher doses included sperm granulomas, decrease in epididymal sperm concentration, increase in the percentage of abnormal sperm, changes in sperm motility and efficiency of daily sperm production, increased grip strength in the forelimb and increased relative liver weight. In females, slight changes in the haematology parameters and increased grip strength in the forelimb and hindlimbs were observed at higher doses. The NOAELs from this study were 20 mg/kg bw/day for males and 120 mg/kg bw/day for females (Government of Canada, 2011).

Inhalation

No data are available for the chemical. However, a chemical which is metabolised to carbendazim (benomyl), produced olfactory degeneration in the nasal cavity following exposure of rats (strain not specified) at concentrations of $\geq$ 0.05 mg/L or 13 mg/kg bw/day for males and 0.2 mg/L or 52 mg/kg bw/day for females (Government of Canada, 2011). It is not clear whether these effects are attributable to carbendazim. No further details were provided.

Genotoxicity

The chemical is classified as hazardous with the hazard category 'Germ cell mutagenicity — Category 1B' and hazard statement 'H340 (May cause genetic defects)' in the HCIS (Safe Work Australia). The available data support this classification based on the weight of evidence (APVMA, 2009; Government of Canada, 2011; IPCS, 1995; JMPR, 2005). Based on information provided during the public comment period, further evaluation of the impact of substance purity on genotoxicity and whether there is a threshold effect for carbendazim-induced aneuploidy is required.

In vitro, the chemical gave positive results in the following assays:

- bacterial reverse mutation assays (with metabolic activation) in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, TA1538 and weakly positive in TA1530, TA1950 and G46 his^- (Fiscor et al., 1978; IPCS, 1995);

- mutation in the thymidine kinase (*tk*) locus in L5178Y mouse lymphoma cells with metabolic activation;
- induction of aneuploidy in human lymphocytes at ≥ 200 ng/mL; and
- disruption of meiotic cell cycle in CF-1 mouse oocytes at ≥ 600 ng/mL (JMPR, 2005).

The minor metabolite of carbendazim, 2-amino-benzimidazole, induced forward and reverse bacterial mutation (Government of Canada, 2011).

In vitro, the chemical gave negative results in the following assays:

- bacterial gene mutation assays using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1530, TA1950 (with and without activation) (Fiscor et al., 1978; Pandita, 1988; IPCS, 1995);
- bacterial gene mutation assays using *Escherichia coli* strain WP2 hcr;
- hypoxanthine phosphoribosyl transferase (HRPT) gene mutation in Chinese hamster ovary (CHO) cells at ≤654 µmol/L (IPCS, 1995);
- sister chromatid exchange (SCE) in CHO cells at ≤40 µg/mL and human lymphocytes at ≤30 µg/mL;
- chromosomal aberration (CA) in human lymphocytes at ≤0.5 mg/mL;
- recombination assays in *Bacillus subtilis* (≤1000 µg/disc), *S. typhimurium* TA1535, TA1538, and *E. coli* K12 (≤2000 µg/plate);
- unscheduled DNA synthesis in rat and mouse hepatocytes (≤12.5 µg/mL) (IPCS, 1995); and
- aneuploidy in *Saccharomyces cerevisiae* (Government of Canada, 2011).

In vivo, the chemical gave positive results in the following assays:

- CA in ICR mouse nucleated anaphase cells following oral exposure to 1000 mg/kg bw twice (spindle effects) (IPCS, 1995);
- gene mutation in mouse embryos with in utero exposure to the chemical by treating the mother with 200 mg/kg bw of carbendazim; and
- aneuploidy induction in Syrian hamster oocytes and Wistar rat sperm (≥150 mg/kg bw) (JMPR, 2005).

