Proposed Registration Decision PRD2011-04

# Carbendazim

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# Overview

## Proposed Registration Decision for Carbendazim

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Carbendazim Technical and Polyphase 678, containing the technical grade active ingredients carbendazim and 3-iodo-2-propynyl N-butylcarbamate (iodocarb), as a material preservative.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Carbendazim Technical and Polyphase 678.

## What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on carbendazim, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on carbendazim, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

## What Is Carbendazim?

Carbendazim is currently registered in Canada as a fungicide to control Dutch elm disease (*Ophiostoma ulmi* and *Ophiostoma novo-ulmi*). Carbendazim is a broad spectrum fungicide with systemic activity that inhibits fungal mitotic microtubule formation, thus affecting the growth and division of spores.

## Health Considerations

### Can Approved Uses of Carbendazim Affect Human Health?

Potential exposure to carbendazim may occur during the treatment of materials or when handling treated materials. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers).

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. In general, the health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when products are used according to label directions. The risk assessment is conducted to ensure that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The end-use product, Polyphase 678, was of low acute toxicity in rats via the oral, dermal and inhalation routes, was minimally irritating to the eye and slightly irritating to the skin of rabbits, and was not a dermal sensitizer in guinea pigs.

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Health effects in animals exposed to carbendazim included effects on the liver, kidney, testis and blood parameters. Carbendazim does not cause mutations in genetic material, but affects cell division, resulting in an alteration in the number of chromosomes in cells. Carbendazim produced tumours of the liver and ovaries in mice given daily doses over their life span. No effects on reproduction were observed in animal reproductive toxicity tests, but other studies have demonstrated that the reproductive system, including fertility, of male rodents is affected following exposure to carbendazim. When carbendazim was given to pregnant animals, serious effects on the developing fetus were observed at doses that were not toxic to the mother, indicating that the fetus is more sensitive to carbendazim than the adult animal. These effects included malformations of the head, spine, ribs and sternum as well as early death of the embryo. There is currently a lack of information regarding the potential for carbendazim to impair development of the nervous system in the young. Because of these observations, extra protective factors were applied in the risk assessment to further reduce the allowable level of human exposure to carbendazim.

**Risks in Residential and Other Non-Occupational Environments**

**Estimated risks for non-occupational exposure are not of concern.**

Homeowners handling consumer products containing Polyphase 678 and individuals contacting surfaces treated with products containing Polyphase 678 can be exposed to residues of carbendazim and 3-iodo-2-propynyl N-butylcarbamate (iodocarb) on the skin and through incidental oral (hand-to-mouth) exposure. Taking into consideration the expected exposure, risks to these individuals are not of concern.

**Risks in Secondary Occupational Environments**

**Estimated occupational risks to secondary workers are not of concern.**

Workers handling consumer products containing Polyphase 678 can come in direct contact with carbendazim and 3-iodo-2-propynyl N-butylcarbamate (iodocarb) residues on the skin. Taking into consideration the expected exposure, risks to these individuals are not of concern.

**Occupational Risks From Handling Polyphase 678**

**Occupational risks are not of concern when Polyphase 678 is used according to the proposed label directions, which include protective measures.**

Chemical handlers who mix and load Polyphase 678 can come in direct contact with carbendazim and 3-iodo-2-propynyl N-butylcarbamate (iodocarb) residues on the skin or by inhalation. Therefore, the label specifies that chemical handlers mixing and loading Polyphase 678 must wear full face protection with cartridge respirator and chemical resistant gloves, coveralls, cap and boots. The label also requires that a closed system be used when mixing and loading Polyphase 678. Taking into consideration these label statements, the amount of product

handled and the expectation of the exposure period for chemical handlers, risks to these individuals are not a concern.

## Environmental Considerations

### What Happens When Carbendazim Is Introduced Into the Environment?

Carbendazim is persistent in soil and moderately persistent in water, but is not likely to leach to groundwater. Carbendazim has a low solubility in water and is not likely to volatilize. Carbendazim was found to be somewhat toxic to aquatic organisms but bioaccumulation is unlikely. As carbendazim is to be used as a material preservative for use in aqueous paints and stains, masonry coatings, adhesives, caulks and sealants, joint cements, and inks, exposure to non-target organisms in the environment is considered to be negligible if used according to the product label.

## Value Considerations

### What Is the Value of Polyphase 678?

**Polyphase 678 is a broad spectrum fungicide for use as a dry-film and in-can material preservative.**

Polyphase 678 contains two active ingredients; carbendazim and iodocarb. Together they provide a broad spectrum activity against fungal organisms that are known to create spoilage problems under industrial conditions, therefore increasing the service life of the materials in which the product will be added. Polyphase 678 provides effective protection against decay fungi as a dry-film preservative for paints, stains and adhesives. It will also provide fungal control as an in-can and a dry-film preservative in joint cements, sealants, caulks, grout, and inks.

## Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Polyphase 678 to address the potential risks identified in this assessment are as follows.

### Key Risk-Reduction Measures

### Human Health

Because there is a concern with users coming into direct contact with Polyphase 678 on the skin or through inhalation of spray mists, chemical handlers mixing and loading Polyphase 678 must wear full face protection with cartridge respirator and chemical resistant gloves, coveralls, cap and boots. The label also requires that a closed system be used when mixing and loading Polyphase 678.

## Next Steps

Before making a final registration decision on carbendazim, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

## Other Information

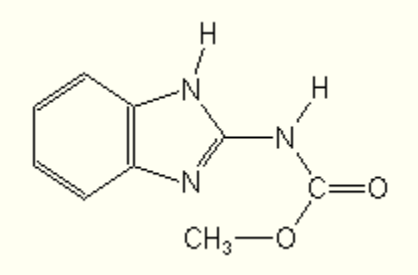
When the PMRA makes its registration decision, it will publish a Registration Decision on carbendazim (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

# Science Evaluation

## Carbendazim

## 1.0 The Active Ingredient, Its Properties and Uses

### 1.1 Identity of the Active Ingredient

| | |
|---|---|
| **Active substance** | Carbendazim |
| **Function** | Fungicide |
| **Chemical name** | |
| **1. International Union of Pure and Applied Chemistry (IUPAC)** | Methyl benzimidazol-2-ylcarbamate |
| **2. Chemical Abstracts Service (CAS)** | Methyl *N*-1*H*-benzimidazol-2-ylcarbamate |
| **CAS number** | 10605-21-7 |
| **Molecular formula** | $C_9H_9N_3O_2$ |
| **Molecular weight** | 191.2 |
| **Structural formula** |  |
| **Purity of the active ingredient** | 99.0% |

## 1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

### Technical Product—Carbendazim Technical

| Property | Result |
|---|---|
| Colour and physical state | White |
| Odour | Odourless |
| Melting range | 302–307°C |
| Boiling point or range | Not applicable |
| Density | 0.40–0.50 g/cm$^3$ at 20°C |
| Vapour pressure at 20°C | $<1 \times 10^{-7}$ Pa |
| Ultraviolet (UV)-visible spectrum | $\lambda_{max}$ = 242.5 – 244 nm, not expected to absorb at $\lambda$ >300 nm |
| Solubility in water at 20°C | pH: 4, 7, 8<br>Solubility (mg/L): 28, 8, 7 |
| Solubility in organic solvents at 20°C | Solvent: hexane, benzene, dichloromethane, chloroform, acetone, ethanol, dimethylformamide<br>Solubility (mg/L): 0.5, 36, 68, 100, 300, 300, 5000 |
| *n*–Octanol-water partition coefficient ($K_{ow}$) | log $K_{ow}$ = 1.49 |
| Dissociation constant (p$K_a$) | 4.2 |
| Stability (temperature, metal) | Stable at 35–50°C |

**End-Use Product—Polyphase 678**

| Property | Result |
|---|---|
| Colour | Off-white |
| Odour | Slight |
| Physical state | Liquid |
| Formulation type | Solution |
| Guarantee | Carbendazim … 15.0%<br>3-iodo-2-propynyl butyl carbamate ... 5.0% |
| Container material and description | Metal or plastic drums, pails and intermediate bulk containers, 0.45 kg to 1043.28 kg |
| Density | 1.15–1.25 g/cm$^3$ at 25°C |
| pH of 1% dispersion in water | 7.1–7.8 |
| Oxidizing or reducing action | Not an oxidizing or reducing substance |
| Storage stability | Stable for 1 year at room temperature |
| Corrosion characteristics | Not corrosive to the container after one year storage at room temperature |
| Explodability | Not explosive |

## 1.3 Directions for Use

The following are use levels for Polyphase 678. Use rates are provided in percentage by weight and refer to the product Polyphase 678. In order to determine the most effective use level for Polyphase 678 in a given use, field trials are suggested within the label rates.

PAINTS AND STAINS. For dry-film protection of aqueous latex-based paints and stains:
Interior use: 0.2% to 0.4%
Exterior use: 0.8% to 1.5%
ADHESIVES (Dry-film protection):
Use 0.08% to 0.2%.
GROUTS, CAULKS and SEALANTS (In-can and dry-film protection):
For water-based grouts, silicone-based caulks, water-borne and latex-based sealants, use 0.2% to 0.3%.
JOINT CEMENTS (In-can and dry-film protection):
Use 0.02% to 0.5%.
INKS (In-can and dry-film protection):
Use 0.03% to 0.3%.

### 1.4 Mode of Action

Carbendazim is a systemic fungicide with protective and curative action. It inhibits fungal mitotic microtubule formation.

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Carbendazim Technical have been validated and assessed to be acceptable for the determinations.

### 2.2 Method for Formulation Analysis

Not applicable.

### 2.3 Methods for Residue Analysis

Not applicable.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

Carbendazim is an active ingredient currently registered to control Dutch Elm Disease through application by tree injection. Carbendazim is also a metabolite of another pesticidally active ingredient registered for use in Canada, thiophanate-methyl, as well as a metabolite of benomyl, a pesticide that is no longer registered for use in Canada. A detailed review of the toxicological database for carbendazim was conducted for the registered tree injection use of carbendazim and more recently as part of the re-evaluation of thiophanate-methyl (PMRA Toxicology Re-evaluation of Carbendazim, 2004; REV2007-12). The toxicology re-evaluation of carbendazim relied on registrant-supplied data and reviews from other jurisdictions (i.e. the USEPA, the United Kingdom, Germany, and the World Health Organization). Available published studies were also considered in the evaluation.

With the exception of a developmental neurotoxicity (DNT) study and a repeated-dose (28-day or 90-day) inhalation study, which were identified as data requirements in REV2007-12, the database for carbendazim is complete and consists of the full array of toxicity studies currently required for hazard assessment purposes. Most of these toxicity studies were conducted in accordance with accepted international testing protocols and good laboratory practices in place at the time of conduct. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to carbendazim.

To support the current application for a major new use for carbendazim, the applicant supplied a 28-day rat dermal toxicity study that was conducted subsequent to the PMRA re-evaluation, as well as a 5-day rat inhalation study conducted in 2003 that was not included in the re-evaluation. It should be noted that the applicant plans to conduct a one-generation reproductive toxicity study in rats with carbendazim in the near future, which will include an assessment of developmental neurotoxicity as per the OECD extended one-generation reproductive toxicity test guideline.

The major critical effects noted in the toxicological database for carbendazim were liver, testicular and developmental toxicity. The manifestation of these effects may be related to the mode of action of carbendazim. Carbendazim is an aneugen (a substance which produces aneuploidy, chromosome loss, non-disjunction, etc.) that acts by interfering with the assembly of microtubules, particularly with the spindle apparatus necessary for normal cellular division.

Metabolism studies in rats and mice indicated rapid absorption, metabolism and excretion following oral administration of radiolabelled carbendazim, with maximum blood concentrations occurring 15-40 minutes after administration of a single low dose (3 mg/kg bw) and within four hours after administration of a single high dose (300 mg/kg bw). One study indicated approximately 85% of orally administered carbendazim was absorbed following a single dose (12 mg/kg bw). Mice that were subjected to whole body autoradiography showed most of the radiolabel was located in the liver ten minutes after a single oral dose, with relatively high amounts in the kidneys as well. Within 24 hours of dosing, more than 80% of radiolabelled carbendazim was excreted, with urine as the main route of excretion. In rats, approximately 60% of the radiolabel was found in the urine and 35% in the feces after single and repeat dosing. Other studies showed that excretion in the rats occurred almost exclusively in the urine, irrespective of sex or dose, with only 1% in the feces, whereas fecal excretion in mice was somewhat higher (10-27%). Residual radiolabel in the tissues was minimal, with only 0.3% and 0.08% of the administered radioactivity detected in the liver of rats at seven and 14 days, respectively, after the last of ten daily doses at 2 mg/kg bw. Levels in blood and other organs (kidney, fat muscle, and gonads) did not exceed 0.03% of the administered dose seven days after the last of ten daily doses. Almost all of the metabolites identified in both urine and feces were in the form of glucuronide and sulphate conjugates. After cleavage of these conjugates, the major compounds were 5-hydroxy-2-benzimidazolecarbamate (5-HBC) (39-90%), carbendazim (2-6%), 2-aminobenzimidazole (2-AB) (2-4%), and hydroxylated-2-aminobenzimidazole (up to 5%) in both rodent species. There was no measurable difference between rats and mice with regard to the metabolism of carbendazim, although the residual content in the liver was generally lower in rats than in mice, indicating that the detoxification capacity of mouse liver was saturated more readily than that of rat liver.

Several studies were conducted to determine if drug metabolizing enzymes were induced in the liver. While the results of most of the studies were equivocal, one study showed slight to moderate induction of phase I and II drug metabolizing enzymes in both rats and mice. As noted previously, the detoxification and elimination of carbendazim and its metabolites proceeded more rapidly in rats than in mice, as reflected by the increased glutathione content in the rat liver and the increased activity of phase-II enzymes. A study examining the effect of carbendazim on respiratory chain enzymes in the rat concluded that the toxicity of carbendazim and its metabolites did not appear to be related to interference with mitochondrial respiratory function.

In acute toxicity testing, carbendazim was of low toxicity in mice, rats, guinea pigs, rabbits and dogs by the oral route. Weight loss was common to all species. In the mouse, liver pathology (pale colour, inflammation, white spots, and extramedullary hematopoesis) was noted. In the rat, toxic effects included changes in the appearance of the testes (soft, small, and dark), interference with spermatogenesis and cellular degeneration of the testes. Carbendazim was of low toxicity in rats and rabbits by the dermal route and in rats by inhalation. Carbendazim was non- to mildly irritating to the eyes of rabbits and skin of rabbits and guinea pigs, and non-sensitizing in guinea pigs in both the Buehler and Maximization tests.

The end-use product, Polyphase 678, was of low acute toxicity in rats via the oral, dermal and inhalation routes, was minimally irritating to the eye and slightly irritating to the skin of rabbits, and was not a dermal sensitizer in guinea pigs using the Maximization method.

Short-term dermal toxicity studies conducted on rabbits revealed dermal irritation but no systemic toxicity. One supplemental study reported slight tremors, increased leucocytes, decreased cholinesterase activity and histological lesions of the stomach, intestines, and kidneys, but these findings were reported to occur at lower doses relative to three other dermal studies where no systemic toxicity was observed. In a recently conducted 28-day dermal toxicity study in rats, no signs of dermal irritation were observed, but systemic effects, in the form of testicular toxicity and non-adverse increases in liver weight, were observed. The testicular effects included seminiferous tubule degeneration, sperm granulomas, and increased abnormal sperm, as well as reduced sperm concentration, production and motility. Slight reductions in red blood cell parameters were noted in females as well as slight increases in forelimb and/or hindlimb grip strength in both sexes.

In a non-guideline 5-day inhalation study with carbendazim, there were no adverse effects up to an exposure concentration of 0.178 mg/L. However, a 90-day inhalation study using benomyl resulted in olfactory degeneration in the nasal cavity of treated rats at an exposure concentration of 0.05 mg/L.

In short- and long-term dietary and gavage studies in the rat and dog, the primary target organs in both species were the liver and kidney, with severe testicular effects observed at higher doses. The nature and severity of effects differed depending on the method of dosing. In short-term dietary studies, increased liver weight was the primary effect in rats and dogs with associated liver pathology and body weight effects at higher doses in the dog. More severe effects occurred at lower doses via gavage in both rats and dogs, including haematological and biochemical

effects, degenerative kidney lesions, and pathological changes in the liver (inflammatory reactions, swollen hepatocytes, hepatic periportal infiltration, hepatic regeneration) as well as mortality in rats.

