Toxicology Overview for Benfuracarb

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DESCRIPTION OF THE TEST CHEMICAL

Benfuracarb (Orgo-50) is a highly effective new carbamate insecticide which has been successfully developed by Osaka Chemical Co., Ltd. throughout the world and currently marketed over fifteen countries in Europe, Africa and Asia including Japan. Benfuracarb is a broad-spectrum systemic insecticide which provides excellent control of many important insects pests and nematodes infesting rice, maize, sugar beet, vegetables and other major food crops.

The chemical structure and physicochemical properties of the insecticide are given below:

Common name: Benfuracarb
Chemical name: Ethyl N-(2,2-dimethyl-2,3-dimethylbenzofuran-7-ylcarbonoyl)methyl)-aminocarbonyl-N-isopropyl-N-alanilinate (IUPAC)
Structural formula: \[ \text{Chemical Structure} \]

Molecular formula: C_{21}H_{21}N_{5}O_{5}S
Molecular weight: 419.5
Appearance: Viscous reddish brown liquid
Melting point: 222°C (decomposed)
Vapour pressure: 6 x 10^{-10} mmHg (20°C)
Solubility: Water 8 ppm, Benzene >50%, Xylene >50%, Acetone >50%, Dichloromethane >50%

ACUTE TOXICITY STUDIES

The acute toxicity of benfuracarb (technical material) and Orgo-50 (contains 5% w/w benfuracarb) for rats, mice and dogs was determined by various routes of administration. The LD₅₀ data and test laboratories for each study are summarized in Tables 1 and 2. Signs of toxicity observed in these studies were those commonly associated with compounds which inhibit acetylcholinesterase including: salivation, lacrimation, diarrhea, exophthalmia, labored breathing, tremors and convulsions.

IRRITATION STUDIES

Benfuracarb (0.1 ml) was instilled into the eyes of rabbits. All animals had slightly congested pupils after 3 hours. Mild conjunctivitis was observed after 3 hours while only slight conjunctivitis was observed after 24 hours. All eyes appeared normal within 48 hours which indicated that benfuracarb is minimally irritating to the eye.

A primary dermal irritation study was conducted with undiluted benfuracarb. No treatment-related effects were observed during 7 days after the application of 0.5 ml benfuracarb on two intact and two abraded skin sites on each of six rabbits.

Otsuka Chemical Co., Ltd., 1981

SKIN SENSITIZATION STUDY

The skin sensitization study was conducted using Hartley guinea-pigs according to the methods of Bendler. Guinea-pigs treated with benfuracarb showed no dermal response after the challenge application, suggesting no potentiality of benfuracarb in producing sensitization.

(Boydynamics Inc., 1982)

ACUTE DELAYED NEUROTOXICITY STUDY

Benfuracarb was orally administered by gavage to groups of mature White Leghorns at 160 mg/kg b.w. and protected with atropine. No signs of residual or delayed
toxicity were observed. Histopathological examin- 
ation revealed no evidence of neurotoxic effects. The results indicate that benfuracarb has no potential to produce delayed neuro- 
toxicity. 

(Bio)design Inc., 1982)

S U B - A C U T E TOXICITY STUDIES

1. Sub-Acute Toxicity Study in Rats

In a 90-day study, groups of Fischer-344 rats (20 per sex per group) were fed a diet con- 
aining 0, 500, 1000 or 10,000 ppm benfuracarb. There was a dose-related increase in the in- 
cidence of urine staining of the fur and rough hair coat. Body weight gain was decreased in 
male rats, and the high dose level and in females at all dose levels. Hematocrit and hemoglobin 
values were decreased in a dose-related manner, and erythrocyte and platelet counts. Plasma 
cholesterol activity was decreased at all dose levels. Brain cholinesterase deter- 
mined at termination, was unaffected by treat- 
ment. Gross examination revealed enlarged and discoloured lymph nodes and lesions of the

glandular stomach both at 400 and 800 ppm, while slight hypotroph of musculus acini of the 
mandibular salivary gland was found at 800 ppm on histopathological examination. A clear 
non-effect level was not established in this study.

(Hazleton Laboratories, Inc., 1983)

2. Sub-Acute Toxicity Study in Mice

In a 90-day study, groups of C57 mice (25 per sex per group) were fed a diet containing 0, 
100, 300 or 1000 ppm benfuracarb. At the high dose level there were transient overt signs of toxicity (transquility, pilocerection and piloerect) while body weight gain was decreased during the entire weeks of the study. Leucocyte and platelet counts were increased in males at 1000 ppm, while erythrocyte counts, hemo-
globin and hematocrit values were decreased at 1000 ppm. These were no treatment- 
related effects on cholinesterase determinations. Relative pituitary, adrenal, thyroid and lung

weights were increased at 1000 ppm, while
absolute heart, liver and kidney weights were decreased. The variation of organ weight was attributed to lower body weights. Gross and histopathological examination failed to reveal any treatment-related effects. Therefore, a non-effect level was established to be 300 ppm (47.1 mg/kg b.w./day in males and 62.7 mg/kg b.w./day in females).