A number of studies reported micronuclei formation in NMRI and B6D2F1/Cr-1BR mouse bone marrow and Swiss mouse colon epithelial cells following oral exposure to ≥500 mg/kg bw/day carbendazim. In the bone marrow of Wistar rats and spermatids of SD rats, micronuclei formation was observed at ≥150 and ≥100 mg/kg bw/day of carbendazim, respectively (JMPR, 2005). In a mouse micronucleus formation assay, a positive result was obtained following intraperitoneal (i.p.) injection of ≤6000 mg/kg bw of carbendazim. However, in a similar study, the chemical gave a negative result at ≤500 mg/kg bw (IPCS, 1995).

The chemical tested negative in the following in vivo assays:

- CA in bone marrow of rats and Chinese hamsters orally treated with 300 and 10000 mg/kg bw of carbendazim, respectively;
- micronucleus formation in mice at 500 mg/kg bw;
- aneuploidy induction in mouse (102/El x C3H/E1)F1) sperm;
- sex-linked recessive lethal assay and germ-line aneuploidy in *Drosophila melanogaster*; and
- dominant lethal mutation in NMRI mouse.

The chemical does not bind directly to DNA. The mechanism of action underlying the toxicity of carbendazim is the ability to bind to tubulin and inhibit polymerisation. As a result, formation of spindles during cell division is prevented and this affects the segregation of chromosomes (JMPR, 2005). Carbendazim has been reported to inhibit microtubule assembly in the testes of young SD rats (Lim & Miller, 1997). It also inhibited mitosis in *Saccharomyces pastorianus* and *Aspergillus nidulans*

(Government of Canada, 2011). The positive results in some of the in vitro and in vivo studies described above support the suggested mode of action.

Carcinogenicity

Several long term studies were conducted to evaluate the carcinogenic potential of carbendazim. The results indicated no evidence of carcinogenicity in rats and dogs and some evidence of carcinogenicity in mice. The available data are not sufficient to recommend hazard classification.

Oral exposure of female Wistar rats (n=60/sex) to 0, 150, 300, or 2000 ppm of carbendazim (approximately equivalent to 0, 7.5, 15 and 100 mg/kg bw/day) for two years did not result in treatment-related mortality. Observed effects included changes in organ weights and biochemical parameters. Although tumours were seen, these were comparable in all groups, including controls. Under the conditions of this study, carbendazim is not considered to be carcinogenic. The NOAEL reported was 300 ppm or 15 mg/kg bw/day (IPCS, 1995). In a similar study, the chemical did not cause an increase in tumour incidences in ChR-CD rats following oral exposure up to 300 mg/kg bw/day (highest dose tested) for two years (MAK, 2015).

In CD-1 mice, liver tumours were reported following oral exposure to 0, 500, 1500, 7500 ppm (approximately equivalent to 0, 81, 257, and 1560 mg/kg bw/day for males and 0, 125, 380 and 1886 mg/kg bw/day in females) for two years. These include hepatocellular adenomas in females in all dose groups and hepatocellular carcinomas in both sexes at ≥ 1500 ppm or 257/380 mg/kg bw/day (Government of Canada, 2011; MAK, 2015).

Groups of 100 male and 100 Swiss mice were exposed to diet containing 0, 150, 300, or 1000 mg/kg of carbendazim (approximately equivalent to 0, 19, 37 or 600 mg/kg bw/day) for two years. The results showed an increased incidence of liver tumours from 300 ppm or 37 mg/kg bw/day and above. These include adenomas and carcinomas combined in males and adenomas in females. The NOAEL reported from this study was 150 ppm or 19 mg/kg bw/day (MAK, 2015).

When tested in a long term study in a mouse strain known to have low incidence of spontaneous tumours, carbendazim did not cause tumours up to 5000 ppm. In this study, NMRK-f mice were given diet containing 0, 50, 150, 300, 1000 or 5000 ppm (equivalent to approximately 0, 5.8, 17.1, 34.4, 522 mg/kg bw/day in males and 0, 7.1, 21.2, 41.9 and 648 mg/kg bw/day in females) for 22 months. Although granulosa cell tumours and luteomas in the ovaries were reported at 300 ppm or 41.9 mg/kg bw/day, these effects were statistically not significant compared with controls (IPCS, 1995; Government of Canada, 2011). Carbendazim has been suggested to enhance spontaneous liver tumours in susceptible strains but is not a direct carcinogen in mice (Government of Canada, 2011).

