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FOOD AND AGRICULTURE ORGANIZATION
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WHO/FAO DATA SHEET ON PESTICIDES

No. 87

BENOMYL

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CLASSIFICATION:

Primary use: Systemic fungicide
Secondary use: Acaricide, mite ovicide
Chemical group: Benzimidazole carbamate

1.0 GENERAL INFORMATION

1.1 COMMON NAME: Benomyl (ISO)

1.1.1 Identity:

IUPAC chemical name: Methyl 1-[(butylamino)carbonyl]-1H-benzimidazol-2-ylcarbamate

CAS chemical name: Carbamic acid, [1-(butylamino)carbonyl]-1H-benzimidazol-2-yl]-, methyl ester.

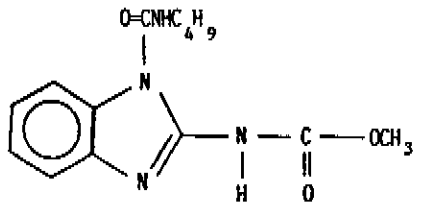
CAS registry number: 17804-35-2

RTECS registry number: DD6475000

Molecular formula: $C_{14}H_{18}N_4O_3$

Relative molecular mass: 290.3

Structural formula:



Trade names and synonyms: Benlate^R; Tersan^R; Fungicide 1991; methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate.

1.2 SYNOPSIS:

Benomyl is a systemic, broad spectrum benzimidazole carbamate fungicide. Acute toxicity is low, and there is no evidence of accumulation. It is only mildly irritant to skin and eyes, but sensitizes skin. Foetotoxic and teratogenic effects have been observed in laboratory animals following gavage administration of high doses, but not following dietary exposure. Inhalation and oral exposure reduced spermatogenic activity in laboratory animals.

1.3 SELECTED PROPERTIES

1.3.1 **Physical characteristics:** A tan-coloured odourless crystalline solid which decomposes at 140 °C just after melting. Technical benomyl is greater than 98% (w/w) pure.

1.3.2 **Solubility:** In water at 25 °C and pH 5 its solubility is 3.6 mg/L. Soluble in several organic solvents, especially heptane and chloroform (40 and 9.4 g/100 g solvent at 25 °C respectively).

1.3.3 **Stability**: Rapidly hydrolysed in dilute aqueous solutions and in soil to butyl isocyanate and the fungicide methyl-2-benzimidazole carbamate (carbendazim). Decomposed by strong acids and alkalis. Stable to light.

1.3.4 **Vapour pressure**: Negligible (less than 5×10^{-6} Pa).

1.4 AGRICULTURE, HORTICULTURE AND FORESTRY

1.4.1 **Common formulations**: Wettable powder (50%) and oil dispersion (50%). In combination with other pesticides as a wettable powder (10-50%) or as a dust (6%).

1.4.2 **Pests mainly controlled**: Controls a wide range of fungal diseases of fruits, nuts, vegetables, field crops, turf and ornamentals. Powdery mildew, apple scab and grey mould fungus are well controlled. It is also effective against mites.

1.4.3 **Use pattern**: Effective as a pre-harvest systemic fungicide, and as a post-harvest dip or dust treatment for the protection of fruits, seeds and vegetables in storage. Compatible in mixtures with non-alkaline pesticides.

1.4.4 **Unintended effects**: Toxic to fish and to earthworms.

1.5 **PUBLIC HEALTH PROGRAMMES:** No recommended usage.

1.6 **HOUSEHOLD USE:**

1.6.1 **Common formulations**: Wettable powder (50%), wettable powder (2%) in combination with other pesticides.

1.6.2 **Pests mainly controlled**: Powdery mildew, botrytis, fusarium basal rot, black spot and blossom rot.

1.6.3 **Use pattern**: As a spray application to ornamentals, domestic fruit, trees and lawns. Application procedures and re-application intervals should be made according to manufacturers' directions.