Testicular changes following high-dose, short-term gavage and dietary dosing included lower testis weight, inhibition of spermatogenesis, degeneration of germinal epithelium, and sperm reduction. Although one study reported testicular effects at lower doses in dogs than in rats, the findings were sporadic with no clear indication of increased species sensitivity to this effect. The germinal cell sloughing noted in the testes following exposure to carbendazim may be due to the inhibition of microtubule formation in the Sertoli cells and in the mitotic apparatus of dividing germinal cells (McCarroll et al., 2002).

Following long-term dosing, liver effects were noted in mice, rats and dogs. Effects in mice included hepatocellular swelling, necrosis, and cell hypertrophy in centrilobular and intermediate areas. Increased liver weights with elevated serum alanine aminotransferase and/or alkaline phosphatase levels were noted in rats and dogs. Studies using a wettable powder formulation containing 53-72% carbendazim showed increased severity of spontaneous pericholangitis and cholangiohepatitis in the rat and swollen, vacuolated hepatic cells, hepatic cirrhosis, and chronic hepatitis in dogs. Testicular effects (atrophic tubules and interstitial mononuclear inflammatory cell infiltration) were noted in one male dog from the 2-year study with carbendazim. Diffuse and focal testicular atrophy were also noted at the low dose in a 2-year dog study using a wettable powder formulation containing 53-72% carbendazim; however, there was no effect at the higher doses and a treatment-related effect was not established.

Carbendazim has been tested in a large number of reverse mutation assays, with slightly more than half showing positive results, usually after activation. However, in those studies in which a compound of high purity was used, the results were generally negative, suggesting that the mutagenicity was likely due to the presence of one or more impurities. Carbendazim samples containing aminophenazines (2,3-diaminophenazine or 2-amino-3-hydroxy-phenazine) were mutagenic, whereas highly purified carbendazim (99.5%) and its main metabolite, 5-HBC, were not. However, 2-AB, a minor metabolite in the rat, was positive in Ames and DNA damage/repair tests. In mammalian mouse lymphoma cell cultures, carbendazim was mutagenic in some tests, but once again, highly purified carbendazim was non-mutagenic. Tests of DNA damage and repair and sister chromatid exchange were also negative.

As indicated previously, carbendazim is a known aneugen. However, aneuploidy induction by carbendazim, thiophanate-methyl and benomyl is an indirect effect, which does not involve direct DNA interaction, and is reported to demonstrate threshold characteristics (Elhajouji et al., 1997; Bentley et al., 2000; Pratt and Barron, 2003; Decordier et al., 2002). There is growing consensus that for aneugens, a NOAEL below which aneuploidy is not induced can and should be defined (Bolt and Degan, 2004; Bolt et al., 2004). McCarroll et al. (2002) suggest that, since cells have an excess of microtubules, spindles can function normally despite some damage, and that carbendazim or other chemicals can reduce the number of functioning spindles without causing perceptible effects until the threshold level is reached.

Carbendazim is also known to affect microtubule polymerization and spindle formation, which in turn affects mitosis/meiosis and chromosome segregation. In strains of yeast and fungus, carbendazim caused chromosome malsegregation and mitotic disjunction. Mitosis was inhibited in *Saccharomyces pastorianus*, and mitosis and cell division were inhibited in *Aspergillus nidulans*. In *Saccaromyces cervisiae*, carbendazim induced mitotic and meiotic chromosome gain (aneuploidy). Carbendazim also inhibited polymerization of mammalian tubulin, although to a lesser extent than in fungal systems. In vitro effects on chromosomes in mammalian cell cultures were generally positive. Carbendazim induced aneuploidy, polyploidy and increased micronuclei formation in cultured human lymphocytes and in a mouse/human hybrid. In in vivo tests, a series of mouse micronuclei tests were positive. Other studies with rats and hamsters as well as studies with *Drosophila melanogaster* were negative. In tests involving germ cells, the mouse and rat dominant lethal assays were largely negative; however, chromosomal aberrations were noted in rat sperm and increases in aneuploidy were noted in unfertilized oocytes of hamsters. A study in hamsters showed that high acute doses given during meiosis I (oocyte maturation) or meiosis II (fertilization), which are microtubule-dependent events, could lead to early pregnancy loss.

No evidence of carcinogenicity was found in the long-term rat studies. Two of the three mouse oncogenicity studies available for carbendazim showed a dose dependent increase in liver adenomas and carcinomas. In one study, the combined incidence of hepatocellular adenomas and carcinomas increased with increasing doses in both males and females. Hepatoblastoma was also noted in this study and was described as a unique finding in this strain of mice. In the second study, a clear carcinogenic response in the form of hepatocellular carcinomas was observed in females at the two higher doses. In a study using a strain of mice which is known to have a low incidence of spontaneous liver tumours, no liver carcinogenicity occurred up to a dietary level of 5000 ppm, although there was marked hepatotoxicity and an increase in ovarian granulosa cell tumours and luteomas. It was suggested that the hepatotoxic action of carbendazim may enhance the spontaneous hepatic tumour rate of susceptible strains; thus, the effect of carbendazim on tumour formation in mice may be the result of a secondary mechanism. However, no mechanistic data have been submitted in support of this hypothesis.

The postulated precursor steps to carbendazim-induced liver tumour formation include inhibition of tubulin polymerization, disruption of spindle formation, inaccurate segregation of chromosomes, and lagging and/or loss of chromosomes in the liver cells. Tumour formation follows as a result of increased cellular hypertrophy, cellular proliferation and increased liver weights (McCarroll et al., 2002). However, data supporting this hypothesis are lacking in a number of areas: there are no studies on mouse tubulin binding, no in vivo assays of aneuploidy in the liver, and no clear data on cell proliferation relative to dose and time (McCarroll et al., 2002). A linear low-dose extrapolation approach for the cancer risk assessment was deemed appropriate.

In a series of developmental toxicity studies in the rat, some of which were single dose studies, treatment-related effects on development included reductions in fetal body weight, delayed or absent ossification, and malformations affecting the head, spine, ribs and sternum (reduction in thoracic vertebral bodies, supernumerary ribs, exencephaly, hydrocephaly, anophthalmia, and

microphthalmia). In a gavage study in hamsters, fetal malformations included exencephaly and fused ribs. Rabbit gavage studies produced fetal effects including malformed cervical vertebrae and interrelated malformations of the ribs and proximal thoracic vertebrae. In several rat and rabbit gavage studies as well as the hamster study, fetal effects occurred at doses lower than those that produced mild maternal toxicity, indicating that the fetus was more sensitive to the toxic effects of carbendazim than maternal animals. Developmental effects in dietary studies occurred at a dose approximately two-fold higher than the dose that produced effects via gavage. Fetal effects from dietary administration were primarily ossification-related, even at increasing doses, which were less severe than the malformations produced in gavage studies.

In two- and three-generation dietary reproductive toxicity studies in the rat, there were no signs of parental or offspring toxicity and no apparent adverse effects on reproduction at the dose levels tested, although it is possible that higher doses could have been tolerated. These reproductive toxicity studies did not include an assessment of some of the endpoints, including spermatogenesis, required by current test guidelines. However, a number of published and unpublished studies have been conducted to analyse the effect of carbendazim on male fertility and spermatogenesis using higher doses than those used in the reproductive toxicity studies. Acute doses in rats blocked division of spermatogonia at the metaphase stage, interfered with spermatogenesis, produced degeneration of germinal epithelium, and reduced testes weight (testes were small, soft, discoloured and sometimes of unequal size). One study measured acute effects on testes, efferent ductules, and spermatozoa at two and 70 days after dosing. Two days after dosing, there was an initial increase in testicular weight, missing germ cells at all stages, sloughing of elongated spermatids, pathological changes in efferent ducts (ductal blockage, ≥50% occluded efferent ductules) and an increase in the mean seminiferous tubular diameter. After 70 days, there was a dose-related decrease in mean testicular weight and mean seminiferous tubule diameter due to increased seminiferous tubular atrophy. A parallel study showed a reduction of sperm head counts, which reached a maximum at eight days post-dosing. By this time many sperm heads were separated from their flagella and 10% of heads were misshapen. Sperm motility was significantly decreased at eight and 16 days after dosing, but returned to control levels by day 32. Two studies in which male rats were gavage-treated with carbendazim for ten consecutive days showed early reversible infertility in some rats and irreversible infertility in others, with reduced testicular weight, epididymal weight and sperm count, and an increase in follicle stimulating hormone (FSH) levels. Severe seminiferous tubular atrophy (>85%) occurred in males that failed to recover fertility. In subchronic gavage studies (~55-85 days), fertility, sperm motility, sperm morphology and hormonal levels were altered, and reproductive potential was reduced. Testicular damage was accompanied by compensatory changes in hypothalamic and pituitary regulation. Increased serum FSH and luteinizing hormone levels were noted. An increase in gonadotropin releasing hormone in the anterior hypothalmus was followed by a dose-related decline. Increased levels of testosterone in seminiferous tubule fluid were observed, while androgen-binding protein was increased in seminiferous tubule fluid and in serum. Hormonal effects appeared to occur indirectly, as a result of carbendazim-induced testicular damage, rather than through direct hormonal interference.

Similar testicular effects were noted in other rodent species, but at higher doses than in the rat. A study in which male mice were treated with carbendazim for five consecutive days and examined at seven, 24 and 39 days post-treatment showed reduced testes weight, increased abnormalities in sperm head morphology and alterations in round, elongating and elongated spermatids. By day 39, the ratios of the various cell types and testicular weight were starting to return to normal. In a direct comparison between rats and hamsters, carbendazim was less toxic to hamsters with respect to both dose and effect. Treatment in hamsters produced reduced testicular and epididymal sperm counts, and reduced testis and seminal vesicle weights, with no effect on fertility or fetal viability, in contrast to the increased post-implantation loss, reduced fertility and effects on sperm morphology and motility that occurred in rats at similar and lower doses.

A study comparing benomyl and carbendazim showed that little testicular damage was caused by injection of benomyl into rat testis after one or two hours; however, carbendazim elicited severe disruption of the seminiferous epithelium. These results suggested that carbendazim, the benomyl metabolite, rather than benomyl itself, is the mediator of testicular toxicity and the inhibitor of testicular microtubule assembly.

The neurotoxic effects of carbendazim, as examined in hens and chickens, were limited to mild transient effects that occurred at high doses only, without histological evidence of neuropathy. In an acute delayed neurotoxicity study in hens, systemic toxicity and transient/reversible neurotoxic signs (slight leg weakness and ataxia) were noted at the highest dose (5000 mg/kg bw); however, no neurotoxic signs were found at lower doses and no clear evidence of neuropathy was found upon histological examination (no axonal degeneration or demyelination at any dose). In a study where chickens were fed carbendazim for 21 days, one chicken showed a slight increase in serum cholinesterase and slight ataxia for approximately two days. No other neurotoxic signs appeared in any of the other chickens. As noted previously, slight increases in forelimb and/or hindlimb grip strength were observed in rats dermally dosed with carbendazim for 28 days. No neurotoxicity studies conducted via the oral route in rodents are available for carbendazim, nor are any studies available that assess the effects of carbendazim on the developing nervous system. As indicated previously, an enhanced one-generation reproductive toxicity study in rats is to be conducted with carbendazim as per the OECD test guideline and will include an assessment of developmental neurotoxicity. In a range-finding study, the applicant reported that no treatment-related effects were noted in offspring or parental animals at 2500 ppm, estimated to be equivalent to 125 mg/kg bw/day, a dose which is several orders of magnitude greater than the point of departure for the the critical endpoint of developmental toxicity.

Results of the toxicology studies conducted with carbendazim and its associated end-use product, Polyphase 678, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix I, Tables 1, 2, and 3.

**Epidemiology**
No lasting adverse effects on human health have been reported. Blood profiles of 50 workers involved in the manufacture of both benomyl and carbendazim were comparable to a control group of 48 workers not exposed to the fungicides (WHO, 1993). A study of 298 male manufacturing workers, exposed to benomyl between 1970 and 1977, indicated no reduction in fertility in the study population compared to a control population (WHO, 1993).

**Incident Reports**
Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. There were no incident reports submitted to the PMRA for carbendazim as of March 24, 2010.

In eight poisoning incidents (four confirmed), investigated by the United Kingdom Agriculture and Factory Inspectorates from 1988-1991, exposure occurred as a result of spray drift during crop spraying, and eye and face irritation were the most common complaints along with sore throats and headaches (MAFF, 1992). In each case, the spray contained a mixture of chemicals including carbendazim.

### 3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account completeness of the data with respect to the exposure of and toxicity to infants and children and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to toxicity to infants and children, extensive data were available for carbendazim. Several developmental toxicity and reproductive toxicity studies were available. However, the reproductive toxicity studies were not conducted according to the most recent test guidelines, and certain endpoints, such as sperm assessments and developmental landmarks, were not examined in these studies. The requirement for a DNT study was triggered by evidence in the toxicology database indicating the potential for carbendazim to impair development of the nervous system. This data gap is expected to be addressed by the planned conduct of an enhanced one-generation reproductive toxicity study.

With respect to concerns regarding prenatal and postnatal toxicity, there was no offspring toxicity observed in the reproductive toxicity studies in rats. However, the prenatal developmental toxicity studies provided indications of increased susceptibility of rat, rabbit and hamster fetuses following in utero exposure to carbendazim. Malformations, including hydrocephaly, microphthalmia, anophthalmia, malformed scapulae, exencephaly, hemivertebrae, and fused ribs and vertebrae, as well as increased resorptions were observed in rat fetuses in one study in the presence of mild maternal toxicity (i.e. increased liver weight and reduced body weight gain). In another rat study, malformations in fetuses included anasarca, exencephaly, meningocele, abbreviated tail, microphthalmia, hydrocephalus, and cleft vertebrae, which

occurred in the absence of effects on maternal animals. In the rabbit and hamster, increased resorptions occurred in the absence of maternal toxicity, while malformations, such as malformed cervical vertebrae and interrelated malformations of the ribs and proximate thoracic vertebrae in the rabbit and exencephaly and fused ribs in the hamster, were observed in the presence of mild maternal toxicity (i.e. decreased body weight or body weight gain).

On the basis of this information, the full 10-fold factor required under the *Pest Control Products Act* was retained in the risk assessments for residential exposure via the dermal and inhalation routes. The information driving the retention of the 10-fold factor is the high degree of concern for prenatal toxicity that is predicated on the evidence that carbendazim induces serious developmental effects (i.e. malformations and reduced viability) in fetuses in the absence of maternal toxicity. Concern regarding the lack of testing for neurotoxicity in the young is also accounted for under the 10-fold PCPA factor.

For incidental oral exposure, the concerns regarding prenatal toxicity observed in the developmental toxicity studies conducted with carbendazim are not applicable to the population of interest (i.e. children). From the available studies, no post-natal toxicity concerns were identified. However, the residual uncertainty regarding the postnatal toxicity of carbendazim remains due to the lack of a study investigating neurotoxicity in the young. For these reasons, the 10-fold factor required under the *Pest Control Products Act* was reduced to 3-fold for this exposure scenario.

### 3.2 Determination of Acute Reference Dose

An Acute Reference Dose was not required as there is no dietary exposure to carbendazim for this major new use.

### 3.3 Determination of Acceptable Daily Intake

An Acceptable Daily Intake was not required as there is no dietary exposure to carbendazim for this major new use.

### 3.4 Occupational and Residential Risk Assessment

#### 3.4.1 Toxicological Endpoints

Occupational exposure to Polyphase 678 is characterized as short- to long-term in duration and is predominantly by the dermal and inhalation routes. Residential exposure to Polyphase 678 may occur by the dermal and oral routes of exposure and is characterized as short-term.

**Short- to Long-Term Dermal and Inhalation Exposure**
To estimate the risk from short- to long-term dermal and inhalation exposure, a NOAEL of 10 mg/kg bw/day for developmental toxicity was selected from several developmental toxicity studies in the rat and rabbit, based on increased resorptions at 20 mg/kg bw/day in rabbits and increased skeletal malformations at 30 mg/kg bw/day in rats, both occurring in the absence of maternal toxicity.

Although several dermal toxicity studies conducted with carbendazim were available, these studies were not selected for use in the risk assessment as they did not examine the critical toxicological effect of prenatal developmental toxicity.

For **residential scenarios**, the target Margin of Exposure (MOE) is 1000. This includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. In consideration of the completeness of database, developmental effects being observed in the absence of maternal toxicity and the concern for the seriousness of endpoint, the PCPA factor of 10-fold has been retained. This MOE is considered to be protective of all sensitive subpopulations including the unborn children of exposed women.

For **occupational scenarios**, the target MOE is 1000, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As the worker population could include pregnant females, it was necessary to ensure adequate protection of the fetus who may be exposed via their mother. In light of concerns regarding prenatal toxicity (as outlined in Section 3.1.1), an additional 10-fold factor was applied to these endpoints.