No tumours were reported in beagle dogs following oral exposure to carbendazim (doses: 100-2500 ppm) for up two years (Government of Canada, 2011).

Reproductive and Developmental Toxicity

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.

During the public comment period, a two-generation reproductive toxicity study and additional information on the mode of action and role of substance purity were received. Further evaluation of the information is required and as such this information has not been included in this assessment.

Developmental 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 most commonly observed effects are foetal malformations, in particular of the head and eyes. In these studies, the lowest reported NOAELs were 10 mg/kg bw/day with corresponding lowest observed adverse effect levels (LOAELs) of 20 mg/kg bw/day in rats and rabbits. For maternal toxicity, the following were reported: NOAEL of 30 mg/kg bw/day in rats and 20 mg/kg

bw/day in rabbits; and LOAEL of 60 mg/kg bw/day in rats and 125 mg/kg bw/day in rabbits. In hamsters, no developmental effects were observed at 15 mg/kg bw/day.

In several studies in different species of rats (SD, Crl:CD BR, ChR-CD), oral exposure (by gavage or dietary) to carbendazim at doses from 5 to 3000 mg/kg bw/day during gestational days (GD) 6-15 resulted in the following foetal effects:

- increased skeletal variations at ≥ 20 mg/kg bw/day;
- 42 % of the foetuses had malformed head, spine, ribs and sternum and decreased placental and foetal weights at 30 mg/kg bw/day;
- significantly delayed or in some cases, absent ossification in cervical vertebral bodies at 44.9 mg/kg bw/day;
- 51 % resorptions and malformations in 90 % of surviving foetuses at 60 mg/kg bw/day;
- increased malformations including fluid accumulation in the cranium (hydrocephaly) and abnormally small (microphthalmia) or missing eyes (anophthalmia) at 90 mg/kg bw/day;
- high incidence of embryolethality with the surviving foetuses all being malformed at 100 mg/kg bw/day;
- delayed or absent ossification in the limbs, sternebrae, and skull bones and increased incidence of supernumerary ribs at 371.4 mg/kg bw/day; and
- all foetuses died and 100 % early resorptions at ≥ 300 mg/kg bw/day.

Single dose exposure (gavage) of rats to carbendazim produced higher rates of stillbirth at GD13 and induced increased rates of malformations from 15.6 mg/kg bw/day. In hamsters, a single dose exposure (gavage) to carbendazim at GD8, increased percentages of resorptions and dead foetuses were noted at 30 mg/kg bw/day. Malformations including exencephaly and fused ribs were reported at doses from ≥ 75-150 mg/kg bw/day (Government of Canada, 2011).

The corresponding maternal effects observed in these studies include the following:

- reduced bodyweight from 60 mg/kg bw/day;
- increased liver weight at 90 mg/kg bw/day; and
- reduced food consumption at 371.4 mg/kg bw/day (Government of Canada, 2011).

However, overt maternal and foetal toxicity were not reported in 2- and 3-generation reproduction studies in rats up to 100 mg/kg bw/day carbendazim (Government of Canada, 2011).

In an animal cap assay (embryo manipulation), the chemical induced severe embryotoxic effects in *Xenopus laevis*. In this study, the isolated tissues from the pole region of the frog embryos (n=25) (late blastula stage) were exposed to 0 (control) and 1-7 µM carbendazim for 96 hours. This study reported an LC50 of 5-6 µm. Among the carbendazim-induced embryotoxic effects were optic hernias, malformations in the neural tube, notochord and tail, cephalic and abdominal oedema, gut dysplasia, narrow head, and disaggregation of brain cells (Yoon et al., 2007).

The chemical was reported to cross the placental barrier in rats.

In vitro, 24 hours' exposure of the human trophoblast HTR-cells to carbendazim and a chemical which metabolises to carbendazim (benomyl) (up to 5 µM) caused cell viability inhibition, cell cycle abnormality, promoted apoptotic cell death and disrupted cellular migration (Zhou et al., 2014).