2.0 TOXICOLOGY AND RISKS

2.1 TOXICOLOGY - MAMMALS

2.1.1 **Absorption route**: Benomyl is readily absorbed after oral and inhalation exposure, but much less following dermal exposure.

2.1.2 **Mode of action**: Benomyl and its main metabolite carbendazim bind to microtubuli, an essential structure of all cells, thereby interfering with their functions (cell division, intracellular transports, etc.). Selective toxicity of benomyl is thought to be due to its higher affinity for fungal as compared with mammalian microtubuli.

2.1.3 **Excretion products**: Benomyl is almost completely transformed and excreted in the urine as methly(5-hydroxy-1H-benzimidazol-2-yl)-carbamate (5-HBC) and to a less extent as carbendazim. 5-HBC is the major metabolite in milk.

2.1.4 **Toxicity, single dose**:

Oral LD_{50}

Rat (M & F)	≥ 10 000 mg/kg b.w. (peanut oil)
Rat (M & F)	≥ 10 000 mg/kg b.w. (aqueous suspension of Benlate^R, 53% a.i.)

Dermal LD_{50}

Rabbit (M & F)	10 000 mg/kg b.w. (50% w.p.)

Inhalation LC_{50} - 4 hour exposure

Rat	>4.01 mg/L (50% w.p.)
Dog	>1.65 mg/L (50% w.p.)

Oral administration of benomyl to rats and inhalation exposure to dogs caused testicular toxicity. Doses were >100 mg/kg and 1.65 mg/L for oral and inhalation exposure respectively.

Primary irritancy: Mild erythema was observed following application of an aqueous suspension of 25% benomyl to shaved guinea pig skin. Mild conjunctival irritation was observed in rabbit eyes following instillation of 10 mg of a dry powder formulation (5 mg a.i.) or 0.1 ml of an oil suspension (10 mg a.i.).

2.1.5 **Toxicity, repeated doses**:

Oral: Gavage studies in rats of various age showed that benomyl (≥200 mg/kg/day for 10 days and ≥45 mg/kg/day for about 80 days) caused reduced sperm count and various histopathological lesions of testes and epididymus indicating disruption of all stages of spermatogenesis.

Inhalation: Nose exposure of rats to benomyl (6 h/day for 90 days) caused degeneration of olfactory epitelium at ≥50 mg benomyl/m^3.

Dermal: Skin exposure of rabbits to 50% benomyl formulation equivalent to 1000 mg/kg (6 h/day, 5 days/week for 3 weeks) caused mild erythema and moderate desquamation of the sites of application. Testicular toxicity (degeneration of spermatogenic elements) was observed at microscopic examination. Benomyl was found to produce sensitization in guinea pigs.

Cumulation of compound: No evidence of cumulative residues was seen in the tissues of laboratory and domestic animals.

Cumulation of effects: No evidence of cumulative effects was observed in rats following gavage, dietary or inhalation exposure.

2.1.6 **Dietary studies**:

Short term: No signs of toxicity were observed in rats following 90 days administration of benomyl up to and including 2500 mg/kg/diet. In a 90-day study, beagle dogs received 0, 100, 500 and 2500 mg/kg/diet (up to 84 mg/kg b.w./day). Minor changes in clinical chemistry and some histopathological lesions observed, at the high dose level only, were probably not due to benomyl.

Long term: Administration of up to and including 2500 mg/kg diet to rats for two years was without adverse effect on growth, clinical chemistry, haematologic or histopathologic parameters.

No adverse effects on clinical chemistry parameters or haematological indices were observed in male and female CD-1 mice receiving up to 5000 mg/kg/diet for two years. Compound related changes were found in the absolute and relative liver weights for males (highest dose) and females (up to and including 1500 mg/kg diet). Male mice had decreased testes weights and testes degeneration at the highest dose.