**Short-Term Incidental Oral Exposure**
To estimate the risk from short-term incidental oral exposure, a NOAEL of 20 mg/kg bw/day was selected from several developmental toxicity studies in the rat, based on reduced body weight gain and increased liver weight in maternal animals at 90 mg/kg bw/day. The results of other toxicity studies conducted with carbendazim confirmed that decreases in body weight and/or body weight gain were consistent endpoints of concern following oral exposure. Thus, the most relevant study to assess short-term incidental oral exposure was the repeat-dose developmental toxicity studies in rats and rabbits.
A target MOE of 300 was deemed appropriate, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. In consideration of the completeness of database and the residual uncertainty regarding developmental neurotoxicity, the PCPA factor has been reduced to 3-fold.

**Cancer Risk**
For the cancer risk assessment, the unit risks for carbendazim, denoted by $Q_1$* (representing the upper 95% confidence limit on the slope of the dose-response curve in the low-dose region) were calculated based on the data from the carcinogenicity studies in the mouse. The most potent unit risk, $1.6 \times 10^{-2}$ $(\text{mg/kg bw/day})^{-1}$, was calculated on the basis of the hepatocellular tumours (adenomas and/or carcinomas) in CD-1 female mice and was used in the cancer risk assessment.

#### 3.4.1.1 Dermal Absorption

Two in vivo and three in vitro dermal absorption studies were submitted. The studies were designed to determine the percutaneous absorption of carbendazim in water based or alkyd based paint formulations. In the in vivo studies, the radio labelled test substance was applied at a single concentration of 0.1% w/w (12 or 14 $\mu g/cm^2$) to the back and shoulders of rats for 8 hours. This dose level is higher than the minimum concentration of carbendazim in paint products (0.03%) and may underestimate absorption at lower concentrations. After the exposure period, the applied paint was removed with an ethanol/white spirit mixture which is not necessarily representative of how washing would occur in the field for latex paints.

Recovery of the applied dose was acceptable with group mean mass balances above 90%. The majority of the administered dose was recovered from the skin wash, with only 0.23 to 0.40 % of the applied dose retained at the application site. Estimates of dermal absorption were based on the sum of residues retained at the skin site (including tape strips) + urine (including cage wash and rinse) + feces + carcass + blood. Absorbed dose was approximately 1.5-2.0% of the applied dose, and was predominantly excreted via the renal route.

The in vitro dermal absorption data demonstrated that human skin is expected to be less permeable than rat skin when carbendazim was applied within a water or alkyd based paint formulation. However, given the limitations noted in the in vivo study (see above), the in vitro studies were not considered to quantitatively refine the dermal absorption factor selected for risk assessment. A dermal absorption value of 2% is considered to be appropriate for use in the risk assessment. This value is applicable to painting scenarios only. For all other scenarios, a default dermal absorption of 100% was assumed for carbendazim.

### 3.4.2 Occupational Exposure and Risk

#### 3.4.2.1 Chemical Handler Exposure and Risk Assessment

Exposure to workers mixing and loading Polyphase 678 is expected to be intermediate- to long-term in duration and to occur primarily by the dermal and inhalation routes.

Since 3-iodo-2-propynyl N-butylcarbamate (iodocarb) is registered for use in other consumer products at rates greater than those for Polyphase 678, no increase in exposure is expected over the existing use pattern for iodocarb, and no change in exposure to iodocarb is anticipated as a result of this use. However, chemical handler assessments were conducted for carbendazim.

Chemical-specific data for assessing human exposures during pesticide handling activities was not submitted. Exposure estimates for chemical handlers mixing and loading Polyphase 678 into paints, coatings, sealants, etc., were generated from the Chemical Manufacturers Association (CMA) Antimicrobial Exposure study. The CMA study measured worker exposure to several antimicrobial scenarios in non-agricultural settings such as, preservatives in paints, coatings and fuels, cooling towers, metal working fluids and pulp and paper processes. Liquid products (open pour and closed pump applications) and solid products (pour and place) were tested and both

dermal and inhalation exposure were measured during the mixing/loading of products. The majority of exposure was via the dermal route. Due to the diversity of the products used, there was significant variability in the types of protective clothing worn although most individuals wore a single layer of clothing during the study. The 90$^{th}$ percentile of exposure was considered appropriate for use in the current assessment.

The liquid pour and liquid pump scenarios from the paints and coatings, metalworking fluids, cooling towers and pulp and paper plants of the CMA study were used to determine the potential exposure to carbendazim. In the absence of chemical-specific data, a dermal absorption factor of 100% was assumed for carbendazim for the chemical handler scenarios. Since there is potential for exposure all year round, a long-term dermal and inhalation NOAEL (10 mg/kg bw/day) was used to calculate the margin of exposure (MOE).

For the liquid open pour system, estimated amounts for active ingredient handled per day were calculated using 1000 kg production vessels, 1.5% Polyphase 678 concentration and 2 batches produced per day (4.5 kg a.i./day). For the liquid pump closed system, estimates were calculated based on 4763 kg vessels, 1.5% Polyphase 678 concentration and 3 batches per day as a conservative estimate of amount handled per day (32.2 kg a.i./day).
Since the upper bound estimates for the liquid pour and the liquid pump scenarios fall within the range of the exposure values from the CMA study (0.01-38 kg a.i./day for open pour; 0.27-265 kg a.i./day for closed transfer), the exposure for carbendazim was not normalized for amount handled per day, and exposure units were used directly. Only replicates for workers wearing gloves were included in the calculation of total daily carbendazim exposure.

**Table 1 Exposure to Carbendazim and Resulting Non-Cancer Risk Estimates for Chemical Handlers**

| Scenario/PPE | Total Daily Carbendazim Exposure (mg/kg bw/day) | MOE* |
|---|---|---|
| Open transfer equipment; coveralls, gloves, respirator[ab] | 0.0171 | 585 |
| Closed transfer equipment; coveralls, gloves[a] | 0.00790 | 1270 |
| Closed transfer equipment; coveralls, gloves, respirator[ab] | 0.00558 | 1790 |

[a] A 75% protection factor (PF) was applied to dermal exposure estimate for the addition of coveralls
[b] A 90% PF was applied to the inhalation exposure to account for the addition of a respirator
* Based on a NOAEL of 10 mg/kg bw/day for long term exposure. The target MOE is 1000.

Calculated MOEs for open system mixing and loading of Polyphase 678 fail to reach the target MOE and are considered unacceptable even with the addition of coveralls and a respirator (Table 1). Closed mixing and loading of Polyphase 678 with baseline personal protective equipment (PPE) also fails to reach the target MOE, but mitigation with coveralls over a single layer of clothing on the label results in acceptable non-cancer risk.

To estimate cancer risk, exposure was amortized over a lifetime to estimate a lifetime average daily dose (LADD). Assumptions made include that an industrial working lifetime comprises 36 years of a 75 year life span (NAFTA default values). Additionally, risks were calculated for workers producing 2 batches per week (2 days of exposure per week) over 50 weeks a year. The batch number chosen is intended to be a more average estimation of how many days of exposure occur over a year taking into account low and high seasons of production. A lifetime cancer risk below $1 \times 10^{-5}$ in worker populations is considered acceptable. LADD and cancer risk were calculated using the following equations:

$$\text{LADD} = \frac{\text{Daily Exposure} \times \text{Days exposure/year} \times \text{Work lifespan (years)}}{\text{Life expectancy (years)} \times 365 \text{ days/year}}$$

$$\text{Cancer risk} = \text{LADD} \times Q_1^*$$

**Table 2 Carbendazim Cancer Risk Estimates for Chemical Handlers**

| Scenario/PPE | Exposure (mg/kg bw/day) | LADD mg/kg bw/day | Cancer risk* |
|---|---|---|---|
| Open transfer; coveralls, gloves, respirator[ab] | 0.0171 | 0.00225 | $4 \times 10^{-5}$ |
| Closed transfer; coveralls, gloves[a] | 0.00790 | 0.00115 | $2 \times 10^{-5}$ |
| Closed transfer; coveralls, gloves, respirator[ab] | 0.00558 | 0.000734 | $1 \times 10^{-5}$ |

[a] A 75% protection factor (PF) was applied to dermal exposure estimate for the addition of coveralls
[b] A 90% PF was applied to the inhalation exposure to account for the addition of a respirator
* Based on a $Q_1^*$ of 0.016 $(\text{mg/kg bw/day})^{-1}$. Acceptable cancer risk is $1 \times 10^{-5}$ in worker populations.

Cancer risk estimates fail to reach the acceptable levels for open mixing and loading systems (Table 2). However, for closed transfer, while wearing coveralls and a respirator, the calculated risk is $1 \times 10^{-5}$. Given the limitations of the CMA study and the large variability in exposure estimates, this risk is considered acceptable.

### 3.4.2.2 Exposure and Risk Assessment for Workers Handling Products Containing Polyphase 678

A potential for secondary exposure exists for individuals applying treated products by paintbrush, roller and airless sprayer as well as using coatings, adhesives, sealants, grouts and inks. The duration of exposure is considered to be intermediate- to long-term for commercial workers, and the primary route of exposure for workers is through dermal contact with products containing Polyphase 678.

Since iodocarb is registered for the use in other consumer products at rates greater than those for Polyphase 678, no increase in exposure is expected over the existing use pattern for iodocarb, and no change in exposure to iodocarb is anticipated as a result of this use. However, assessments for secondary exposure were conducted for carbendazim.

The exposure from painting is expected to be greater than for the other uses due to the greater amount of product handled per day. Potential exposure from applying paint containing Polyphase 678 by paintbrush or airless sprayer was estimated by using PHED surrogate data and the USEPA Residential SOPs.

Exposure to professional painters is calculated while wearing a long sleeved shirt and long pants without gloves. Professional painters are expected to handle 15 L of paint per day when using a paint brush and 38 L per day when using an airless sprayer. The USEPA Residential SOPs estimate the density of latex paint to be 1.24 g/mL. The estimated amount of carbendazim handled per day is between 0.01 and 0.11 kg per day for professional painters (Table 3).

**Table 3 Amount of Carbendazim Handled per Day**

| Scenario | Concentration of Polyphase | Concentration of Carbendazim | Density of Paint (g/mL) | Amount handled/day (L) | Amount handled/day (kg)* |
|---|---|---|---|---|---|
| Paintbrush | | | | | |
| Interior | 0.4% | 15% | 1.24 | 15 | 0.01116 |
| Exterior | 1.5% | 15% | 1.24 | 15 | 0.04185 |
| Airless sprayer | | | | | |
| Interior | 0.4% | 15% | 1.24 | 38 | 0.0283 |
| Exterior | 1.5% | 15% | 1.24 | 38 | 0.106 |

* Amount handled per day = Concentration of product in paint × concentration a.i. × amount of paint/day × density of paint

**Table 4 Exposure Estimates and MOEs for Workers Applying Paint Containing Carbendazim.**

| Method | Dermal Unit Exposure (mg a.i./kg handled) | Inhalation Unit Exposure (mg a.i./kg handled) | Amount Handled/Day (kg) | Exposure* (mg/kg bw/day) | MOE # |
|---|---|---|---|---|---|
| Paintbrush Interior | 399.6 | 0.7 | 0.01116 | 0.00139 | 7181 |
| Paintbrush Exterior | 399.6 | 0.7 | 0.04185 | 0.00522 | 1915 |
| Airless | 84.7 | 1.1 | 0.0283 | 0.00112 | 8946 |

| Method | Dermal Unit Exposure (mg a.i./kg handled) | Inhalation Unit Exposure (mg a.i./kg handled) | Amount Handled/Day (kg) | Exposure* (mg/kg bw/day) | MOE # |
|---|---|---|---|---|---|
| sprayer Interior | | | | | |
| Airless sprayer Exterior | 84.7 | 1.1 | 0.106 | 0.00419 | 2386 |

* Exposure = (PHED dermal unit exposure × dermal absorption (2%) + inhalation unit exposure) × amount handled per day / bw

\# Based on a long term NOAEL of 10 mg/kg bw/day. The target MOE is 1000

Assuming a dermal absorption value of 2% for carbendazim in paint formulations, based on the submitted dermal penetration studies, calculated non-cancer MOEs for professional painters reach the target MOE and are considered acceptable (Table 4). Even though the dermal absorption value is specific to the paint scenario, the exposure estimated for painters is expected to serve as a worst case scenario for secondary worker exposure, since the amount of paint handled per day is higher and the concentration of carbendazim in other consumer products is expected to be lower than in paints.

To estimate cancer risk, exposure was amortized over a lifetime to estimate a lifetime average daily dose (LADD). Assumptions made include that each application is done in one day and that a lifetime comprises a 75 year life span (NAFTA Position Papers, 1999). Professional painters were assumed to be exposed for 18 years over a lifespan based on the median occupational tenure of operators, fabricators and laborers from the USEPA Exposure Factors Handbook (USEPA, 1997). This is considered to be a conservative estimate since information specific to painters indicates that the median occupational tenure for painters may be as low as 6 or 7 years. Professional painters may be potentially exposed 5 days per week for 50 weeks of the year (250 days/year) for interior painting and 26 weeks of the year (130 days/year) for exterior painting. LADD and cancer risk were calculated using the following equations:

$$\text{LADD} = \frac{\text{Daily Exposure} \times \text{Days exposure/year} \times \text{Work lifespan (years)}}{\text{Life expectancy (years)} \times 365 \text{ days/year}}$$

$$\text{Cancer risk} = \text{LADD} \times Q_1^*$$

**Table 5 Cancer Risk Estimates for Applying Carbendazim as a Paint Product**

| Method | PPE Scenario | Exposure (mg/kg bw/day) | LADD (mg/kg bw/day) | Cancer Risk* |
|---|---|---|---|---|
| Paintbrush Interior | Single layer, no gloves | 0.00139 | $2.3 \times 10^{-4}$ | $4 \times 10^{-6}$ |
| Paintbrush Exterior | Single layer, no gloves | 0.00522 | $4.5 \times 10^{-4}$ | $7 \times 10^{-6}$ |
| Airless sprayer Interior | Single layer, no gloves | 0.00112 | $1.8 \times 10^{-4}$ | $3 \times 10^{-6}$ |
| Airless sprayer Exterior | Single layer, no gloves | 0.00419 | $3.6 \times 10^{-4}$ | $6 \times 10^{-6}$ |

* Based on a $Q_1$* of 0.016 $(mg/kg\ bw/day)^{-1}$. Acceptable cancer risk is $1 \times 10^{-5}$ in worker populations.

Cancer risk estimates for professional painters are below $1 \times 10^{-5}$ and are considered to be acceptable (Table 5). Even though the dermal absorption value is specific to the paint scenario, the exposure estimated for painters is expected to serve as a worst case scenario for secondary worker exposure, since the amount of paint handled per day is higher and the concentration of carbendazim in other consumer products is expected to be lower than in paints.

### 3.4.3 Residential Exposure and Risk Assessment

#### 3.4.3.1 Residential Handler Exposure and Risk

A potential for secondary exposure exists for homeowners applying treated products by paintbrush, roller and airless sprayer as well as using coatings, adhesives, sealants, grouts and inks. The duration of exposure is considered to be short-term for homeowners, and the primary route of exposure would be through dermal contact with products containing Polyphase 678. Since iodocarb is registered for the use in other consumer products at rates greater than those for Polyphase 678, no increase in exposure is expected over the existing use pattern for iodocarb, and no change in exposure to iodocarb is anticipated as a result of this use. However, residential exposure assessments were conducted for carbendazim.

Potential exposure from applying paint containing Polyphase 678 by paintbrush or airless sprayer was estimated by using PHED surrogate data and the USEPA Residential SOP.

Exposure calculations were performed for homeowners wearing either shorts and a t-shirt or a single layer without gloves. Homeowners are expected to handle 7.6 L of paint per day when using a paintbrush, and up to 19 L per day when using an airless sprayer (USEPA Residential SOP). The USEPA Residential SOP estimates the density of latex paint to be 1.24 g/mL. The amount of carbendazim handled per day ranges from 0.006 to 0.05 kg for homeowners (Table 6).