(Bozo Research Center, 1982)

CHRONIC TOXICITY STUDIES

1. Chronic Toxicity / Carcinogenicity Study in Rats

In a 2-year study, groups of Fischer-344 rats (50 per sex per group) were fed a diet containing 0, 100, 200 or 400 ppm benzafuracarb, while satellite groups terminated after 1 year of feeding were fed 0, 200, 400 or 800 ppm. Although there were no overt signs of toxicity during the first year of treatment even at 800 ppm, there was an increased incidence of rough hair coat, urine staining of the fur and squinted eyes at 200 and 400 ppm during the second year of treatment. There was a dose-related decrease in body weight gain at all dose levels, although only males were affected at 100 ppm. There were some variations in erythrocyte values, particularly during the first year of the study, but these were not consistent dose-related trends. Clinical chemistry values also varied, but there was no consistency between main and satellite groups. Plasma cholinesterase activity was consistently decreased in a dose-related manner at all dose levels, as was erythrocyte cholinesterase at weeks 70 and 105, but at other time intervals erythrocyte cholinesterase activity was increased at 200 ppm and above. There were no treatment-related effects on urinalysis values, ophthalmoscopic examination, and otic and neurological examination. In liver and heart residues and relative weight decrease due to lower body weight was observed in the satellite groups but not in the main groups. Gross and histopathological examination of all tissues revealed no treatment-related lesions. Due to the treatment-related effects even at 100 ppm, a clear non-effect level was not established in this study.

In a further 2-year study, groups of Fischer-344 rats (50 per sex per group) were fed a diet containing 0 or 25 ppm benzafuracarb. No consistent or apparent treatment-related overt signs of toxicity were noted throughout the study. Body weight gain and food consumption were unaffected by treatment. There were no consistent treatment-related effects on hematology or urinalysis values or organ weights. No depression of plasma, erythrocyte and brain cholinesterase was noted at 25 ppm throughout the study. Gross and histopathological examination failed to reveal any treatment-related lesions. Therefore, a non-effect level for benzafuracarb administered via the diet for 2 years was established to be 25 ppm (1.3 mg/kg b.w./day in males and 1.8 mg/kg b.w./day in females).


2. Chronic Toxicity Study in Dogs

In a 2-year study, benzafuracarb was orally administered daily by gavage to groups of beagle dogs (6 per sex per group) at 0, 2.5, 5 or 10 mg/kg b.w./day. The animals treated at 5 and 10 mg/kg exhibited signs of toxicity, including tremors and hind limb ataxia, shortly after administration. There were variations in a number of hematological and clinical chemistry values, but these were not related to either dose or the duration of treatment. Plasma cholinesterase activity was decreased 5 hours after dosing at 5 mg/kg in males and 10 mg/kg in males and females, while no inhibition was observed after 24 hours. Erythrocyte cholinesterase was not inhibited at any dose levels. Brain cholinesterase determined at termination, was unaffected by treatment. There were variations in some organ weights but these were not related to treatment. Gross and histopathological examination failed to reveal any treatment-related lesions. The non-effect level was established to be 2.5 mg/kg b.w./day both in males and females.

(Bozo Research Center, 1984)

3. Carcinogenicity Study in Mice

In an 18-month study, groups of CD-1 mice (50 per sex per group) were fed a diet containing 0, 100, 300 or 1000 ppm benzafuracarb. There were no overt signs of toxicity, and survival was unaffected by treatment. Body weight
gain was decreased at 1000 ppm in males, while there were sporadic variations in body weight among females at this dose level. Food consumption was unaffected by treat-
ment. Hematological values were equivalent in all groups. There were no treatment-
related effects on absolute or relative organ weights nor any treatment-related lesions detected at gross and histopathological ex-
amination. The results indicate that ben-
fluarcarb is not carcinogenic.
(Bio)dynamics Inc., 1984)

REPRODUCTION STUDY
In a 2-generation reproduction study, groups of CD rats (15 males and 30 females per group) were fed a diet containing 0, 25, 100 or 400 ppm benfluarcarb and bred to produce a single litter in each generation. The body weight gain of parent animals was generally decreased at 400 ppm. Reproductive performance was unaffected by treatment in the first generation, but pregnancy rates and male fertility index were reduced at 400 ppm in the second genera-
tion. There was a reduction in pup weight at birth at 400 ppm, while body weight gain during lactation was decreased. A reduction in litter sizes in both F1 and F2 generations was apparent at 100 and 400 ppm, but not at 25 ppm. Pup survival was reduced at 400 ppm in the second generation, while at 100 ppm the survival was slightly reduced. Therefore, a non-effect level was established to be 25 ppm (1.6 mg/kg b.w./day in males and 2.0 mg/kg b.w./day in females).
(Bio)dynamics Inc., 1984)