2.1.7 **Supplementary studies of toxicity**:

Carcinogenicity: Rats were exposed up to 2500 mg/kg benomyl in the diet for two years and no oncogenic effects were detected. Mice were exposed to 0, 500, 1500 and 5000 mg/kg/diet for two years. The incidence of hepatocellular adenomas and carcinomas in female mice was increased in a dose-dependent manner. In male mice, the number of hepatocellular adenomas and carcinomas were significantly increased at 500 and 1500 mg/kg but not at 5000 mg/kg dose. The increased number of lung alveolar carcinomas in male mice was still within the range of historical controls.

Teratogenicity: A mouse gavage study (0, 50, 100 and 200 mg/kg per day on days 7 to 17 of gestation) showed teratogenic effects at all dose levels. Abnormalities included; exencephaly, hydrocephaly, cleft palate, hydronephrosis, polydactyly, oligodactyly, umbilical hernia, fused ribs, fused vertebrae and short/kinky tail.

Teratogenicity was also observed in a rat gavage study (0, 3, 10, 30, 62.5 and 125 mg/kg per day on days 7 to 16 of gestation). Malformations included, microphthalmia, anophthalmia and hydrocephaly. The NOEL was 30 mg/kg benomyl. In another study in rats the NOEL for similar teratogenic effects was found to be 31.2 mg/kg.

In a rat study aimed at evaluating the effects of low levels of benomyl as the pups aged the compound was administered by gavage at dose levels of 0, 15.6, and 31.2 mg/kg per day from day 7 of gestation to day 15 of lactation). No teratogenicity was found but testes weight was significantly reduced in males given 31.2 mg/kg.

A further gavage study in rats produced similar teratogenic effects at 62.4 mg/kg per day on day 7 - 21 of gestation. The incidence of these effects increased when a semipurified protein-deficient diet was given together with the same level of benomyl. Some malformations (primarily hydrocephaly) also appeared at the lower dose when the same diet was provided.

Reproduction: No adverse effect was observed in a three generation reproduction study with ChR-CD rats receiving 2500 mg/kg diet (the maximum dose administered).

Pre-pubertal exposure of Sprague-Dawley rats to 10 daily gavage doses of 200 mg technical benomyl/kg b.w./day in oil had no effect on the time of puberty onset or on the sperm count at that time. However, the same regimen caused depression of the total epididymal and vas deferens sperm counts at doses of 200 or 400 mg/kg b.w./day in adult rats. At the 400 mg/kg b.w./day dose the testes weights were maintained but showed evidence of hypospermatogenesis.

Dietary administration of 1, 6.3 or 203 mg/kg (diet) for 70 days had no effect on reproductive behaviour of adult Wistar rats. Decreased ejaculate sperm concentration was observed in the high dose group and testes weights were decreased at all doses. Both effects were reversed during a 70 day recovery period.

Permanent reductions were observed in the size of testes and male accessory glands in 100 day old offspring of Wistar rat dams receiving 31.2 mg benomyl/kg b.w./day on gestation day 7 through to day 15 of lactation.

Reduced spermatogenic activity has been reported in rats following acute inhalation exposure, acute and sub-chronic oral exposure and dogs following a single four hour inhalation exposure (section 2.1.4).

Mutagenicity: In a dominant lethal mutation study administration of upto 203 mg benomyl/kg/diet for 46-53 days to Wistar rats, or 2500 mg/kg/diet for 7 days to ChR-CD rats did not induce mutations. Intraperitoneal administration of 1000 mg benomyl/kg b.w. to rats induced mitotic arrest in bone-marrow cells within four hours of dosing. Serum from these rats collected 30 minutes after dosing was cytotoxic to mammalian cell lines *in vitro*. Orally administered doses of 1000 mg/kg b.w. did not affect the bone marrow, and the serum was only weakly cytotoxic.

Benomyl was not mutagenic in *Escherichia coli* WP2 hcr, or *Salmonella typhimurium*, nor in mitotic gene conversion studies in *Saccharomyces cerevisiae*, but was a mitotic spindle poison in *Aspergillus nidulans*.