**Table 6 Amount of Carbendazim Handled per Day**

| Scenario | Concentration of Polyphase | Concentration of Carbendazim | Density of Paint (g/mL) | Amount handled/day (L) | Amount handled/day* (kg) |
|---|---|---|---|---|---|
| Paintbrush | | | | | |
| Interior | 0.4% | 15% | 1.24 | 7.6 | 0.00565 |
| Exterior | 1.5% | 15% | 1.24 | 7.6 | 0.0212 |
| Airless sprayer | | | | | |
| Interior | 0.4% | 15% | 1.24 | 19 | 0.0141 |
| Exterior | 1.5% | 15% | 1.24 | 19 | 0.0530 |

* Amount handled per day= Concentration of product in paint × concentration ai × amount of paint/day × density of paint

**Table 7 Exposure Estimates and MOEs for Individuals Applying Paint Containing Carbendazim.**

| Method | PPE Scenario | Dermal Unit Exposure (mg a.i./kg handled) | Inhalation Unit Exposure (mg a.i./kg handled) | Amount Handled/Day (kg) | Exposure* (mg/kg bw/day) | MOE# |
|---|---|---|---|---|---|---|
| Paintbrush Interior | Shorts, t-shirt, no gloves | 513.4 | 0.7 | 0.00565 | 0.000828 | 12052 |
| Paintbrush Interior | Single layer, no gloves | 399.6 | 0.7 | 0.00565 | 0.000646 | 15480 |
| Paintbrush Exterior | Shorts, t-shirt, no gloves | 513.4 | 0.7 | 0.0212 | 0.00312 | 3205 |
| Paintbrush Exterior | Single layer, no gloves | 399.6 | 0.7 | 0.0212 | 0.00242 | 4132 |
| Airless sprayer Exterior | Shorts, t-shirt, no gloves | 182.1 | 1.1 | 0.0530 | 0.00278 | 3597 |
| Airless sprayer Exterior | Single layer, no gloves | 84.7 | 1.1 | 0.0530 | 0.0013 | 7692 |

* Exposure = (PHED dermal unit exposure × dermal absorption (2%) + inhalation unit exposure) × amount handled per day / bw

\# Based on a short-term NOAEL of 10 mg/kg bw/day. The target MOE is 1000

Assuming a dermal absorption value of 2% for carbendazim in paint formulations, based on the submitted in vivo dermal penetration studies, calculated non-cancer MOEs for homeowner painters reach the target MOE and are considered acceptable (Table 7). The exposure from painting is expected to be greater than for the other uses due to the greater amount of product used per day. Even though the dermal absorption value is specific to the paint scenario, the exposure estimated for painters is expected to serve as a worst case scenario for homeowner exposure.

To estimate cancer risk, exposure was amortized over a lifetime to estimate a lifetime average daily dose (LADD). Assumptions made include that each application is done in one day and that a lifetime comprises a 75 year life span (NAFTA Position Papers, 1999). Homeowners were assumed to paint 4 days per year and to be exposed for 40 years over a lifespan (NAFTA Position Papers, 1999). LADD and cancer risk were calculated using the following equations:

$$\text{LADD} = \frac{\text{Daily Exposure} \times \text{Days exposure/year} \times \text{Work lifespan (years)}}{\text{Life expectancy (years)} \times 365 \text{ days/year}}$$

$$\text{Cancer risk} = \text{LADD} \times Q_1^*$$

**Table 8 Cancer Risk Estimates for Applying Carbendazim as a Paint Product**

| Method | PPE Scenario | Exposure (mg/kg bw/day) | LADD (mg/kg bw/day) | Cancer Risk* |
|---|---|---|---|---|
| Homeowner | | | | |
| Paintbrush Interior | Shorts, t-shirt, no gloves | 0.00089 | $5.2 \times 10^{-6}$ | $8 \times 10^{-8}$ |
| Paintbrush Interior | Single layer, no gloves | 0.00071 | $4.1 \times 10^{-6}$ | $7 \times 10^{-8}$ |
| Paintbrush Exterior | Shorts, t-shirt, no gloves | 0.00333 | $2.0 \times 10^{-5}$ | $3 \times 10^{-7}$ |
| Paintbrush Exterior | Single layer, no gloves | 0.00265 | $1.6 \times 10^{-5}$ | $3 \times 10^{-7}$ |
| Airless sprayer Exterior | Shorts, t-shirt, no gloves | 0.00357 | $2.1 \times 10^{-5}$ | $3 \times 10^{-7}$ |
| Airless sprayer Exterior | Single layer, no gloves | 0.00210 | $1.2 \times 10^{-5}$ | $2 \times 10^{-7}$ |

* Based on a $Q_1^*$ of 0.016 $(\text{mg/kg bw/day})^{-1}$. Acceptable cancer risk is $1 \times 10^{-6}$ in residential populations.

Cancer risk estimates for homeowners painting are all below $1 \times 10^{-6}$ and are considered to be acceptable (Table 8).

### 3.4.3.2 Residential Postapplication Exposure and Risk

Potential post-application exposure scenarios include: dermal, oral from hand-to-mouth (children), and oral from ingestion of paint chips (children). Dermal exposure from contact with treated materials and oral exposure from hand-to-mouth contact are not expected to exceed exposure from ingestion of paint chips. Infants (aged 0.5 to 1.5 years) are assumed to be exposed to paint chips on a short-term basis and only in an indoor scenario. Tier 1 data from the USEPA SOPs for Residential Exposure Assessments was used for the assessment. The maximum percent of carbendazim in indoor paints is 0.06% (for example, a maximum concentration of 0.4% Polyphase 678, containing 15% carbendazim). The amount of paint ingested by a 10 kg child is assumed to be 40 mg with 20% of the ingested active ingredient available for absorption. Exposure was calculated based on the following equation:

$$\text{Exposure (mg/kg bw/day)} = \frac{\text{Ingestion rate (40 mg)} \times \text{Active \% (0.0006)} \times \text{Fraction of a.i. available (20\%)}}{\text{Body weight (10 kg)}}$$

$$\text{Exposure} = 0.00048 \text{ mg/kg bw/day}$$

Based on a short term oral, dermal and inhalation NOAEL of 20 mg/kg bw/day, the MOE was calculated to be 41 700. The calculate MOE for the ingestion of paint chips by infants exceeds the target MOE (300) and is considered acceptable. As such, there are no concerns with the post-application exposure of individuals contacting materials treated with Polyphase 678. Given this low estimated exposure value and the limited number of events over a lifetime, cancer risk for residential exposure is expected to be lower than for homeowners painting.

### 3.5 Food Residues Exposure Assessment

A food residue exposure assessment was not required for this application.

## 4.0 Impact on the Environment

An environmental assessment was conducted on Carbendazim Technical fungicide (99.0% carbendazim) for the formulation of Polyphase 678 as a material preservative for use in aqueous paints and stains, adhesives, caulks and sealants, joint cements, and inks.

Carbendazim Technical fungicide is currently registered (Registration number 27184) in the end-use product Eertavas Liquid Concentrate Fungicide (Registration number 23663, 4.7% carbendazim) for the control of Dutch Elm Disease in various species of elm trees.

A hydrolysis study is normally required for this use. Although a study report was not provided, a detailed summary of a hydrolysis study was submitted for the current application. A re-evaluation monograph was also done within the PMRA using the USEPA RED. Both these documents state that carbendazim is stable to hydrolysis at pH 7, which is consistent with the submitted summary. It is noted in the summary that hydrolysis of carbendazim will occur with an increase in temperature and pH. On the basis of the provided information in the summary and USEPA RED, the hydrolysis study report will not be required at this time.

The new proposed use (material preservative) is not expected to result in significant exposure of non-target organisms in the environment to the active ingredient carbendazim. The risk to non-target organisms is considered to be negligible if used according to the product label.

# 5.0 Value

## 5.1 Effectiveness Against Pests

Data from several laboratory trials and one field trial carried out with a variety of materials were submitted. These studies demonstrated the in-can and/or dry-film preservation capacity of Polyphase 678 against various fungi when incorporated in the materials.

### 5.1.1 Acceptable Efficacy Claims

The submitted data established acceptable use rates that are displayed in Table 5.1.1.

**Table 5.1.1 Use rates as supported by data**

| End Use | Rates (% by weight of Polyphase 678) |
|---|---|
| PAINTS AND STAINS (Dry-film protection) For aqueous (latex-based)paints and stains for interior use | 0.2% to 0.4% |
| PAINTS AND STAINS (Dry-film protection) For aqueous (latex-based) paints and stains for exterior use | 0.8% to 1.5% |
| ADHESIVES (Dry-film protection) | 0.08% to 0.2% |
| GROUTS, CAULKS and SEALANTS (In-can and dry-film protection) For water-based grouts, silicone-based caulks, water-borne and latex-based sealants | 0.2% to 0.3 % |
| JOINT CEMENTS (In-can and dry-film protection) | 0.02% to 0.5% |
| INKS (In-can and dry-film protection) | 0.03% to 0.3% |

## 5.2 Economics

No information provided.

### 5.3 Sustainability

#### 5.3.1 Survey of Alternatives

The availability of carbendazim as a new antimicrobial product will provide a new option for the preservation of different materials. There are currently 54 active ingredients or combinations of active ingredients registered for material preservation, a few of which are summarized in Table 5.3.1.

**Table 5.3.1 Some of the registered material preservatives and associated uses**

| Active ingredient | Registration number | End-product name | Uses |
|---|---|---|---|
| Barium metaborate (as BaB2O4.H2O) | 12033 | BUSAN 11-M1 | Paints, other coatings, and plastics |
| Captan (N-trichloromethyl thio-4-cyclohexene-1, 2-di carboximide) | 13877 | Vancide 89 | Vinyl, Paint, Lacquer, Wallpaper flour paste, Rubber, Polyethylene |
| Chlorothalonil | 18965 | Tuffcide N-40-D Paint Microbiocide | Latex and solvent based paint film |
| Glutaraldehyde | 23784 | UCARCIDE 250 Preservative | Aqueous or water containing products and systems, including industrial, institutional and consumer pesticide products, in-can processes and products |
| [[[1-Methyl-2-(5-methyl-3-oxazolidinyl)ethoxy] metho xy] methoxy] methanol | 25554 | NUOSEPT 145 PRESERVATIVE | Paints, inks, adhesives and caulking compounds |
| O-phenylphenol (present as sodium o-phenylphenate | 27633 | PREVENTOL ON EXTRA | Adhesives, paints, leather, metal working fluids, pulp and paper, extinguisher solutions, floor wax emulsions, concrete additives, ceramic glazes and clay slips, polish |

## 6.0 Pest Control Product Policy Considerations

The end-use product, Polyphase 678, contains TSMP Track 1 polychlorinated dioxins and furans from the preservative at a combined maximum level of 6 ppq.

# 7.0 Summary

## 7.1 Human Health and Safety

The toxicology database submitted for carbendazim is adequate to define the majority of toxic effects that may result from exposure to carbendazim. In subchronic and chronic studies on laboratory animals, the primary targets were the liver, kidney, and testis. There was no evidence of carcinogenicity in rats after longer-term dosing, but liver and ovarian tumours were observed in mice. There was no evidence of increased susceptibility of the young in reproductive toxicity studies; however, there was evidence of increased susceptibility of fetuses following in utero exposure to carbendazim. Malformations of the head, spine, ribs and sternum and increased embryo and fetal loss were observed at doses that resulted in no or minimal toxicity to maternal animals. Signs of neurotoxicity were evident in hens at high doses.

Chemical handlers mixing and loading Polyphase 678 and workers handling consumer products containing Polyphase 678 are not expected to be exposed to levels of Polyphase 678 that will result in an unacceptable risk when the Polyphase 678 is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

Residential exposure to individuals handling and contacting treated articles or areas is not expected to result in unacceptable risk when Polyphase 678 is used according to label directions.

## 7.2 Environmental Risk

Because Polyphase 678 (containing 15% carbendazim and 5% iodocarb) is to be used as a material preservative for use in aqueous paints and stains, adhesives, caulks and sealants, joint cements, and inks, the risk to non-target organisms is considered to be negligible when used according to the label.

## 7.3 Value

The data submitted in support of Polyphase 678 were adequate to demonstrate its efficacy for use as a material preservative. The availability of Polyphase 678 will provide the industry with a new alternative in a market in which there are currently a large number of products.

## 7.4 Unsupported Uses

Certain uses originally proposed with this application are not supported as their efficacy and value not been adequately demonstrated. Unsupported uses are outlined in Appendix I, Table 4.

## 8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of of Carbendazim Technical and Polyphase 678, containing the technical grade active ingredient carbendazim and 3-iodo-2-propynyl N-butylcarbamate (iodocarb), as a material preservative.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

# List of Abbreviations

| | |
|---|---|
| µg | micrograms |
| 2-AB | 2-amino-benzimidazole |
| AHP | 2-amino-3-hydroxy phenazine |
| a.i. | active ingredient |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BUN | blood urea nitrogen |
| bw | body weight |
| CAS | Chemical Abstracts Service |
| ChE | cholinesterase |
| cm | centimetres |
| CMA | Chemical Manufacturers Association |
| CMC | carboxymethylcellulose |
| DAP | 2,3-diaminophenazine |
| DNA | deoxyribonucleic acid |
| DNT | developmental neurotoxicity study |
| F | female(s) |
| FSH | follicle stimulating hormone |
| g | gram |
| GD | gestation day |
| GnRH | gonadotropin releasing hormone |
| 5-HBC | 5-hydroxy-2-benzimidazole carbamate |
| HCG | Human chorionic gonadotropin |
| Hct | hematocrit |
| Hgb | haemoglobin |
| hr | hour |
| i.p. | intraperitoneal |
| i.v. | intravenous |
| IUPAC | International Union of Pure and Applied Chemistry |
| kg | kilogram |
| $K_{ow}$ | *n*–octanol-water partition coefficient |
| L | litre |
| LADD | lifetime average daily dose |
| $LC_{50}$ | lethal concentration 50% |
| $LD_{50}$ | lethal dose 50% |
| LH | luteinizing hormone |
| M | male(s) |
| MAS | maximum average score |
| MIS | Maximum Irritation Score |
| mg | milligram |
| mL | millilitre |
| MOE | margin of exposure |
| N/A | not applicable |
| NAFTA | North American Free Trade Agreement |

| | |
|---|---|
| nm | nanometres |
| NOAEL | no observed adverse effect level |
| OECD | Organization for Economic Co-operation and Development |
| Pa | pascals |
| PCPA | *Pest Control Product Act* |
| PCV | packed cell volume |
| PF | protection factor |
| PHED | Pesticide Handlers Exposure Database |
| PMRA | Pest Management Regulatory Agency |
| PPE | personal protective equipment |
| ppm | parts per million |
| ppq | parts per quadrillion |
| $Q_1$* | cancer potency factor |
| RBC | red blood cell |
| RED | Reregistration Eligibility Decision Document |
| SOP | standard operating procedure |
| TGAI | technical grade active ingredient |
| TSMP | Toxic Substances Management Policy |
| USEPA | United States Environmental Protection Agency |
| UV | ultraviolet |
| WBC | white blood cell |
| WHO | World Health Organization |

# Appendix I Tables and Figures

## Table 1 Acute Toxicity the End-use Product Polyphase 678

| Acute Toxicity Studies – Polyphase 678 | | | | |
|---|---|---|---|---|
| **Study Type** | **Species** | **Result** | **Comment** | **Reference** |
| Oral | Rat | $LD_{50}$ > 2000 mg/kg bw | Low Toxicity | PMRA #1077205 |
| Dermal | Rat | $LD_{50}$ > 2000 mg/kg bw | Low Toxicity | PMRA #1077206 |
| Inhalation | Rat | $LC_{50}$ > 2.04 mg/L | Low Toxicity | PMRA #1077207 |
| Skin irritation | Rabbit | MAS[a] = 2.67/110<br>MIS[b] = 11.3/110 (at 1 hr) | Minimally Irritating | PMRA #1077208 |
| Eye irritation | Rabbit | MAS = 1.0/8<br>MIS = 2.0/8 (at 1 & 24 hrs) | Slightly Irritating | PMRA #1077209 |
| Skin sensitization | Guinea pig | The frequency of dermal reactions (scores of 0.5 or greater): 95% versus 100% in controls 24 hrs after challenge; 65% versus 70% in controls 24 hrs after re-challenge. | Non-sensitizing | PMRA #1077210 |

a MAS = maximum average score for 24, 48 and 72 hours

b MIS = maximum irritation score

## Table 2 Toxicity Profile of Technical Carbendazim

**NOTE:** Effects noted below are known or assumed to occur in both sexes unless otherwise specified. Organ weight changes reflect changes in both absolute and relative weights, unless otherwise specified.