Reproductive toxicity

Results from a number of studies (acute, subacute, longer term, and multigeneration) conducted in Wistar rats, mice and Syrian hamsters indicated that carbendazim is 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. The most commonly observed effects in these studies were testicular effects and abnormalities in spermatogenesis. Additionally, carbendazim has androgenic activity and caused alterations in hormones associated with reproduction (see **Other effects**: **endocrine disruption** section).

A special study was conducted in male rats (strain not specified; n=20/group) to evaluate the effects of carbendazim on spermatogenesis. A single oral exposure of 50 mg/kg bw carbendazim induced morphological alterations of spermatids (sloughing of round and elongated spermatids) and slight growth abnormality of the efferent ductules in rats. In one animal, atrophy of a few seminiferous tubules in one testicle was seen at 50 mg/kg bw (JMPR, 2005). At 100 mg/kg bw, germ cells disappeared and a dose-dependent increase in testicular weights was noted. A dose-dependent increased incidence in occlusion of efferent ductules in the testes and atrophy of the seminiferous tubules was observed at doses ≥100 mg/kg bw. The occluded ducts showed compacted luminal contents, spermatic granulomas, and fibrotic connective tissue which was mineralised and obliterated the original lumen. The mean diameter of the seminiferous tubules was significantly increased at 400 and 800 mg/kg bw (JMPR, 2005).

Another study in rats reported testicular atrophy and very low sperm count at 200 and 400 mg/kg bw/day. These resulted in reduced numbers of pregnant females and lower foetal viability. Reduction or impairment of sperm motility, fertility, total epididymal and vas deferens sperm count and atrophy of the seminiferous tubules were also seen at 400 mg/kg bw/day. Carbendazim exposure resulted in enlarged spermatids causing chromosomal anomalies in an embryo (APVMA, 2009).

In a five-day mouse (unspecified strain) oral gavage study, exposure to 500-1000 mg/kg bw/day of carbendazim resulted in reduced percentage of round spermatids, increased sperm head abnormalities, reduced testicular weight and altered chromatin structure (Government of Canada, 2011).

Significant reductions in testicular and seminal vesicle weights and epididymal sperm counts were observed in male offspring of Syrian hamsters with prenatal exposure to 400 mg/kg bw/day carbendazim. At this dose, post-implantation losses were reported in the parental females. Litter sizes at 200 and 400 mg/kg bw/day were also significantly reduced. Compared to rats, carbendazim was less toxic to Syrian hamsters (IPCS, 1995).

Other Health Effects

Neurotoxicity

The chemical has been reported to disrupt the outgrowth of neurites during development (APVMA, 2009). In an older study, transient loss of full control of bodily movements (ataxia) and leg weakness were reported to occur in hens following oral exposure to 5000 mg/kg bw/day of carbendazim (APVMA, 2009; Government of Canada, 2011).

Endocrine Disruption

The potential endocrine-disrupting activity of carbendazim has been investigated in laboratory animals.

In SD rats (n=5/group), changes in the endocrine function, reproductive and developmental toxicity and the ability of flutamide (androgen receptor antagonist) to block the carbendazim-induced reproductive toxicity were examined. A preliminary dose ranging study was conducted to determine the doses (up to 800 mg/kg of carbendazim and 100 mg/kg of flutamide) and exposure period (28 and 56 days).

Carbendazim produced androgenic activity in the reproductive organs of female SD rat offspring with prenatal exposure to 200 mg/kg bw/day dose. The vagina in 1/5 females failed to develop; 3/5 had an enlarged urethra; and incomplete development of the uterus occured in 2/5 females. A pair of seminal vesicles near the intersection of the uterus and vagina was observed in 1/5 female offspring. Carbendazim-induced testicular toxicity at 675 mg/kg bw/day was blocked by co-treatment with the anti-androgen flutamide. In males, carbendazim caused dose-dependent increases in concentrations of androgen receptors in rat testis and epididymis. In a ligand binding assay part of this study, 5-alpha-dihydrotestosterone was displaced from the androgen receptor when carbendazim doses of 5, 50 and 500 µM were added to rat testis or epididymis homogenates. Based on these findings, the authors suggested that carbendazim has potential endocrine-disrupting activity (Lu et al., 2004).