2.2 TOXICOLOGY - MAN

2.2.1 **Absorption route**: No specific information published but animal data suggest rapid absorption from the gastro-intestinal tract, and by the inhalation route. Benomyl is probably absorbed only slowly through intact skin.

2.2.2 **Dangerous doses**:

Single: No published information available.

Repeated: No published information available.

2.2.3 **Observations on occupationally exposed workers**:

No inadvertent poisoning of agricultural or forestry workers has been documented.

Benomyl caused contact dermatitis and dermal sensitization in some farm workers. Cross-sensitization between benomyl and other pesticides such as diazinon, daconil, saturon and 2-bordeaux has been reported.

Blood profiles from workers involved in the manufacture of benomyl were not different from those of a control group of workers. Workers exposed for 1-95 months during benomyl manufacture were examined for reproduction performance. There was no reduction in fertility as shown by the birth rates, which were generally higher than those of the control populations.

2.2.4 **Observations on exposure of the general population**: No published information available. With good agricultural practice, exposure of the public to hazardous quantities of benomyl is unlikely.

2.2.5 **Observations on volunteers**: No published information available.

2.2.6 **Reported mishaps**: None reported.

2.3 TOXICITY - NON-MAMMALIAN SPECIES

2.3.1 **Fish**:

LC_{50} (96 hour):

Carp	7.5 mg/L
Fathead minnow	2.2 mg/L
Bluegill	1.3 mg/L
Rainbow trout	0.17 mg/L
Channel catfish	0.031 mg/L

2.3.2 **Birds**:

LC_{50} (5 days)

Mallard duck	> 10 000 mg/kg diet
Bobwhite quail	> 10 000 mg/kg diet

Body weight gain, feed consumption and egg production in Leghorn hens were unaffected by 25 mg benomyl/kg diet (as Benlate^{R} 50% w.p.) for 28 days. No residues were found in the fat or breast tissue. A low concentration of the methyl 5-hydroxy-metabolite was found in the eggs during exposure, but not 7 days after cessation of exposure.

2.3.3 **Beneficial insects**: Benomyl is not toxic to bees.

2.3.4 **Other species**:

LC_{50} *Daphnia magna* 0.64 mg/L

Exposure of earthworms to residues or suspensions of benomyl may have a delayed lethal effect. Low concentrations on the foliage may suppress feeding. Reduced populations of earthworms have been reported in benomyl treated orchards.

3.0 FOR REGULATORY AUTHORITIES - RECOMMENDATIONS OF COMPOUND

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY

[For definition of categories see the 'Introduction to Data Sheets'].

All liquid formulations of 50% or less and all solid formulations - Category 5

3.2 TRANSPORT AND STORAGE

Formulations in Category 5: Should be stored and transported in clearly labelled leakproof containers out of the reach of children, away from food and drink.

3.3 HANDLING

Formulations in Category 5: Handling of large quantities of solid formulations (2 kg bags or greater) requires use of a dust mask and protective clothing (see section 4.1.3 - 4.1.4). For handling small quantities and liquid formulations no facilities other than those required for handling of any chemical are required.

3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINERS

Decontamination of containers is probably not practical due to the low water solubility of benomyl. Containers must be disposed of in an approved manner. Care must be taken to avoid contamination of water sources.

3.5 SELECTION, TRAINING AND MEDICAL SUPERVISION OF WORKERS

Formulations in Category 5: Warning of workers to minimize contact is essential particularly in view of the sensitizing effects of benomyl.

3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT

All formulations: Benomyl is normally not distributed by aircraft. If it is, pilots and loaders should have special training in application methods. All workers must wear a dust mask, overalls and impermeable gloves.

3.7 LABELLING

Formulations in category 5 - Minimum cautionary statement.