| Acute Toxicity Studies | | | |
|---|---|---|---|
| **Study Type** | **Species** | **Results** | **Comment** |
| Oral | Mouse | $LD_{50}$ > 10,000 - 15,000 mg/kg bw | Low Toxicity |
| Oral | Rat | $LD_{50}$ > 6400 - 15,000 mg/kg bw | Low Toxicity |
| Oral | Guinea pig | $LD_{50}$ > 5,000 mg/kg bw | Low Toxicity |
| Oral | Rabbit | $LD_{50}$ > 8000 mg/kg bw | Low Toxicity |
| Oral | Dog | $LD_{50}$ > 5000 - 8000 mg/kg bw | Low Toxicity |
| Dermal | Rat | $LD_{50}$ > 2000 - 20,000 mg/kg bw | Low Toxicity |
| Dermal | Rabbit | $LD_{50}$ > 10,000 mg/kg bw | Low Toxicity |
| Inhalation | Rat | $LC_{50}$ > 5- 5.8 mg/L | Low Toxicity |
| Eye irritation | Rabbit | Non to Mildly Irritating | |
| Dermal irritation | Guinea pig | Non to Mildly Irritating | |
| Dermal irritation | Rabbit | Non Irritating | |
| Skin sensitization | Guinea pig | Non Sensitizing | |

| Metabolism/Toxicokinetics Studies | | |
|---|---|---|
| **Study / Species** | **Dose Levels** | **Results/Effects** |
| Metabolism - Rat | 8 mg/kg $^{14}$C-carbendazim by gavage for 10 days | **Excretion:** Approximately 60% of the total radiolabel was excreted in the urine. Approximately 35% of the total radiolabel was excreted in the feces.<br><br>**Metabolism:** Three polar metabolites were found in the urine and determined to be conjugates of 2-(methoxy-carbonylamino)-5-hydroxybenzimidazole. Two metabolites were discovered in the feces: 2-(methoxy-carbonylamino)-5-hydroxybenzimidazole, and a conjugated form. The main metabolite 2-(methoxy-carbonyl amino)-5-hydroxybenzimidazole becomes conjugated, at least in part, in the liver and is excreted in urine and feces in the conjugated form (and in the latter partially in the unconjugated form). Two of the same conjugates found in the liver were detected in the urine.<br><br>**Distribution:** liver residues ≈ 0.7 ppm equivalents of carbendazim. |
| Metabolism - Rat | 2 mg/kg bw/day $^{14}$C-carbendazim by gavage for 10 days | **Excretion:** Cleared from the blood rapidly: 59% excreted in the urine, 36% in the feces. Elimination was biphasic with a rapid rate during the first 3 days and slower phase thereafter.<br><br>**Distribution:** Residues in the liver 0.3% 7 days after last dose, 0.08% 14 days after last dose; levels in blood and other organs (kidney, fat, muscle, and gonads) did not exceed 0.03% after 7 days. |
| Metabolism - Rat | 20 mg/kg bw $^{14}$C-carbendazim by gavage and i.p. injection | **Excretion:** Radioactivity eliminated through urine (oral - 48%; i.p. - 44%) and feces (oral - 28%; i.p. - 16%) mainly during first 24 hours.<br><br>**Metabolism:** The main product of metabolism was 5-hydroxy-2-benzimidazole carbamate, which was eliminated as a conjugate of sulfuric acid. |
| Metabolism – Rat & Mouse | 3 or 300 mg/kg bw $^{14}$C-carbendazim | **Absorption:** Rats: $C_{max}$ = 1.03 mg/ml in blood within 15-40 min at 3 mg/kg bw; $C_{max}$ = 16 mg/ml in blood within 0.4-4 h at 300 mg/kg bw. Mice: similar $C_{max}$ as rats at 3 mg/kg bw, but at 300 mg/kg bw $C_{max}$ was higher (36-53 mg/ml).<br><br>**Excretion:** In rats excretion occurred almost exclusively in urine, irrespective of sex and dose; only about 1% in the faeces. Faecal excretion was higher in mice representing 10-27%. Pretreatment with unlabeled carbendazim had no effect on excretory patterns. The radioactivity was almost completely excreted within 24 h after treatment; excretion faster in rat than mouse where higher concentration in liver was observed.<br><br>**Distribution:** The excretory organs (liver, kidney) contained the highest tissue concentrations; those in the gonads were near or below the blood concentrations. The distribution patterns were confirmed in rats and mice by whole body autoradiography after intravenous and oral administration of 3 mg/kg bw [2-$^{14}$C]- carbendazim. |

| Metabolism/Toxicokinetics Studies | | |
|---|---|---|
| **Study / Species** | **Dose Levels** | **Results/Effects** |
| Metabolism - Rat | 12 mg/kg bw/day $^{14}$C-carbendazim (in diethyl glycol-ethanol) given as single gavage dose or as i.v. injection | **Absorption:** Urinary excretion of $^{14}$C-carbendazim and two of its metabolites indicated 85% had been absorbed.<br><br>**Metabolism:** 94% of radiolabel in urine 12 hr after treatment was as 5-hydroxy-2-benzimidazole carbamate (5-HBC), 3% as 2-aminobenzimidazole (2-AB), and 3% as carbendazim.<br><br>**Distribution:** Highest concentrations of radiolabel were found in kidney and lowest in blood.<br><br>**Excretion:** Elimination followed the kinetics of a two-compartment model. By 12 hours, only small quantities of radiolabel were present in blood, liver and kidney. |
| Whole body autoradiography - Mouse | $^{14}$C-carbendazim (single oral dose in corn oil). Animals were sacrificed 10 minutes after dosing | **Distribution:** After 10 minutes, most of the radiolabel was found in the liver with relatively high amounts also seen in the kidneys. In C57BL mice only, accumulation in the retina was seen. Exceedingly low accumulation in testes confined to interstitial spaces. |
| Metabolism - Rat | 50 mg/kg bw [phenyl (U) - $^{14}$C] - carbendazim<br><br>50 mg/kg bw [phenyl (U) - $^{14}$C] - carbendazim after 14 days pretreatment with 50 mg/kg bw unlabelled carbendazim<br><br>1000 mg/kg bw [phenyl (U) - $^{14}$C] - carbendazim by gavage | **Excretion:** > 98% of the recovered radiolabel had been excreted in the urine or faeces by time of sacrifice at 72 hr. Urinary excretion accounted for 62-66% (M) or 54-62% (F) at the low dose with or without pretreatment or 41% at the high dose (elimination in the faeces accounting for the rest). There were no apparent differences between male and female rats with respect to the extent of absorption or the extent or rate of elimination of $^{14}$C-carbendazim within each dose group. The label remaining in the tissue represented < 1% of the administered dose.<br><br>**Metabolism:** The primary metabolic reactions involved oxidation and conjugation at the phenyl ring to yield sulphate and glucuronide conjugates of 5-hydroxy- and 5,6-dihydroxy-carbendazim. Subsequent phenyl-ring oxidation and N-oxidation also occurred, especially in female rats. The main metabolite was 5-HBC-S (21-43%, except in F at the high dose or receiving pretreatment 5.5-10%); in all groups of F, 5,6-HOBC-N-oxide was the predominant metabolite (10-19%). 5,6-DHBC-S and 5,6-DHBC-G were identified as minor metabolites |

| Metabolism/Toxicokinetics Studies | | |
|---|---|---|
| **Study / Species** | **Dose Levels** | **Results/Effects** |
| Metabolism – Rat & Mouse | 3 or 300 mg/kg bw radiolabelled carbendazim, single dose by gavage<br><br>28 days unlabelled carbendazim followed by 3 or 300 mg/kg bw radiolabelled carbendazim | **Metabolism:** Urine collected during first 6 hr. Almost all the metabolites were in the form of glucuronide and sulphate conjugates. TLC after cleavage of these conjugates by β-glucuronidase-arylsulfatase tentatively identified the major compound 5-HBC (39% - 90%), carbendazim (2%-6%), 2-amino-benzimidazole (<2%-4%), hydroxylated-2-amino-benzimidazole (0%-5%). Mouse urine contained more compounds that remained polar after enzyme treatment than the urine of rats.<br><br>**Distribution:** The residual content in the liver was generally lower in rats (12-18%, single dose; 2-4% repeated dose) than mice (26-29%, single dose, <2-28% repeated dose), i.e. detoxification capacity of mouse liver was saturated at a higher dose. Livers from animals in both experiments contained the metabolites 5- and 4-hydroxy-2-amino-benzimidazole. |
| Liver enzyme induction – Rat | 0, 10, 30, 100, 300, 1000, 3000 ppm in the diet for 28 days | **≥300 ppm:** ↑ absolute liver weight (F).<br>**≥1000 ppm:** ↑ absolute liver weight (M), epoxide hydrolase induced<br>**3000 ppm:** glutathione-S-transferase induced (level of induction slightly greater in F; no difference between rats and mice). |
| Liver enzyme induction - Mouse | 0, 100, 1000 mg/kg bw/day by gavage in corn oil for 5 days | ↑ styrene-7,8-hydrolase and glutathione-S-transferase activity; ↓ 7-ethoxycoumarin-deethylase activity; total microsomal cytochrome P450 level did not increase.<br><br>Carbendazim did not cause overall microsomal induction, however some hepatic microsomal enzymes are induced (no substantial difference in enzyme induction between rats and mice). |

| Metabolism/Toxicokinetics Studies | | |
|---|---|---|
| **Study / Species** | **Dose Levels** | **Results/Effects** |
| Liver enzyme induction – Rat & Mouse | Rat: 0, 300, 600, 2000, 10,000 ppm in the diet for 29, 43, or 60 days<br><br>Mouse: 0, 150, 300, 1000, 5000 ppm in the diet for 29, 46 or 60 days | **(1) <u>Mice:</u>**<br>**≥1000 ppm:** ↑ relative liver weight; moderate to marked increases in the activities of the phase-I drug metabolizing enzymes including cytochrome P-450 and aminopyrine-*N*-demethylase; cytochome-c-reductase activity was decreased; glucuronyl transferase and glutathione-S-transferase activity as well as glutathione content were slightly increased.<br>**5000 ppm:** ↑ protein concentration in total homogenates and post-mitochondrial fraction of liver.<br><br>**(2) <u>Rats</u>:**<br>**≥2000 ppm:** ↑ relative liver weight; slight to moderate induction of several phase-I drug metabolizing enzymes (7-ethoxycoumarin-O-deethylase, biphenyl-4-hydroxylase, aniline hydroxylase, 4-methoxybiphenol-N-demethylase, cytochrome-c-reductase), moderate to marked increase of the phase-II drug metabolizing enzymes glucuronyl transferase I and II, as well as the glutathione content.<br>**10,000 ppm:** ↓ growth and food consumption.<br><br>No measurable difference between rats and mice with regard to the metabolism of carbendazim, although exhaustion of the detoxification mechanism was more evident in mice at high doses. Detoxification and elimination of carbendazim and its metabolites proceeded more rapidly in rats than in mice, as reflected by increased glutathione content of rat liver and increased phase-II enzyme activity. |
| Effect on respiratory chain enzymes - Rat | 0.1-1.0 nmol of carbendazim, 5-hydroxy-2-benzimidazole-carbamate (5-HBC), or 2-amino-benzimidazole (2-AB) | No effect of carbendazim or 5-HBC on mitochondria respiratory function; 2-AB inhibited the mitochondrial respiratory chain more strongly in the region of NADH-flavoprotein than in the region of cytochrome b; at high conc. 2-AB also exerted a dissociating effect on the oxidising phosphorylation of rat liver mitochondria.<br><br>The action of carbendazim and its metabolites on the mitochondria respiratory chain does not play a major part in the toxic action of this compound. |

| Subchronic Oral Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 2-week gavage - Rat | 0, 10, 20, 30, 40 mg/kg bw/day in 1% methyl cellulose | Not established as study was considered supplemental<br><br>No effects noted at 10 mg/kg bw/day | **≥20 mg/kg bw/day:** ↓ relative testes weight - but not dose-related; testes weights relative to heart or brain weights were not reduced (lower relative testes weights did not show any histopathological correlation) - *non-adverse*<br>**40 mg/kg bw/day:** ↑ liver weight. |

| Subchronic Oral Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 2-week gavage - Rat | 5000 mg/kg bw/day in peanut oil | Not established as study was considered supplemental | Clinical Signs: weakness, hair loss, polyuria.<br><br>Pathological changes: small, soft testes and inhibition of spermatogenesis (with no evidence of recovery 10 days after treatment) |
| 2-week gavage - Rat | 5000 mg/kg bw/day | Not established as study was considered supplemental | **5000 mg/kg bw/day:** effects on spermatogenesis |
| 2-week gavage - Rat | 0, 200, 3400, mg/kg bw/day in peanut oil | Not established as study was considered supplemental<br><br>Effects noted at 200 mg/kg bw/day, the lowest dose tested | **200 mg/kg bw/day:** no mortality; testes weight and ratio low in 1/3 rats; testes small, discoloured and soft in 1/3 rats sacrificed immediately; testes in 2/3 rats showed degeneration of germinal epithelium (less than 10% of tubules); sperm reduced in 2/3 rats sacrificed immediately.<br><br>**3,400 mg/kg bw/day:** 2/6 deaths; mild diarrhea and weight loss first week, gained weight slowly second week; testes small, discoloured and soft; degeneration of germinal epithelium (70% of tubules) and absence of sperm from epididymis of all rats (3/3).<br><br>Other compound-related changes (not assessed at 200 mg/kg bw): edema and focal necrosis of the duodenum; reduction of blood-forming elements of the bone marrow; decrease in the large globular-shaped centrilobular vacuoles in the liver. |
| 28-day dietary - Rat | 0, 2000, 4000, 8000 ppm (0, 100, 200, 400 mg/kg bw/day) | Not established as this was a range-finding study | **≥100 mg/kg bw/day:** ↑ liver weight.<br>**≥200 mg/kg bw/day:** ↓ food consumption and growth, degeneration of testicular tissue, spermatogenesis and oogenesis were affected.<br>**400 mg/kg bw/day:** ↑ Hgb, ↑ RBC, ↑ WBC. |
| 30-day dietary - Rat | 0, 80, 400, 2000, 10,000, 50,000 ppm (0, 4, 20, 100, 500, 2500 mg/kg bw/day) | Not established as this was a range-finding study | **≥500 mg/kg bw/day:** ↓ bw, ↓ bw gain, azoospermia<br>**2500 mg/kg bw/day:** ↓ food consumption, ↑ mortality (16/20 rats), ↓ leukocytes; pathology showed emaciation, siderosis in liver and kidney. |
| 4-week dietary - Rat | 0, 150, 300, 2000 ppm (0, 7.5, 15, 100 mg/kg bw/day) | Not established as the study was considered supplemental | **100 mg/kg bw/day:** non-adverse ↑ liver weight (F) and ↓ spleen weight (F).<br>There was limited organ histopathology and no kidney data. |

| Subchronic Oral Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 90-day dietary-Rat | 0, 50, 150, 450, 1350 ppm (0, 4/4, 12/13, 35/39, 106/116 mg/kg bw/day in M/F) | 106/116 (M/F)<br><br>**Note:** dose levels via diet not high enough to elicit testicular effects - generally seen at ≥200 mg/kg bw | **35/39 mg/kg bw/day:** slight non-adverse ↑ liver weight (F).<br>**106/116 mg/kg bw/day:** ↑ spleen and thyroid weight (F), ↑ kidney weight (M), ↑ liver weight, slight ↓ food consumption during recovery phase (F), ↓ total serum proteins (F).<br>No treatment-related differences in relative or absolute liver wt in rats after a 6 week recovery period. |
| 93-day dietary - Rat | 0, 80, 400, 2000, 10,000 ppm (0, 6.5/6.9, 32/36 163/174, 780/847 mg/kg bw/day in M/F) | 163/174<br>(M/F) | **≥ 6.5/6.9 mg/kg bw/day:** non-adverse ↑ liver weight (F).<br>**≥163/174 mg/kg bw/day:** non-advserse ↑ liver weight (M).<br>**780/847 mg/kg bw/day:** mortality, slight ↓ growth, slight ↑ uric acid in blood.<br>*(Testes examined histologically - no effects indicated)* |
| 90-day gavage – Rat | 0, 16, 32, 64 mg/kg bw/day in 4% gum acacia | <16<br><br>Effects noted at all dose levels | **≥16 mg/kg bw/day:** kidney effects (tubular dilation and hydropic degeneration), ↓ bw, ↑ ALT (M).<br>**≥32 mg/kg bw/day:** ↓ erythrocyte counts (M) (trend; not dose-dependent), ↓ BUN (M), ↑ serum bilirubin, ↑ ALT, kidneys (fibrosis and congestion).<br>**64 mg/kg bw/day:** ↑ ALP (M), kidney effects (hyalinisation and extensive vascular congestion).<br><br>Dose-related changes in the liver ranged from sparse infiltration by inflammatory cells to inflammatory and degenerative changes. |
| 28-day dietary - Dog | 0, 500, 2500 ppm (0, 21/19, 96/99 mg/kg bw/day in M/F) | <21/19 (M/F)<br><br>Effects noted at all dose levels | **≥21/19 mg/kg bw/day:** ↑ liver weight (F), liver pathology (hepatocytes slightly swollen - F).<br>**96/99 mg/kg bw/day:** ↑ ALT (M), ↑ ALP (M), liver pathology (disseminated focal lesions - M, greatly enlarged hepatocytes - F).<br><br>Testes were not weighed. |
| 90-day dietary - Dog | 0, 100, 300, 1000→2000 ppm (after 6 weeks) (0, 3.3/3.4, 9.7/10.2, 48.9/52.6 mg/kg bw/day in M/F) | 9.7/10.2 (M/F) | **≥9.7/10.2 mg/kg bw/da**y: slight non-adverse ↓ albumin (M).<br>**48.9/52.6 mg/kg bw/da**y: slight ↓ blood clotting time, slight ↑ relative liver and thyroid weight, ↓ relative heart weight (no microscopic changes associated with treatment in these or other organs, therefore non-adverse). |
| 90-day dietary - Dog | 0, 500, 1500, 4500 ppm (0, 15, 45, 135 mg/kg bw/day) | 45 | **45 mg/kg bw/day:** ↑ liver weight (F), slight ↑ relative adrenal weight (M).<br>**135 mg/kg bw/day:** ↓ bw, ↑ liver weight, ↓ heart weight (F). |