TERATOLOGY STUDIES
In a rat teratology study, benfluarcarb was orally administered daily by gavage to groups of CD rats (24 pregnant females) at 0, 2, 10 or 40 mg/kg b.w./day on days 6 to 19 of gestation. Cesarean section was performed on day 20. The uterine contents were evaluated, and all fetuses were examined for external, visceral and skeletal abnormalities. At 2 mg/kg benfluarcarb was maternally toxic, embryotoxic and teratogenic. At 10 mg/kg benfluarcarb was maternally toxic (lower body weight); however, no embryotoxicity or ter-
atogenicity was indicated. At 40 mg/kg ben-
fluarcarb demonstrated maternal toxicity (lower body weight, tremors) and embryotoxicity (reduced fetal weight) but was not teratogenic. In a rabbit teratology study, benfluarcarb was orally administered daily by gavage to groups of New Zealand White rabbits (18 to 20 pregnant females) on days 7 to 29 of gesta-
tion at 0, 5, 10 or 15 mg/kg b.w./day. Cesarean section was performed on day 30. The uterine contents were evaluated, and all fetuses were examined for external, visceral and skeletal abnormalities. At 5 mg/kg benfluarcarb was neither maternally toxic, embryotoxic nor teratogenic. At 10 mg/kg benfluarcarb pro-
duced maternal toxicity (ano-genital staining); however, no embryotoxicity or teratogenicity was indicated. At 15 mg/kg benfluarcarb demonstrated maternal toxicity and embry-
oxotoxicity (reduced fetal weight); however, no teratogenicity was indicated.
(Bio)dynamics Inc., 1983)

MUTAGENICITY STUDIES
The mutagenic potential of benfluarcarb was assessed in a number of short-term assays. In 2 Ames tests, both using 5 strains of Salmonella typhimurium and/ or Escherichia coli, negative results were obtained at dose levels of up to 5000 ag/ml, both in the presence and absence of a metabolic activation system. (The Institute of Environmental Toxicology, 1982)

(Haakeston Laboratories America, Inc., 1983)
In a cytogenetic assay, CD rats were given either a single or 5 multiple daily doses of 5, 15 or 50 mg/kg b.w./day. Negative results were obtained at sampling times of 6, 24 and 48 hours after the single dose, and 6 hours after the final dose in the multiple dose groups.
(Haakeston Laboratories America, Inc., 1983)
In a micronucleus test, CD-1 mice were given 2 consecutive daily doses of 5 or 50 mg/kg b.w. When cells were examined 6 hours after the second dose there was no increase in micro-
nuclei.
(Haakeston Laboratories America, Inc., 1983)
In a rec-assay, using the recombination wild (R-17) and DNA deficient (M-45) strains of Bacillus subtilis, negative results were obtained at dose levels of up to 10,000 ag/ml.
(The Institute of Environmental
Toxicology, (1982)

CONCLUSION

A large number of toxicological studies for benfuracarb have been conducted at different toxicology laboratories in order to assess its safety.

Acute toxicity studies in mice, rats and dogs indicated that benfuracarb is relatively low toxic compared to the other existing carbamate insecticides. Irritation studies in rabbits revealed that benfuracarb is not irritating to the skin, but minimally irritating to the eye. Skin sensitization was not noted with benfuracarb in guinea-pigs. Benfuracarb was proved to have no potential to produce delayed neurotoxicity in atropinized hens. In sub-acute toxicity studies in rats and mice a transient cholinesterase inhibition, which is common among carbamate insecticides, was observed, and suppression of body weight gain was demonstrated, especially at the high dose level. No consistent treatment-related effects were observed at hematology, gross and histopathological examination, and clinical chemistry except for cholinesterase determination. In chronic toxicity/carcinogenicity studies in rats, dogs and mice, no treatment-related effects were apparent with histopathological examination, though anticholinesterase activity was observed. The non-effect level for rats and dogs was 25 ppm and 2.5 mg/kg b.w./day, respectively, based on depression of cholinesterase activity. It was concluded that benfuracarb is not carcinogenic. In teratology studies in rats and rabbits, benfuracarb was proved to be non-teratogenic, though some maternal toxicity due to cholinesterase inhibition was observed at the high dose level. No effects were noted in a battery of mutagenicity studies conducted.

Benfuracarb was registered in Japan in October 1986 as a soil insecticide (Oncol® 5G) for the control of rice water weevil on rice, thrips and diamondback moth on vegetables, and many other pests on major food crops. The tolerance for rice, fruits, vegetables and beans was established to be 0.2, 0.5, 1.0 and 0.2 ppm, respectively. The results of various toxicological studies support the view that benfuracarb is safe in practical use when used as recommended.

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