This formulation contains the fungicide benomyl which is poisonous if swallowed or if the dust is inhaled. Keep out of reach of children and pets, and well away from foodstuffs or animal feeds.

3.8 RESIDUES IN FOOD

Maximum levels have been recommended for a variety of agricultural products and foodstuffs by the FAO/WHO Joint Meeting on Pesticide Residues on Food and the Environment. In 1983 the JMPR established an Acceptable Daily Intake (ADI) of 0-0.02 mg/kg/b.w.

4.0 PREVENTION OF POISONING IN MAN AND EMERGENCY AID

4.1 PRECAUTIONS IN USE

4.1.1 General: Benomyl is a benzimidazole fungicide. Acute toxicity of benomyl is low, but it has the potential of causing sensitization.

4.1.2 Manufacture and formulation: TLV 10 mg/m^3. Dusts should be controlled, preferably by mechanical means. Protective equipment for respiratory tract and skin is necessary.

4.1.3 Mixers and applicators: Light respiratory protection should be used when handling dusty formulations. For all formulations clean overalls and gloves should be used to prevent skin contamination. When opening the container and when mixing, care should be taken to avoid contact with the eyes and mouth. Mixing if not mechanical, should always be carried out with a paddle of

appropriate length. The applicator should avoid working in spray mist and avoid contact with the mouth. Splashes must be washed from the skin or eyes immediately with large volumes of water. Before eating, drinking or smoking, hands and exposed skin should be washed.

4.1.4 **Other associated workers**: Persons exposed to benomyl and associated with its application should wear protective clothing and observe the precautions described above in 4.1.3. under "Mixers and Applicators".

4.1.5 **Other populations likely to be affected**: Subject to 4.2 below, other persons are not likely to be exposed to hazardous amounts of benomyl.

4.2 ENTRY OF PERSONS INTO TREATED AREAS

No exclusion from treated areas is indicated.

4.3 DECONTAMINATION OF SPILLAGE AND CONTAINERS

Residues in containers should be buried in a deep dry pit (>0.5 m) taking care to avoid contamination of water sources. Spillage of liquid formulations should be contained and absorbed by absorbent material. This material, or spillage of dry formulations, should be collected and buried in a deep dry pit. Care must be taken to avoid contamination of water sources. Residues should be washed from the spillage site with water and detergent.

4.4 EMERGENCY AID

4.4.1 **Early symptoms of poisoning**: No details reported.

4.4.2 **Treatment before person is seen by physician, if these symptoms appear following exposure**: The person should stop work immediately, remove contaminated clothing and wash contaminated skin with soap and water and flush with large volumes of clean water. If the eyes are contaminated, they should be flushed with large volumes of clean water.

5.0 FOR MEDICAL AND LABORATORY PERSONNEL

5.1 MEDICAL DIAGNOSIS AND TREATMENT IN CASE OF POISONING

5.1.1 **General information**: Benomyl is a benzimidazole fungicide of low acute toxicity. At high doses benomyl has been shown in animals to be teratogenic and to cause testicular changes.

5.1.2 **Symptoms and signs**: No cases of human poisoning have been recorded.

5.1.3 **Laboratory**: No tests in humans to measure exposure have been reported.

5.1.4 **Treatment**: Symptomatic, because no specific antidote is available. In the case of skin contamination the exposed area should be washed with soap and water. If the compound has entered the eyes they should be washed with copious volumes of isotonic saline or water.

5.1.5 **Prognosis**: Unknown.

5.1.6 **References to previously reported cases**: No reports.

5.2 **SURVEILLANCE TESTS:** There are no readily available field techniques to determine the degree of exposure.

5.3 **LABORATORY METHODS**

5.3.1 **Detection and assay of compound and residues:**

Assay methods may not distinguish between benomyl and methyl 2-benzimidazole carbamate, which forms rapidly when benomyl is in aqueous solution.

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5.3.2 **Other tests in case of poisoning**: None.

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