| Subchronic Oral Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 90-day dietary - Dog | 0, 500, 1500, 4500 ppm (0, 16.1/17.8, 50.1/56.2, 153.8/177.4 mg/kg bw/day in M/F) | 50.1/56.5 (M/F) | **16.1 mg/kg bw/day:** ↓ testicular weight (no histopath changes)<br>**50.1/56.2 mg/kg bw/day:** ↑ relative liver weight (F; no histopath. lesions), ↑ relative adrenal weight (M), seminiferous tubule degeneration (in 1/3 dogs; not seen at next dose).<br>**153.8/177.4 mg/kg bw/day:** ↓ bw gain, ↑ relative liver weight, ↑ relative adrenal weight (M), histopathological findings in the liver in one female (perivenous infiltrates, unorganised zones of proliferation, local hepatocyte regeneration, local hyperemia). |
| 90-day gavage - Dog | 0, 20, 40, 80 mg/kg bw/day | Not established as study was considered supplemental | Effects included ↓ Hgb, ↓ leukocytes, variable erythrocyte count, ↑ ALT, ↑ AST, ↑ urea, ↑ bilirubin, ↑ liver and spleen weight (M), ↓ adrenal, testes and ovary weight, ↓spleen weight (F), dose related liver and kidney degenerative lesions, liver inflammatory reactions.<br><br>Effects at specific doses were not indicated. |
| 90-day gavage - Dog | 0, 80, 160, 800 mg/kg bw/day | < 80<br><br>Effects noted at all dose levels | **≥ 80 mg/kg bw/day:** dose-related ↓ RBC; microscopic lesions included mucosal erosion in the stomach, focal degeneration, sinusoidal dilatation and congestion in the liver, patchy congestion in the spleen, degeneration of glomeruli and tubuli in the kidney, degeneration with fibrosis in testes and ovaries.<br>**800 mg/kg bw/day:** ↓ bw. |
| 1-year dietary - Dog | 0, 100, 200, 500 ppm (0, 2.9/3.2, 6.4/7.2, 16.5/17.1 mg/kg bw/day in M/F) | 6.4/7.2 (M/F) | **16.5/17.1 mg/kg bw/day:** ↑ serum cholesterol, ↑ platelet counts, ↓ serum calcium (M), ↑ serum globulin (F), ↑ liver weight. |

| Subchronic Dermal and Inhalation Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 5-day dermal - Rabbit | 800 mg/kg bw (40% in sesame oil) applied 5 hrs/day | Not established | No overt signs of toxicity; gross pathology not reported. The skin on the necks of all rabbits was slightly reddened from the third treatment onward, but this may have been due to the use of plastic neck collars. |
| 10-day dermal - Rabbit | 0, 2000 mg/kg bw (50% aqueous paste) applied 6 hrs/day | ≥ 2000 (systemic) | No systemic toxicity; no treatment-related clinical chemistry or pathological findings.<br><br>Skin irritation (focal epidermal and sub-epidermal necrosis with polymorphonuclear cell infiltrations) was observed in 5/6 rabbits. |

| **Subchronic Dermal and Inhalation Studies** | | | |
|---|---|---|---|
| 21-day dermal - Rabbit | 0, 10, 50, 250 mg/kg bw/day (aqueous suspension) applied 6 hrs/day, 5 days/wk | ≥250 (systemic) | No systemic toxicity.<br><br>Dermal effects included erythema, dryness of skin at scarified sites and skin thickening; slight effects on the skin were observed at the lowest dose. |
| 28-day dermal - Rat | 0, 20, 120, 480, 720 mg/kg bw/day in corn oil applied 6 hrs/day, 5 days/week | 20/120 (M/F)<br><br>$BMDL_{10}$ (seminiferous tubule degeneration) = 68 | **≥ 120 mg/kg bw/day:** ↑ liver weight (F), mild to severe seminiferous tubule degeneration, mild to severe hypospermia in the lumen of epididymal tubules.<br><br>**≥ 480 mg/kg bw/day:** sperm granulomas, ↓ epididymal sperm concentration, ↑ percent abnormal sperm, ↓% motile sperm, ↓ % progressively motile sperm; slight ↓ RBC, Hgb & Hct (F), ↑ forelimb & hindlimb grip strength (F).<br><br>**720 mg/kg bw/day:** ↑ relative liver weight (M), ↓ homogenization-resistant spermatid head concentration, ↓ daily sperm production/testis, ↓ efficiency of daily sperm production; ↑ forelimb grip strength (M).<br><br>Seminiferous tubule degeneration, hypospermia in the lumen of epididymal tubules, and ↑ percent abnormal sperm persisted at 720 mg/kg bw/day after a 10-week recovery period. |
| 5-day inhalation - Rat | 0, 0.058, 0.178 mg/L, nose-only, 4 hrs/day (0, 10.1, 31.0 mg/kg bw/day) | Not established as study was considered supplemental | No adverse effects observed up to 31 mg/kg bw/day. |
| 90-day inhalation – Rat<br><br>**Benomyl** | 0, 0.01, 0.05, 0.2 mg/L, nose-only, 6 hrs/day, 5 days/week (0, 2.6, 13, 52 mg/kg bw/day) | 2.6 | **≥ 13 mg/kg bw/day:** olfactory degeneration in the nasal cavity (M).<br><br>**52 mg/kg bw/day:** olfactory degeneration in the nasal cavity (F). |

| **Chronic Toxicity/Oncogenicity Studies** | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 80-week dietary - Mouse | 0, 150, 300, 5000* ppm (0, 22.5, 43, 714 mg/kg bw/day)<br><br>*1000 (4 weeks) → 2000 (4 weeks) → 5000 ppm | <22.5 | **≥ 22.5 mg/kg bw/day:** ↑ incidences of foci and nodular hyperplasia.<br><br>**714 mg/kg bw/day:** ↑ relative liver weight, ↑ incidence of clear cell foci, mixed cell foci and hepatoblastoma in liver (M), ↑ incidence of clear cell foci and neoplastic nodules in liver (F).<br><br>A basophilic tumour (hepatoblastoma) was a unique finding & metastasized to the lungs in 2 mice. |

| Chronic Toxicity/Oncogenicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| | | | The combined incidence of hepatocellular adenomas and carcinomas was found to increase with increasing dose in both sexes.<br><br>**Evidence of carcinogenicity** |
| 2-year dietary - Mouse | 0, 500,1500, 7500* ppm (0, 81/125, 257/380, 1560/1886 mg/kg bw/day in M/F)<br><br>*7500 ppm reduced to 3750 ppm after 15 months (M only) | 81/125 (M/F) | **≥ 81/125 mg/kg bw/day:** bile duct hyperplasia (F); centrilobular hepatocellular hypertrophy (M); ↓ absolute thymus and kidney weight (M); slight ↓ bw (M) *(effects considered minimal and non-adverse).*<br><br>**≥ 257/380 mg/kg bw/day:** sperm stasis in testes, thymic lymphoid depletion, ↑ liver weight, centrilobular hepatocellular necrosis (F), single cell hepatocellular necrosis (M), centrilobular hepatocellular swelling (M).<br><br>**1560/1886 mg/kg bw/day:** ↓ time to death in M, centrilobular hepatocelular hypertrophy (F), eosinophilic foci of cellular alterations (F), macrophages containing yellow-brown pigment (F).<br><br>Increase in hepatocellullar adenomas (F all doses) and hepatocellular carcinomas (both sexes at ≥1500 ppm).<br><br>**Evidence of carcinogenicity** |
| 22-month dietary - Mouse | 0, 50, 150, 300, 1000-5000* ppm (0, 5.8/7.1, 17.1/21.2, 34.4/41.9, 522/648 mg/kg bw/day in M/F)<br><br>* 1000 (4 weeks) → 2000 (4 weeks) → 5000 ppm | 34.4/41.9 (M/F) | **≥ 34.4/41.9 mg/kg bw/day:** non-statistical ↑ in incidence of granulosa cell tumours and luteomas in the ovaries.<br><br>**522/648 mg/kg bw/day:** ↑ relative liver weight, marked liver cell hypertrophy in the centrilobular and intermediate areas, other liver effects (necrosis, mitotic cells, pigmented Kupffer cells, clear cell foci).<br><br>**Evidence of carcinogenicity** |
| 2-year dietary - Rat | 0, 150, 300, 10,000* ppm (0, 8.9/9.6, 17.8/18.7, 600/640 mg/kg bw/day in M/F)<br><br>* 2000 (1 week) → 5000 (1 week) → 10,000 ppm | 17.8/18.7 (M/F) | **600/640 mg/kg bw/da**y: ↓ bw gain (F), ↓ Hgb (F), ↓ Hct (F), ↓ PCV (F), ↑ Hgb and PCV (M), ↑ relative liver weight (F), ↓ AST (M), ↑ ALP (F), ↑ ALT (F), ↓ total serum protein (F), ↑ BUN (M).<br><br>**No evidence of carcinogenicity** |
| 2-year dietary – Dog | 0, 100, 500, 1500-2500* ppm (0, 2.5, 12.5, 37.5-62.5 mg/kg | 2.5 | **≥ 12.5 mg/kg bw/day:** ↓ bw, anorexia, mortality, ↑ cholesterol, ↑ BUN, ↑ ALT, ↑ total protein, ↑ ALP, ↑ albumin and albumin/globulin ratio, hepatitis, liver cirrhosis. |

| Chronic Toxicity/Oncogenicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| Wettable powder formulation of 72.2% and 53%; concentrations adjusted for active ingredient | bw/day)<br><br>* 500 (2 days) → 1000 (3 days) → 1500 (2 days) → 2500 ppm | | **No evidence of carcinogenicity** |
| 2-year dietary - Dog | 0, 150, 300, 2000-5000* ppm (0, 4.3/4.4, 9.3/8.9, 80.8/84.2 → 150.4/135.8 mg/kg bw/day in M/F)<br><br>* 2000 (33 weeks) → 5000 ppm | 9.3/8.9 | **80.8/84.2 → 150.4/135.8 mg/kg bw/day:** ↓ bw gain; ↓ food consumption (F); ↓ clotting time; ↑ ALP; ↑ relative liver, pituitary, and thyroid weight, one male showed a few atrophic tubules and interstitial mononuclear inflammatory cell infiltrates of the testes. |

| Reproductive and Developmental Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 2-generation reproduction - Rat | 0, 50, 200, 600 ppm [0, 2.3, 9, 27.4 mg/kg bw/day (parental); 0, 2.8, 10.7, 31.2 mg/kg bw/day (offspring)] | Parental, offspring & reproduction<br>>27.4 | No signs of toxicity in parents and offspring and no developmental effects observed at any dose level. |
| 3-generation reproduction – Rat | 0, 150, 300, 2000 ppm (0, 7.5, 15, 100 mg/kg bw/ day) | Parental, offspring & reproduction<br>>100 | No signs of toxicity in parents and offspring and no developmental effects observed at any dose level. |
| Effect on uterine decidual cell response during pseudo-pregnancy - Rat | 0, 400 mg/kg bw/day for 8 days during pseudo-pregnancy; uterine decidual cell response induced on day 4 | < 400 | **400 mg/kg bw/day:** partial inhibition of decidual growth<br><br>Only treatment related effect observed in pseudopregnant animals was reduced uterine weight which is a measure of uterine decidual growth during pseudopregnancy. No changes in ovarian weight, number of corpora lutea, bw gain or serum progesterone and estradiol levels |

| Reproductive and Developmental Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| Acute effect on microtubule-dependent meiotic events - Hamster | 0, 250, 500, 750, 1000 mg/kg bw (by gavage) during meiosis I (oocyte maturation)<br><br>0, 1000 mg/kg bw (by gavage) during meiosis II (fertilization) | <250<br>during meiosis I<br><br><1000<br>during meiosis II | **During meiosis I:**<br>**≥250 mg/kg bw:** ↓ average number live pups.<br>**≥750 mg/kg bw:** ↓% pregnant animals.<br><br>**During meiosis II:**<br>**1000 mg/kg bw***:* ↓ average number live pups (no change in % pregnant animals).<br><br>Administration of carbendazim at the time of microtubule-dependent meiotic events can result in early pregnancy loss in hamsters. |
| Developmental study (dietary) - Rat | 0, 150, 300, 2000 ppm (0, 7.5, 15, 100 mg/kg bw/day) | Maternal<br>≥100<br><br>Developmental<br>Not established since endpoints not assessed at all doses | **100 mg/kg bw/day:** ↑ incidence of thoracic vertebral bodies being reduced in number, ↑ incidence of absent ossification in cervical vertebral bodies, ↑ incidence of incomplete ossification of skull bones.<br>Malformations and variations were assessed only in the 0 and 2000 ppm dose groups<br><br>**Increased fetal sensitivity** |
| Developmental study (dietary) - Rat | 0, 600, 2000, 6000 ppm (0, 44.9, 141.4, 371.4 mg/kg bw/day) from GD 6 to 15 | Maternal<br>141.4<br><br>Developmental<br><44.9<br><br>Developmental effects noted at all dose levels | **Maternal:**<br>**371.4 mg/kg bw/day:** ↓ bw, ↓ food consumption.<br><br>**Developmental:**<br>**44.9 mg/kg bw/day:** ossification significantly delayed or absent in cervical vertebral bodies.<br>**371.4 mg/kg bw/day:** ossification significantly delayed or absent, in forelimbs, hindlimbs, sternebrae, and skull bones, increased incidence of supernumerary ribs.<br><br>**Increased fetal sensitivity** |
| Developmental study (gavage) - Rat | 0, 5, 10, 20, 90 mg/kg bw/day from GD 6 to 15 in 0.5% CMC | Maternal<br>20<br><br>Developmental<br>10 | **Maternal:**<br>**90 mg/kg bw/day:** ↓ bw gain, ↑ liver weight, ↓ # live fetuses /litter (increased resorptions).<br><br>**Developmental:**<br>**≥20 mg/kg bw/day:** ↓ fetal weight, ↑ skeletal variations.<br>**90 mg/kg bw/day:** ↑ fetal malformations (hydrocephaly, microphthalmia, anophthalmia, malformed scapulae, and axial malformations).<br><br>**Increased fetal sensitivity** |