In another study, in utero exposure of SD rats to carbendazim affected offspring viability and demonstrated androgenic activity in male rats as shown by increased anogenital distance, an androgen-dependent marker on PND2. However, no androgenic effects were noted in female offspring (Lu et al., 2006).

Changes in the endocrine function of rats were observed in two oral gavage studies in male Long-Evans rats following exposure to 0, 50, 100, 200 and 400 mg/kg bw/day carbendazim for 85 days. The results indicated compensatory changes in hypothalamic and pituitary control of the testes in carbendazim-induced testicular damage. This is evident in the increase of the anterior hypothalamic gonadotropin-releasing hormone (GnRH) following exposure to 50 mg/kg bw/day carbendazim. At doses ≥100 mg/kg bw, changes in other hormones were observed including increase in anterior pituitary luteinizing hormone (LH) and slight decrease in medio-basal hypothalamic GnRH. Increase in serum follicle stimulating hormone (FSH) was reported at ≥200 mg/kg bw/day. At ≥200 mg/kg bw/day, the decrease in rat testis and caput (head) epididymis weights and seminiferous tubule fluid volume was accompanied by increase in androgen binding protein in interstitial and seminiferous tubule fluid. The concentrations of androgen binding protein in the serum and the testosterone in the interstitial fluid were elevated at 400 mg/kg bw/day (IPCS, 1995; Government of Canada, 2011). In another study, 150 mg/kg bw/day carbendazim induced histological changes in the thyroid, parathyroid and adrenals of rats following oral gavage for 15 weeks. At 300 mg/kg bw/day, rats showed increased level of triiodothyronine (T3) (Barlas et al., 2002).

In vitro, exposure of the decapsulated testes to 200 and 400 mg/kg bw/day of carbendazim has increased the synthesis and release of testosterone by Leydig cells after challenge with human chorionic gonadotrophin (HCG) (IPCS, 1995; Government of Canada, 2011).

Based on these observations, the potential for the chemical to cause endrocrine disruption cannot be ruled out. In the priority list of endocrine disruptors created by the EU for further assessment, the chemical was assigned to 'Category 2—at least some in vitro evidence of biological activity related to endocrine disruption' (APVMA, 2012). The endrocrine disrupting activity is largely addressed by the classification for fertility which addresses the consequences of the androgenic activity.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects including mutagenicity, reproductive toxicity and developmental toxicity. Further evaluation of the mode of action, whether there is a threshold effect for carbendazim-induced aneuploidy and the impact of substance purity is required.

Public Risk Characterisation

The chemical is currently listed in Schedule 7 of the Poisons Standard. At concentrations greater than 0.1 %, a number of warning statements, first aid instructions and safety directions relating to chemical apply and is only available only to specialised or authorised users who have the skills necessary to handle them safely. These current controls are considered adequate to limit the public exposure and minimise the risk to public health posed by products containing the chemical.

Any further evaluation of the reproductive toxicity and genotoxicity data should consider whether any amendments to the Poisons Standard are warranted.

Occupational Risk Characterisation

During product formulation, 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

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

Based on the available data, the hazard classification in the HCIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. Further evaluation of the reproductive toxicity and genotoxicity data should be undertaken.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2020).

Work Health and Safety

The chemical is classified as hazardous for human health in the Hazardous Chemicals Information System (HCIS). This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Genotoxicity	*	May cause genetic defects - Cat. 1B (H340)
Reproductive and Developmental Toxicity	*	May damage fertility or the unborn child - Cat. 1B (H360FD)

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

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

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

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

- air monitoring to ensure control measures in place are working effectively and continue to do so;

- health monitoring for any worker who is at risk of exposure to the chemical[s], if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

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