| Reproductive and Developmental Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| Developmental study (gavage) - Rat | 0, 10, 30, 60, 100, 300, 1000, 3000 mg/kg bw/day from GD 6 to 15 in 0.5% CMC | Maternal<br>30<br><br>Developmental<br>10 | **Maternal:**<br>**60 mg/kg bw/day:** ↓ maternal bw, 2/23 animals aborted, 51% resorptions.<br>**100 mg/kg bw/day:** 15 pregnant animals produced only 4 live fetuses in 3 litters, all of which were malformed.<br><br>**Developmental:**<br>**30 mg/kg bw/day:** 42% of the fetuses in 19/21 litters had malformations affecting the head, spine, ribs and sternum<br>**60 mg/kg bw/day:** 51% resorptions, malformations in 90% of fetuses, and all litters were affected.<br>**100 mg/kg bw/day:** only 4 live fetuses in 3 litters, all of which were malformed.<br>**≥300 mg/kg bw/day:** 100% early resorptions, no live fetuses.<br><br>**Increased fetal sensitivity** |
| Developmental study (gavage) - Rat | 0, 10, 30 mg/kg bw/day from day from GD 6 to 15 in 0.5% CMC | Maternal<br>≥30<br><br>Developmental<br>10 | **30 mg/kg bw/day:** ↓ placenta weight, ↓ fetal weight; ↑ malformations, variations and retardations (hydrocephalus in 17/358 fetuses; malformations of the head, spine and ribs in 81/358 fetuses from 22 litters).<br><br>**Increased fetal sensitivity** |
| Developmental study (gavage) - Rat | 0, 10, 30, 60 mg/kg bw/day from GD 6 to 15 in distilled water with Tween 40 | Maternal<br>30<br><br>Developmental<br>10 | **Maternal:**<br>**60 mg/kg bw/day:** ↓ maternal bw<br><br>**Developmental:**<br>**≥30 mg/kg bw/day:** high resorption rate, ↓ fetal bw<br><br>**Increased fetal sensitivity** |
| Developmental study (gavage - single dose) - Rat | 0, 250, 1000, 5000 mg/kg bw on GD 7, 9, 11, 12 or 13<br><br>0, 15.6 - 125 mg/kg bw on GD 13 | Not established as study was considered supplemental<br><br>Effects noted at 250 mg/kg bw/day, the lowest dose tested | Doses of 250 - 5000 mg/kg bw on GD 11 produced no live fetuses in any of the dose groups. Doses of 250 - 5000 mg/kg bw on GD 13 produced live fetuses but all had anomalies esp. encephalon and limbs. Doses of 15.6-125 mg/kg bw on GD 13 produced higher rate of stillbirth; meningocele and an increased postnatal period were also observed.<br><br>**Malformations after single dose** |

| Reproductive and Developmental Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| Developmental study (gavage-single dose) - effect on behaviour - Rat | 0, 15.6, 31.2, 62.5 mg/kg bw on GD 13 | Not established as study was considered supplemental<br><br>No effects noted at 15.6 mg/kg bw/day | **≥31.2 mg/kg bw:** ↓ number of live-born/litter, ↓ offspring viability.<br>**62.5 mg/kg bw:** hydrocephalus (20% - 3/14).<br><br>Possible behavioural teratogenic effects observed at 31.2 and 62.5 mg/kg bw, but could not be conclusively established.<br><br>**Malformations after single dose** |
| Developmental study (gavage) - Rat | 10, 19 mg/kg bw/day and higher from GD 8 to 15 | Not established as study was considered supplemental<br><br>No effects noted at 10 mg/kg bw/day | **≥19 mg/kg bw/day:** drastic increase in embryolethality and incidence of external anomalies, in particular exencephalia; ↓ fetal weight. |
| Developmental study (gavage - single dose) - Rat | 0, 15, 30, 60, 150, 300 mg/kg bw on day GD 10 in 10% gum arabic | Not established as study was considered supplemental<br><br>No effects noted at 15 mg/kg bw/day | **≥30 mg/kg bw:** Dose-dependent ↓ number of live fetuses due to deaths and resorptions, ↑ runts.<br>**150 mg/kg bw:** ↓ number of fetuses /litter.<br><br>No significant or dose -related increase in the incidence of malformations, but at 30 mg/kg bw one fetus had exencephaly, and one had hydrocephalus; two fetuses at 60 mg/kg bw had hydrocephaly.<br><br>**Malformations after single dose** |
| Developmental study (gavage-single dose) - Hamster | 0, 15, 30, 75, 150 mg/kg bw/day on GD 8 in 10 % gum arabic | Not established as study was considered supplemental<br><br>No developmental effects noted at 15 mg/kg bw/day | **Maternal:**<br>**≥75 mg/kg bw/day:** ↓ bw gain<br><br>**Developmental:**<br>**30 mg/kg bw/day:** slight ↑ % resorptions/dead fetuses.<br>**≥75 mg/kg bw/day:** ↓ fetal weight, ↑ malformations including exencephaly, embryotoxic (31% resorptions), 10/57 fetuses displayed fused ribs.<br>**150 mg/kg bw/day**: ↓ fetuses/litter, embryotoxic (45% resorptions), 14/52 fetuses displayed fused ribs.<br><br>**Increased fetal sensitivity, malformations after single dose** |

| Reproductive and Developmental Toxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| Developmental study (gavage-single or few doses) - Rabbit | 0, 150, 300 mg/kg bw on GD 9<br><br>10, 60, 150 mg/kg bw/day on GD 8, 10 and 12<br><br>10 mg/kg bw/day on GD 10, 13 and18<br><br>in 10% gum arabic | Not established as study was considered supplemental<br><br>Effects noted at 10 mg/kg bw/day, the lowest dose tested | **10 mg/kg bw/day (dosing GD 10, 13, &18):** 22% of fetuses were runts.<br>**10 mg/kg bw/day (dosing GD 8, 10, &12):** slight ↑ dead / resorbed fetuses.<br>**60 mg/kg bw/day (dosing GD 8, 10, &12):** ↓ in fetuses/litter (31 live fetuses from 40 implantations; of live fetuses, 26% were runts and ↑ % had fused ribs).<br>**150 mg/kg bw (dosing GD 9):** ↓ in fetuses/litter (28 live fetuses from 54 implantations; of live fetuses, 30% were runts and 57% had fused ribs).<br>**150 mg/kg bw/day (dosing GD 8, 10 & 12):** no live fetuses.<br>**300 mg/kg bw (dosing GD 9):** no live fetuses.<br><br>Fused ribs observed in 2 dose groups (150 and 60 mg/kg ) were the only malformations noted. |
| Developmental study (gavage) - Rabbit | 0, 10, 20, 125 mg/kg bw/day from GD 7 to 19 in 0.5% CMC | <u>Maternal</u><br>20<br><br><u>Developmental</u><br>10 | **Maternal:**<br>**125 mg/kg bw/day:** ↓ bw.<br><br>**Developmental:**<br>**≥20 mg/kg bw/day:** ↓ implantation rate (not treatment related since dosing is post implantation), ↑ resorptions & ↓ live litter size.<br>**125 mg/kg bw/day:** ↑ resorptions, ↑ malformed fetuses/litter (malformed cervical vertebrae and interrelated malformation of the ribs and proximate thoracic vertebrae).<br><br>**Increased fetal sensitivity** |

| Special Studies: Male Fertility / Hormonal Effects and Spermatogenesis | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| Acute male fertility - effect on spermatogonia (gavage) - Rat | 200, 1000 mg/kg bw; 3 µg/kg bw colchicine or 200 mg/kg bw carbendazim with 3 µg/kg colchicine | Not established as study was considered supplemental | No chromosome aberrations in spermatogonia; ↑ mitotic index and induced development of c-mitosis in dividing cells (reaction was more intense with carbendazim than colchicine). Carbendazim-induced inhibition of cell division (increased mitotic index) and accumulation of c-metaphases was reversible. |
| Acute male fertility effects (gavage) - Rat | 670, 1000, 1500, 2250, 5000, 7500, 11000 mg/kg bw (25% in peanut oil) | Not established as study was considered supplemental<br><br>No effects noted at 670 mg/kg bw/day | **≥1000 mg/kg bw:** pathological changes in testes (soft).<br>**≥1500 mg/kg bw:** pathological changes in testes (soft, small, occasionally dark), interference with spermatogenesis.<br>**≥5000 mg/kg bw:** initial weight loss, diarrhea.<br>**11000 mg/kg bw:** cellular degeneration (testes). |

| Special Studies: Male Fertility / Hormonal Effects and Spermatogenesis | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| Acute male fertility study - effect on testes (gavage) - Rat | 200, 450, 670, 1000, 2250, 3400, 5000, 7500, 11,000, 17,000 mg/kg bw (5-30% in peanut oil) | Not established as study was considered supplemental<br><br>No effects noted at 450 mg/kg bw/day | **≥1000 mg/kg bw:** ↓ sperm in epididymis; germinal epithelium degeneration with multinucleated giant cells.<br>**≥2250 mg/kg bw:** testes discoloured, small and soft and sometimes of unequal size (except at 7500 mg/kg bw).<br>**≥3400 mg/kg bw:** sperm absent from epididymis.<br>**≥11,000 mg/kg bw:** ↓ testis weight.<br>Effects not fully dose-related: fewer tubules affected at 5000 and 7500 mg/kg bw. |
| Acute male fertility study (gavage)- Rat | 200, 1000 mg/kg bw | Not established as study was considered supplemental | Carbendazim reversibly blocked division of spermatogonia at the metaphase stage without producing chromosome aberrations. |
| Acute male fertility study - Rat | Benomyl or carbendazim; 859 µmol/kg via i.p. injection or 1.37 µmol injected into testis | Not established as study was considered supplemental | Little testicular damage was caused by injection of benomyl after 1 or 2 hrs; carbendazim elicited severe disruption of the seminiferous epithelium. Results strongly suggest that benomyl metabolite carbendazim, not benomyl, is mediator of benomyl-induced testicular toxicity and inhibitor of testicular microtubule assembly. |
| Acute effect on testes, efferent ductules, and spermatozoa (gavage) - Rat | 0, 50, 100, 200, 400, 800 mg/kg bw<br><br>Testes examined at 2 or 70 days | Not established as study was considered supplemental<br><br>Effects noted at 50 mg/kg bw, the lowest dose tested | **On day 2:**<br>**50 mg/kg bw:** missing immature germ cells with round spermatids (stage I and II), elongated spermatids sloughed from stage VII epithelium.<br>**≥100 mg/kg bw:** ↑ testicular weight, absence of germ cells, sloughing of spermatids extended to stages XII and XIV, swollen rete testis with sloughed germ cells, ≥50% efferent ductules were occluded.<br>**≥200 mg/kg bw:** germ cells missing at most stages.<br>**≥400 mg/kg bw:** ↑ mean seminiferous tubular diameter.<br><br>**On day 70:** ↓ testicular weight and seminiferous tubule diameter due to ↑ seminiferous tubular atrophy. |
| Acute effect on testes, efferent ductules, and spermatozoa (gavage) - Rat | 0, 400 mg/kg bw<br><br>Testes examined at 2, 4 or 8 hrs and 1, 4, 8, 16, 32 days | Not established as study was considered supplemental | ↑ testicular weight at 8 hrs (↓ day 16 & 32); ↓ sperm head counts/testis at 8 hr, 24 hr and day 8; ↑ epididymal weight day 4, but ↓ % normal sperm; by day 8 many sperm heads were separated from flagella, 10% of heads misshapen; numerous sloughed, round germ cells and cytoplasmic testicular debris evident; ↓ sperm motility days 8 and 16. |
| 5-day male fertility study (gavage) - Mouse | 0, 250, 500, 1000 mg/kg bw/day<br><br>Mice sacrificed on days 7, 24 & 39 post-treatment | Not established as study was supplemental<br><br>No effects noted at 250 mg/kg bw/day | **500 mg/kg bw/day:** ↓ % round spermatids (7 and 24 days), ↑ sperm head abnormalities (day 39).<br>**1000 mg/kg bw/day:** ↓ testis weight and ↓ % round, elongating and elongated spermatids at 7 and 24 days; recovery by day 39; ↑ sperm head abnormalities (days 7, 24 & 39), chromatin structure altered (days 7 & 39). |

| Special Studies: Male Fertility / Hormonal Effects and Spermatogenesis | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 10-day male fertility study (gavage) - Rat | 0, 400 mg/kg bw/day<br><br>Rats bred once a week for 14 weeks following initial treatment | Not established as study was considered supplemental | **400 mg/kg bw/day:** ↓ testis, cauda and caput epididymal weight, ↓ total epidiymal sperm count and vas deferens sperm concentration, ↑ serum FSH levels, bilateral seminiferous tubular atrophy, ↓ male fertility.<br><br>Dosing did not span full spermatogenesis period (70days) |
| 10-day male fertility study (gavage) - Rat | 0, 400 mg/kg bw/day in corn oil<br><br>Rats bred once a week starting 3 days after the beginning of treatment, ending 32 days after end of treatment | Not established as study was considered supplemental | Male fertility was depressed starting first week after treatment, some recovery after 5-11 consecutive breeding periods; severe seminiferous tubular atrophy occurred in males that failed to recover fertility.<br><br>Histology of testes from infertile males 245 days after treatment revealed severe seminiferous tubular atrophy (< 2% of the tubules contained spermatozoa).<br><br>Infertility reversible in some males, irreversible in others |
| Developmental stage study (gavage) - Rat | 0, 50, 100, 200, 400 mg/kg bw/day<br><br>Dosed from weaning, through puberty, gestation & lactation; males examined 50 days post-dose | Not established as study was considered supplemental<br><br>Effects noted at 50 mg/kg bw/day, the lowest dose tested | **≥50 mg/kg bw/day:** ↓caudal epididymal sperm count.<br>**≥100 mg/kg bw/day:** a few malformed pups.<br>**≥200 mg/kg bw/day:** ↓ litter size, ↓ reproductive potential due to effects on sperm production and fetal viability, altered sperm morphology; ↓ testicular and epididymal weight, ↓ sperm number; testicular histology; fertility, sperm mobility and hormonal levels were altered in males with very low sperm count.<br>**400 mg/kg bw/day:** ↑ post-implantation loss. |
| Developmental stage study - Hamster | 0, 400 mg/kg bw/day<br>Dosed from weaning, through puberty, gestation & lactation; M examined 50 days post-dose | Not established as study was considered supplemental | **400 mg/kg bw/day:** ↓ testicular and epididymal sperm counts, testis and seminal vesicle weights.<br><br>Overall, carbendazim was less toxic to hamsters than to rats: the only reproductive effect was on sperm measures; fertility as well as foetal and neonatal viability was not altered. |
| 85-day male fertility study - testes/ endocrine function (gavage)- Rats | 0, 50, 100, 200, 400 mg/kg bw/day in corn oil | Not established as study was considered supplemental<br><br>No effects noted at 100 mg/kg bw/day | **≥200 mg/kg bw/day:** ↓ testes and caput epididymides weight, ↓ seminiferous tubule fluid volume, ↑ androgen binding protein in interstitial and seminiferous tubule fluid, ↑ testosterone in seminiferous tubule fluid.<br>**400 mg/kg bw/day:** ↓ caput epididymides weight, ↓ interstitial fluid volume, ↑ testosterone concentration in interstitial fluid, ↑ serum androgen binding protein.<br><br>HCG stimulation of the decapsulated testes caused ↑ in in vitro testosterone synthesis/release at 200 and 400 mg/kg bw/day after 1, 2 and 3 hrs incubation.<br><br>Carbendazim directly affects the gonads causing testicular atrophy with secondary hormone changes. |

| Special Studies: Male Fertility / Hormonal Effects and Spermatogenesis | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| 85-day male fertility study (gavage) - Rat | 0, 50, 100, 200, 400 mg/kg bw/day in corn oil<br><br>Rats mated after 64 days of dosing; hypothalmic and pituitary control of testis assessed | Not established as study was considered supplemental<br><br>Effects noted at 50 mg/kg bw/day, the lowest dose tested | **50 mg/kg bw/day:** ↑ anterior hypothalamic GnRH (progressive ↓ at higher doses).<br>**≥100 mg/kg bw/day:** ↑ anterior pituitary LH, slight ↓ medio-basal hypothalamic GnRH.<br>**≥200 mg/kg bw/day:** ↑ serum FSH (particularly in fertile rats), ↑ serum LH (not at 400 mg/kg bw/day).<br><br>Carbendazim-induced testicular damage is accompanied by compensatory changes in hypothalmic and pituitary regulation of the testis. |
| Male fertility - effect on spermatogenesis (dietary) - Rat | 0, 10, 70, 500 ppm (0, 0.5, 3.5, 25 mg/kg bw/day) for up to 182 days; M dosed at 0, 500 ppm mated with untreated females on day 182 and sacrificed on day 208 | Not established as study was considered supplemental | Fertility parameters, testicular weight, seminiferous tubules, interstitial tissue, epididymal structures and enzyme activities were not affected by treatment.<br><br>**≥ 0.5 mg/kg bw/day:** ↑ preleptonene spermatocyte nuclear area.<br>**≥ 3.5 mg/kg bw/day:** ↑ incidence of 'degenerating' germ cells undergoing meiosis and spermatogenesis.<br>**25 mg/kg bw/day**: effects indicate that carbendazim affects the physiological 'germinal elimination process'.<br><br>No biologically significant effects on spermatogenesis. |

| Neurotoxicity Studies | | | |
|---|---|---|---|
| **Study / Species** | **Dose Levels** | **NOAEL (mg/kg bw/day)** | **Results/Comments** |
| Acute delayed neurotoxicity study - Hen | 0, 500, 2500, 5000 mg/kg bw in corn oil by gavage | 2500 | **5000 mg/kg bw:** systemic toxicity, transient/reversible neurotoxic signs (slight leg weakness, ataxia)<br><br>No neurotoxic signs at lower doses; no histological signs of neuropathy (no axonal degeneration or demyelination in any group) |
| 21-day neurotoxicity - Chicken | 0, 40, 80, 400 mg/kg bw/day | 80 | **400 mg/kg bw/day:** ↑ serum ChE (F; 33.5%), slight ataxia for approximately 2 days (1 female only).<br><br>No other neurotoxic symptoms appeared in any other chicken |

| Summary - Genotoxicity Studies | | |
|---|---|---|
| **Study (# of studies)** | **Purity or Dose (mg/kg bw)** | **Results/Effects** |
| Bacterial reverse mutation - *S. typhimurium* (36); *S. cervisiae* (1) | various | Negative in 14 studies ±S9. Weakly positive to positive +S9, or at very high concentrations in one or more strains in 15 studies (in some cases, the purity was unknown). Positive in 8 studies using test material with DAP and AHP contaminant. |
| Carbendazim with differing amounts of DAP and AHP seemed to be the reason for positive Ames tests. Also, 2-amino-benzimidazole (a minor metabolite in the rat) was positive in both forward and reverse mutation tests. Highly purified carbendazim and its main metabolite in mammals, 5-OH carbendazim, were not mutagenic. | | |
| Fungi/plant cytogenetics (2) | unknown | Chromosome aberrations and mitotic non-disjunction observed. |
| Mammalian Cells in vitro - Mouse lymphoma, Chinese hamster ovary cells (5) | unknown or 100% | Negative in 3 studies (100% purity in 2/3 studies). Positive (unknown purity) in 2 studies (1 at highly toxic concentrations). |
| Chromosomal Effects (10) | unknown | Positive for aneuploidy in 9 studies (threshold response). |
| In vivo genotoxicity (15) | 97-99% or unspecified | Negative for clastogenicity in 8 studies. Positive for micronucleus formation in 7 studies: aneugenic rather than clastogenic. |
| Tubulin/mitotic effects/DNA synthesis in vitro/in vivo (9) | unknown | Inhibits tubulin polymerization and therefore mitosis; ↓ DNA, RNA and protein synthesis - a reflection of mitotic arrest. |
| Dominant Lethal (4) | 94% | Negative in all 4 studies. |
| DNA damage and repair (7) | 99% or not specified | Negative; but the minor rat metabolite 2-amino-benzimidazole induced DNA damage in *E. coli* strains $WP_2$ uvrA and CM 611. |
| **In vivo Germ Cell Tests** | | |
| DNA binding - Rat liver<br><br>DNA synthesis inhibition - Rat gonads | 2, 20, 200 | Negative for DNA binding. The compound reached the gonads and inhibited DNA and protein synthesis at ≥ 2 mg/kg bw. The affinity of the agent for hepatic proteins, penetration into gonads, and inhibition of DNA and protein synthesis at high doses suggest an epigenetic mechanism of action on reproductive cells. |
| Mouse sperm FISH assay - Aneugenic effects on male germ cells (gavage) | 20, 50, 150, 500 | No aneugenic effect up to the highest dose of 500 mg/kg bw. |
| Aneuploidy frequency in unfertilized oocytes/ preimplantation embryonic development - Hamster | 1000 | ↑ aneuploidy frequency in unfertilized oocytes. In animals allowed to mate, the fertilization rate was not impaired; however, there was a significant ↑ in proportion of pre-implantation embryos that failed to reach expected stage of development (8-cell, morula, blastocyte stage) and ↓ number of implantation sites. |
| Chromosome aberrations in sperm and micronuclei in peripheral RBC – Rat (single oral dose) | 2.5, 800 | ↑ in diploid epididymal sperm sampled after 31 days; induction of aneuploid sperm was not observed; no evidence of micronucleus induction in the erythrocytes. |
| Induction of micronulei in round (immature) spermatids – Rat (single oral dose) | 50, 100, 400 | **100 mg/kg bw:** ↑ micronucleus incidence at 24 hrs; ↑ micronuclei with kinetochores, suggesting that the micronuclei in treated rat-spermids are due to aneuploidy rather than to clastogenic activity. |

**Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Carbendazim**

| Exposure Scenario | Dose (mg/kg bw/day) | Study | Endpoint | Target MOE |
|---|---|---|---|---|
| Short-term incidental oral | NOAEL = 20 mg/kg bw/day | Developmental toxicity studies in rats and rabbits | Decreased body weight and body weight gain and increased liver weight in maternal animals | 300 |
| Short- to Long-term dermal & inhalation | NOAEL = 10 mg/kg bw/day | Developmental toxicity studies in rats and rabbits | Fetal malformations and resorptions | 1000 |
| Cancer unit risk | $q_1^* = 1.6 \times 10^{-2}$ $(mg/kg\ bw/day)^{-1}$ | Carcinogenicity study in mice | Hepatocellular tumours (adenomas and/or carcinomas) in females | N/A |

**Table 4 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported**

| Proposed uses | Proposed rates |
|---|---|
| WOOD PROTECTIVE STAIN: For stains that are used for the film protection | 0.3 - 1.5% |
| ROOF COATINGS: For coatings applied to roofing tiles or for coating roofing membrane surfaces | 0.7 - 3.0% |
| STUCCO AND EIFS COATINGS | 0.5 - 1.5% |

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Chemistry

| PMRA Document Number | Reference |
|---|---|
| 1371967 | Carbendazim Tech registration---Canada, N/S, DACO: 2.13.1,2.14.10,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.3,2.4,2.5,2.6,2.7,2.8,2.9,4.2.1,4.2.2,4.2.3,4.2.4,4.2.5,4.2.6,4.2.9,4.4.2,4.4.3,4.5.1,8.1,9.1 CBI |
| 1415968 | 2007, Data for Amended Registration Carbendazim 99% TGAI. Product Chemistry, and waivers for Toxicology, Environmental Toxicology and fate data, N/S, DACO: 2.13.1,2.14.10,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8, 2.14.9,2.3,2.4,2.5,2.6,2.7,2.8,2.9, |
| 1656664 | Analytical method for determination of carbendazim, DACO: 2.13.1 |
| 1656665 | Analytical method for determination of ortho-phenylenediamine, DACO: 2.13.1 |
| 1656666 | Analytical method for determination of water, DACO: 2.13.1 |
| 1656667 | Appendix B.2 Detailed Analytical Data for Determination of o-phenylenediamine, DACO: 2.13.1 CBI |
| 1656668 | Appendix B.2 Detailed Analytical Data for Determination of Water, DACO: 2.13.1 CBI |
| 1656669 | Batch data for o-phenylenediamine, DACO: 2.13.2 CBI |
| 1656670 | Chromatogram data for determination of carbendazim, DACO: 2.13.1 CBI |
| 1656672 | Chromatogram data for determination of o-phenylenediamine, DACO: 2.13.1 CBI |
| 1673826 | DACO: 2.13.1 CBI |
| 1673827 | DACO: 2.13.1 CBI |
| 1673828 | DACO: 2.13.1 CBI |
| 1673829 | DACO: 2.13.1 CBI |
| 1077202 | 2001, Physical and Chemical Characteristics of Troy EX678: Color,Physical State, Odor, Oxidation/Reduction, Flammability,Explodability, pH,Viscosity and Relative Density., DACO: 3.5 CBI |

1077203 2002, Physical and Chemical Characteristics of Troy EX678:Storage Stability and Corrosion Characteristics., DACO: 3.5.10 CBI

1407055 2007, Polyphase 678 Product Chemistry, DACO: 3.1.1

1407056 2007, Polyphase 678 Product Chemistry, DACO: 3.1.2 CBI

1407057 2007, Polyphase 678 Product Chemistry, DACO: 3.1.3

1407058 2007, Polyphase 678 Product Chemistry, DACO: 3.2.1 CBI

1407059 2007, Polyphase 678 Product Chemistry, DACO: 3.2.2 CBI

1407060 2007, Polyphase 678 Product Chemistry, DACO: 3.2.3 CBI

1407061 2007, Polyphase 678 Product Chemistry, DACO: 3.3.1 CBI

1407062 2002, A Method for the Determination of Percentage of IPBC and BCM in Troy EX678, DACO: 3.4.1 CBI

1407063 2007, Polyphase 678 Product Chemistry, DACO: 3.4.2 CBI

1407064 2002, Physical and Chemical Characteristics of Troy EX678: Storage Stability and Corrosion Characteristics, DACO: 3.5.10,3.5.14

1582202 2008, Formulating Plant Name and Address, DACO: 3.1.2 CBI

## 2.0 Human and Animal Health

**PMRA Document Number** **Reference**

1407065 2003, Five-Day Toxicity Study of Mergal BCM in Rats, DACO: 4.7

1407066 2003, Five-Day Toxicity Study of Mergal BCM in Rats (Amendment), DACO: 4.7

1783049 2007, 28 Day Dermal Toxicity Study of Carbendazim (CAS No. 10605-21-7) Administered to Male and Female CD (Sprague-Dawley) Rats, DACO: 4.3.5

1783050 2007, 28 Day Dermal Toxicity Study of Carbendazim (CAS No. 10605-21-7) Administered to Male and Female CD (Sprague-Dawley) Rats, DACO: 4.3.5

1783054 2007, 28 Day Dermal Toxicity Study of Carbendazim (CAS No. 10605-21-7) Administered to Male and Female CD (Sprague-Dawley) Rats, DACO: 4.3.5

1783063 2008, Benchmark Dose Modeling for Reproductive Endpoints from Dermal Toxicity Study for Carbendazim (47371601), DACO: 4.3.8

1077205 2001, Acute Oral Toxicity Up and Down Procedure in Rats., DACO: 4.6.1

1077206 2001, Acute Dermal Toxicity Study in Rats-Limit Test, DACO: 4.6.2

1077207 2001, Acute Inhalation Toxicity Study in Rats-Limit Test, DACO: 4.6.3

1077208 2001, Primary Eye Irritation Study in Rabbits., DACO: 4.6.4

1077209 2001, Primary skin irritation Study in Rabbits., DACO: 4.6.5

1077210 2001, Dermal Sensitization Study in Guinea Pigs (Magnusson-Kligman Method), DACO: 4.6.6

1939440 2010, *In-vivo* Percutaneous Absorption of [C14] Carbendazim, in a Water-Based Paint Formulation in Rats, DACO: 5.8

1939441 2010, *In-vitro* Percutaneous Absorption of [C14] Carbendazim, Formulated in a Water-Based Paint, Through Human and Rat Skin Membranes, DACO: 4.5,5.8

1939443 2010, *In-vivo* Percutaneous Absorption of [C14] Carbendazim, in an Alkyd Based Paint Formulation in Rats, DACO: 5.8

1939444 2010, *In-vitro* Percutaneous Absorption of [C14] Carbendazim, Formulated in an Alkyd Based Paint through Human and Rat Skin Membranes, DACO: 4.5

1939445 2009, *In-Vitro* Percutaneous Absorption of [C14] Carbendazim Formulated in a Paint, through Human Skin Membranes Using Flow Through Diffusion Cells, DACO: 4.5,5.8

## 3.0 Environment

None.

## 4.0 Value

**PMRA Document Number** **Reference**

1558699 Mode of Action Polyphase 678, DACO: 10.2.1

1558700 Laboratory Trials-Exterior Spackling Compound Addendum-Polyphase 678, DACO: 10.2.3.2

1558702 Laboratory Trials-Joint Compound Addendum-Polyphase 678, DACO: 10.2.3.2

1558703 Laboratory Trials-Adhesives Addendum-Polyphase 678, DACO: 10.2.3.2

1558704 Laboratory Trials-Acrylic Ink Addendum-Polyphase 678, DACO: 10.2.3.2

1558705 Evaluation of Mergal 186, Polyphase AF1, and Polyphase 678 in Seven Water Based Vinyl Acrylic Coating Samples and Evaluation of Two Coded Samples, DACO: 10.2.3.2

1558706 Evaluation of Mergal 186, Mergal 174, Polyphase 678, and Polyphase AF3 in Four Water Based Latex Paint Samples and Evaluation of Four Current Production Samples, DACO: 10.2.3.2

1558708 Evaluation of Polyphase 678 and Polyphase P-20T in an Artist Color Sample, DACO: 10.2.3.2

1558709 Evaluation of Mergal K14, Mergal 680, Polyphase 663 and Polyphase 678 in Nine Latex Coating Samples and Evaluation of Twenty Seven Coded Latex Coatings, DACO: 10.2.3.2

1558710 Evaluation of Troy EX682, Mergal K10N, Troysan 174, and Polyphase 678 in Six Adhesives and Evaluation of Current Production, DACO: 10.2.3.2

1558711 Evaluation of Troysan 174, Mergal K14, Polyphase 641, and Polyphase 678 in an Acrylic Latex Caulk and Evaluation of Polyphase 678 and Mergal BCM in a Silicone Caulk and Evaluation of Current Production, DACO: 10.2.3.2

1558712 Evaluation of Polyphase 678 and Polyphase 663 in a Grout Sealer and Evaluation of a Preserved Sample, DACO: 10.2.3.2

1558713 Evaluation of Polyphase 678 in a Sealant and Evaluation of Current Production, DACO: 10.2.3.2

1558714 Evaluation of Polyphase 678, Polyphase 662, Polyphase 663, and Mergal S90 in a Water Borne Sealant and Evaluation of Two Preserved Samples, DACO: 10.2.3.2

1558715 Evaluation of Mergal 174 and Polyphase 678 in Two Water Based Ink Samples in Comparison with Four Coded Samples, DACO: 10.2.3.2

1558717 Evaluation of Polyphase 678 in a Joint Compound Sample and Evaluation of a Current Production Sample, DACO: 10.2.3.2

1558718 Evaluation of Polyphase 678 in an All Purpose Compound, A Taping Compound and a Spray-Plast Sample, DACO: 10.2.3.2

1558719 Evaluation of Troysan 174, Troy EX671-4, Polyphase 641, and Polyphase 678 in a Joint Treatment Compound and Evaluation of Current Production, DACO: 10.2.3.2

1558720 Dry-Film Preservation Testing-Polyphase 678, DACO: 10.2.3.3

## B. Additional Information Considered

### i) Published Information

#### 1.0 Human and Animal Health


| PMRA Document Number | Reference |
|---|---|
| 2023157 | Bentley, K.S., Kirkland, D., Murphy, M. Marshall, R. (2000). Evaluation of thresholds for benomyl- and carbendazim-induced aneuploidy in cultured human lymphocytes using fluorescence in situ hybridization. Mutation Research, 464: 41-51. |
| 2023167 | Bolt, H.M and Degen, G.H. (2004). Human carcinogenic risk evaluation, Part II: Contributions of the EUROTOX specialty section for carcinogenesis. Toxicological Sciences, 81: 3-6. |
| 2023165 | Bolt, H.M., Foth, H., Hengstler, J.G., Degen, G.H. (2004). Carcinogenicity categorization of chemicals – new aspects to be considered in a European perspective. Toxicology Letters, 151: 29-41. |
| 2023174 | Decordier, I., Dillen, L., Cundari, E., Kirsch-Volders, M. (2002). Elimination of micronucleated cells by apoptosis after treatment with inhibitors of microbules. Mutagenesis, 17: 337-344. |
| 2023175 | Elhajouji, A., Tibaldi, F., Kirsch-Volders, M. (1997). Indication for thresholds of chromosome non-disjunction versus chromosome lagging induced by spindle inhibitors in vivo in human lymphocytes. Mutagenesis, 12:133-140. |
| 2023191 | McCarrol, N.E., Protzel, A., Ioannou, Y., Stack, H.F., Jackson, M.A., Waters, M.D., Dearfield, K.L. (2002). A survey of EPA/OPP and open literature on selected pesticide chemicals. III. Mutagenicity and carcinogenicity of benomyl and carbendazim. Mutation Research, 512:1-35. |
| 2023179 | Pratt, I.S and Barron, T. (2003). Regulatory recognition of indirect genotoxicity mechanisms in the European Union. Toxicology Letters, 140: 53-62. |
| 2023181 | WHO (1993). International Program on Chemical Safety, Environmental Health Criteria 148 – Benomyl, World Health Organization, Geneva, Switzerland. |

## ii) Unpublished Information

### 1.0 Human and Animal Health


| PMRA Document Number | Reference |
|---|---|
| 962905 | MAFF (1992). Evaluation on Carbendazim. Ministry of Agriculture, Fisheries and Food, Pesticides Safety Division, London, UK. July 1992. |
| 1040722 | USEPA (2005). Reregistration Eligibility Decision – Thiophanate-Methyl, United States Environmental Protection Agency, May 12, 2005. |